

# European Journal of Vascular & Endovascular Surgery

## Supervised Exercise Therapy for Intermittent Claudication: A Propensity Score Matched Analysis of Retrospective Data on Long term Cardiovascular Outcomes --Manuscript Draft--

<b>Manuscript Number:</b>	EJVES19380R
<b>Article Type:</b>	Original Article-Other
<b>Keywords:</b>	Intermittent Claudication; outcome assessment; propensity score; ischemia; exercise therapy; resistance training
<b>Corresponding Author:</b>	Bharadhwaj Ravindhran Hull York Medical School Hull, East Riding of Yorkshire UNITED KINGDOM
<b>First Author:</b>	Bharadhwaj Ravindhran
<b>Order of Authors:</b>	Bharadhwaj Ravindhran Arthur JM Lim Thomas Kurian Josephine Walshaw Louise Helen Hitchman Ross Lathan George Smith Daniel Carradice Ian Chetter Sean Pymer
<b>Abstract:</b>	<p><b>Objective:</b> This study aimed to explore the long-term outcomes of patients with intermittent claudication (IC) who completed supervised exercise therapy (SET) versus those who declined or prematurely discontinued SET, focusing on the incidence of chronic limb-threatening ischemia (CLTI), revascularization, major adverse limb events (MALE), and major adverse cardiovascular events (MACE).</p> <p><b>Design:</b> Retrospective registry analysis of consecutive patients with IC who were referred for SET between March 2015 and August 2016 and followed up for a minimum of five years.</p> <p><b>Methods:</b> Serial univariable analysis and logistic regression was performed to identify the statistically significant clinical variables that were independent predictors of each outcome measure. The resulting statistically significant variables were used to guide 1:1 propensity score matching (PSM) using the nearest neighbour method with a calliper of .2. Cox proportional hazards regression was used to estimate the hazard ratio(HR) and 95% CI for the association between SET and the outcomes of interest.</p> <p><b>Results:</b> Two hundred and sixty-six patients were referred to SET between March 2015 and August 2016. Of these, 64 patients completed SET and 202 patients did not. After PSM, 49 patients were analysed in each cohort. The Cox proportional hazards analysis revealed a significant association between completion of SET and revascularisation requirement( HR: 0.46 95% CI 0.25 – 0.84; p =.011), completion of SET and progression to CLTI(HR: 0.091, 95% CI 0.04 – 0.24; p &lt;.001), completion of SET and MACE(HR: 0.52; 95% CI 0.28 – 0.99; p =.05) and completion of SET and MALE( HR: 0.28, 95% CI 0.13 – 0.65; p =.003). The Harrell's C-index for all of these models were greater than .75 indicating good predictive accuracy.</p> <p><b>Conclusion:</b> Completion of SET is associated with better outcomes in patients who completed SET compared to patients who declined or discontinued SET with respect to clinically important cardiovascular outcomes over 7 years.</p>

## Response to reviewers:

Reviewer 1:

**Comment:** My main concern cannot be completely addressed due to the nature of the data/design, but the authors did a good job of nuancing the methods and results. A compelling finding is the high number of patients declining SET (70% of suitable patients) and the documented reason for doing so. This definitely helps to understand and solve the barriers to wide implementation and use of a SET first strategy in claudicants.

**Response:** Thank you very much for your kind comment. As you have rightly suggested, your concern is justified and has been acknowledged as a significant limitation throughout the manuscript with our careful choice of words.

**Comment:** Discussion line 240-241. Please delete '... a reduced risk of requiring revascularisation' as this endpoint was taken out of the analysis.

**Response:** Many thanks for your kind comment. This has been edited accordingly.

**Comment:** Discussion line 321-323. Idem ('... reduced intervention rates')

**Response:** Many thanks for your kind comment. This has been edited accordingly.

**Comment:** Table 2. Title, please modify: Number of cardiovascular events for patients who did and did not complete SET after median follow up of xx years. Please delete p value, as formal comparison is made by cox regression analysis in the text. One may consider to make a bar graph instead of a table to highlight the differences.

**Response:** Many thanks for your kind comment. This has been edited accordingly.

Reviewer 2:

**Comment:** I want to thank the authors for their revision, in which they have addressed previous reviewers' suggestions and comments, particularly facing the study's limitations. Currently, their manuscript presents their findings in a solid and balanced way, making it a potentially valuable addition to our upcoming EJVES issue.

**Response:** Many thanks for your kind comments and suggestions which have significantly improved the quality of the manuscript!

Reviewer 4:

**Comment:** In the current manuscript Ravindhran and colleagues retrospectively report the long-term outcomes of patients that completed SET for IC and compared these with a group of patients that did either not start or prematurely stopped SET. They use propensity score matching to try and correct for potential confounding. However, this does not completely correct for unmeasured confounding and especially since it is reasonable that not participating in SET could well be related to causes that are also related to worse outcomes, such as limited cardiovascular reserve and frailty. As the manuscript has already been scrutinized by some of my colleague experts in this field I mainly focused on methodology and also have some other general comments as well.

**Response:** Thank you for your kind comments and suggestions. We have made every effort to address all the comments to the best of our abilities, taking into account all the suggestions from the reviewers, despite encountering a few contradictory suggestions between them.

Title:

**Comment:** 1. I would recommend to include the study design in more detail in the title and not only that it includes a propensity score matching. The single center and retrospective design are important and also consider to include "long-term cardiovascular and limb related outcomes".

**Response:** Thank you for your kind comment. We greatly appreciate the suggestions provided by reviewers 1-3, which have influenced the changes made to the current title. We agree that these suggestions are important and have accordingly edited the title to "Supervised Exercise Therapy for Intermittent Claudication: A Propensity Score Matched Analysis of Retrospective Data on Long-term Cardiovascular Outcomes" to incorporate all reviewer comments.

#### **What this paper adds**

**Comment:** 2. This part is very limited now. It does not include the fact that a comparison was made with a "control group" using PSM.

**Response:** Thank you for your feedback! We greatly appreciate the suggestions made by reviewers 1-3, which led to the significant truncation of this section. However, we acknowledge the importance of these points raised by you and have made the necessary modifications accordingly.

**Comment:** 3. Would explicitly mention which outcomes were assessed.

**Response:** Many thanks for your kind comment ! This was previously removed as kindly suggested, but have been readded as per your kind suggestion.

Abstract:

**Comment:** 4. Include in the conclusion that completion of SET is "associated with better outcomes than ...". So include the description of the control group and not state "improvement" (this suggests that health status is better than at baseline), but better compared to a reference group.

**Response:** Many thanks for this kind comment. This has been edited accordingly

Introduction:

**Comment:** 5. Minor: CLTI is not spelled out at first time use.

**Response:** Many thanks for this kind comment and apologies for the oversight. This has been edited accordingly

**Comment:** 6. I would consider to rephrase the aim of the study: "Therefore, the aim of this study was to investigate whether completion of SET was associated with better cardiovascular outcomes compared to a group of patients with intermittent claudication that did not complete SET using PSM." Or something similar.

**Response:** Many thanks for this kind comment. This has been edited accordingly

Methods:

**Comment:** 7. I miss any statement on ethics.

**Response:** Thank you for your kind comment and for highlighting this important point. This project was registered as part of a service evaluation project within our institution. It involved a retrospective analysis of anonymised patient data. We've included this information in the submission declaration during the submission.

**Comment:** 8. Why did the authors only include the statistically significant variables in the PSM? Why not choose a more liberal approach? Could well be that you might miss relevant variables due to type II error. Although I believe that you performed a rigorous method to select variables. Please comment.

**Response:** Many thanks for raising this important point! Thank you for your insightful comments and questions. We appreciate your suggestion of adopting a more liberal approach in the selection of variables for PSM. In our study, we initially included statistically significant variables in the PSM to ensure that we were controlling for factors that had a proven association with the outcome. This approach was taken to minimize the risk of overfitting and to ensure the robustness of our findings. However, we acknowledge your concern about the potential for Type II errors and the possibility of missing relevant variables. We agree that a more liberal approach could potentially uncover additional variables of interest which we have now acknowledged as a significant limitation in the limitation section.

**Comment:** 9. The group of patients that completed SET is very small. Why did the authors not consider to use inverse probability weighting and hence retain a larger sample size. Can the authors provide such an analysis to underline the robustness of their findings?

**Response:** Thank you for your extremely insightful comment and for raising yet another important point. We acknowledge that the sample size of patients who completed SET is relatively small, which could potentially limit the generalizability of our findings. The use of inverse probability weighting (IPW) is indeed a valid approach that could allow us to retain a larger sample size and potentially enhance the robustness of our findings. However, we chose Propensity Score Matching for the following reasons specific to our study. Firstly, PSM allows us to closely mimic a randomized controlled trial by matching patients who completed SET with control patients on a range of observed characteristics. This approach helps to reduce bias due to confounding variables. Secondly, while IPW could potentially retain a larger sample size, it can also introduce its own set of challenges. IPW can be highly sensitive to the specification of the model used to estimate the weights. If the model is incorrectly specified, the weights can be biased, leading to biased estimates of the treatment effect. Furthermore, IPW can lead to unstable estimates if there are individuals with extreme weights. This is particularly a concern in our study given the small sample size of patients who completed SET (which is consistent with national reports). While we acknowledge the potential benefits of IPW, we believe that PSM is a more suitable method for our study given these considerations. However, we recognize the limitations of our approach, including the potential for bias due to unobserved confounding and the reduced sample size. We believe that these limitations are balanced by the strengths of PSM, including its ability to reduce bias due to observed confounding variables and its robustness to model specification. This has been acknowledged as yet another significant limitation.

**Comment:** 10. In the methods statements are missing on completeness of data. Were there missing, how many, how was dealt with missing variables in the analyses? Imputation?

**Response:** Many thanks for yet another important point. Given that we do not have a large sample size, patients were missing data were not included. This has now been added to the manuscript.

Results:

**Comment:** 11. It would be nice when a flow diagram could be provided to visualize the patient flow in the study.

**Response:** Thank you for your valuable suggestion. We understand the importance of including additional figures and tables to provide a comprehensive analysis. However, we are significantly limited by the total number of figures and tables allowed, which is set at 5 for this paper. We believe that all the figures and tables included in the manuscript are equally important for presenting our findings and supporting the conclusions. We appreciate your understanding and assure you that we have made every effort to include the most relevant and informative figures and tables.

**Comment:** 12. The lack of differences in Table 1b after PSM could well be the result of type II error, please discuss in limitations.

**Response:** Many thanks for raising yet another important point. We absolutely agree and will add this to the list of limitations.

**Comment:** 13. The values for haemoglobin in the text do differ from the ones in table 1b. Please check and correct. Considering a p of 0.08 I think the values in table 1b are correct.

**Response:** Many thanks for spotting this and sincere apologies for the oversight. This has been addressed as suggested.

Conclusion:

**Comment:** 14. The conclusion that SET leads to improvement of cardiovascular health and potentially mitigates adverse long-term outcomes in IC cannot be made. This study has too high risk of unmeasured confounding to draw conclusions on causal relationships, only draw conclusions on an association.

**Response:** Many thanks for this kind comment! This has been modified as suggested!

References:

**Comment:** 15. I think the amount of references is rather substantial, but if none of the reviewers and the editor consider this a problem I think it is acceptable.

**Response:** Thank you for your feedback. We have made efforts to limit the use of references in the content provided in order to maintain conciseness and readability. However, we understand the importance of providing sufficient elaboration to support the statements made.

Figures:

**Comment:** 16. Figure 3: Think about data maturity and truncation of the KM-curves at a certain number at risk. Extending the KM when the number at risk is 0 or 1 has no use.

**Response:** Many thanks for your kind comment! We absolutely agree and have edited this as suggested.

The Editorial team/Mr. Jonathan Boyle

European Journal of Vascular and Endovascular Surgery (EJVES)

Dear Mr Boyle,

We hope this letter finds you well. We are submitting the revised version of our manuscript titled "supervised exercise therapy for intermittent claudication: a propensity score matched analysis of retrospective data on long term cardiovascular outcomes" for your kind reconsideration for publication in the European Journal of Vascular and Endovascular Surgery.

We are grateful for the opportunity to address the concerns and suggestions raised by the reviewers during the initial review process. We have carefully incorporated all changes recommended by reviewers 1 and 2, as well as the valuable feedback provided by reviewer 4. These revisions have significantly improved the quality and clarity of our manuscript.

We would like to acknowledge the insightful comment raised by reviewer 4 regarding the small sample size of patients who completed SET, which could potentially limit the generalizability of our findings. While the use of inverse probability weighting is a valid approach to retain a larger sample size and enhance the robustness of our findings, we have chosen Propensity Score Matching for specific reasons in our study.

Firstly, PSM allows us to closely mimic a randomized controlled trial by matching patients who completed SET with control patients based on a range of observed characteristics, reducing bias due to confounding variables. Secondly, while IPW could retain a larger sample size, it can introduce challenges such as sensitivity to model specification and unstable estimates with extreme weights. Given the small sample size of patients who completed SET, we believe that PSM is a more suitable method for our study, considering these considerations. However, we acknowledge the limitations of our approach, including the potential for bias due to unobserved confounding and the reduced sample size. We have now acknowledged these limitations in the manuscript.

We appreciate their suggestion of adopting a more liberal approach in the selection of variables for PSM. In our study, we initially included statistically significant variables in the PSM to ensure that we were controlling for factors that had a proven association with the outcome. This approach was taken to minimize the risk of overfitting and to ensure the robustness of our findings. However, we acknowledge the potential for Type II errors and the possibility of missing relevant variables. We have now acknowledged this as a significant limitation in the manuscript.

We kindly request that you reconsider our submission for publication in EJVES, taking into account the significant improvements we have made in response to the reviewers' feedback. We believe that our revised manuscript now meets the high standards set by the journal and contributes valuable insights to the field of vascular and endovascular surgery.

Thank you for your time and consideration. We look forward to hearing from you soon.

Yours sincerely,

Bharadhwaj Ravindhran



Multiple choice questions:

According to the current guidelines, which of the following treatment approaches is considered the first line for intermittent claudication?

- a. Best medical therapy
- b. Best medical therapy, bed rest, and elevation
- c. Best medical therapy, supervised exercise program, smoking cessation
- d. Endovascular revascularization
- e. Surgical revascularization

Which of the following reasons is NOT a valid justification for considering percutaneous transluminal angioplasty as the first approach for intermittent claudication?

- a. Poor patient motivation
- b. Running costs
- c. Lack of availability/required time commitment
- d. Lack of qualified personnel
- e. Percutaneous transluminal angioplasty is more efficacious than supervised exercise therapy (SET)

1 Title: Supervised Exercise Therapy for Intermittent Claudication: A Propensity Score Matched  
2 Analysis of Retrospective Data on Long term Cardiovascular Outcomes:-Supervised exercise therapy  
3 for intermittent claudication: Propensity score matched analysis of long term outcomes

4 Running title: Long-term outcomes following supervised exercise therapy in intermittent claudication

5 Authors: Bharadhwaj Ravindhran,

6 Arthur JM Lim

7 Thomas Kurian

8 Josephine Walshaw

9 Louise H Hitchman

10 Ross Lathan

11 George E Smith

12 Daniel Carradice

13 Ian C Chetter

14 Sean Pymmer

15 <sup>1</sup> Academic Vascular Surgical Unit, 2<sup>nd</sup> Floor, Allam diabetes centre, Hull Royal Infirmary, HU32JZ

16 Corresponding author: Bharadhwaj Ravindhran

17 Academic Vascular Surgical Unit

18 2<sup>nd</sup> Floor, Allam diabetes centre

19 Hull Royal Infirmary

20 Hull HU32JZ

21 Bharadhwaj.Ravindhran@nhs.net

22 This paper was awarded the Norman Williams Prize for the best clinical research paper and is  
23 shortlisted for the BJS Best Manuscript Prize at the Annual Meeting of the Surgical Research Society  
24 in 2023 at Nottingham, UK.

25

26 Word counts

27 Abstract: 285

28 What this paper adds: 37

29 The text body: 2932

30 Number of tables and figures: 3 tables and 3 figures

31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53

**What this paper adds:**

This study contributes to the current body of literature by conducting an initial assessment of long-term outcomes in patients with intermittent claudication (IC) who underwent supervised exercise therapy (SET), with a focus on cardiovascular morbidity and mortality. The results indicate that completing SET is associated with a decreased risk of major adverse limb events, major adverse cardiovascular events, and progression to chronic limb-threatening ischemia based on this retrospective propensity score matched analysis of patients who completed, discontinued or declined SET.

54

55

56

57

58 **Abstract:**

59 Objective: This study aimed to explore the long-term outcomes of patients with intermittent  
60 claudication (IC) who completed supervised exercise therapy (SET) versus those who declined or  
61 prematurely discontinued SET, focusing on the incidence of chronic limb-threatening ischemia  
62 (CLTI), revascularization, major adverse limb events (MALE), and major adverse cardiovascular  
63 events (MACE).

64 Design: Retrospective registry analysis of consecutive patients with IC who were referred for SET  
65 between March 2015 and August 2016 and followed up for a minimum of five years.

66 Methods: Serial univariable analysis and logistic regression was performed to identify the statistically  
67 significant clinical variables that were independent predictors of each outcome measure. The resulting  
68 statistically significant variables were used to guide 1:1 propensity score matching (PSM) using the  
69 nearest neighbour method with a calliper of .2. A Cox proportional hazards regression was used to  
70 estimate the hazard ratio(HR) and 95% CI for the association between SET and the outcomes of  
71 interest.

72 Results: Two hundred and sixty-six patients were referred to SET between March 2015 and August  
73 2016. Of these, 64 patients completed SET and 202 patients did not. After PSM, 49 patients were  
74 analysed in each cohort. The Cox proportional hazards analysis revealed a significant association  
75 between completion of SET and revascularisation requirement( HR: 0.46 95% CI 0.25 – 0.84; p  
76 =.011), completion of SET and progression to CLTI(HR: 0.091, 95% CI 0.04 – 0.24; p <.001),  
77 completion of SET and MACE(HR: 0.52; 95% CI 0.28 – 0.99; p =.05) and completion of SET and

78 MALE( HR: 0.28, 95% CI 0.13 – 0.65; p =.003). The Harrell’s C-index for all of these models were  
79 greater than .75 indicating good predictive accuracy.

80 Conclusion: Completion of SET is associated with ~~significant improvements~~better outcomes in  
81 patients who completed SET compared to patients who declined or discontinued SET with respect to  
82 clinically important cardiovascular outcomes over 7 years.

83 Key words: Intermittent claudication, outcome assessment, propensity score, ischemia, exercise  
84 therapy; resistance training

85

86

87

88

89

90

91

92

93

94

95

96

97

98

99

100

101

102 Introduction:

103 Intermittent claudication (IC) is an ambulatory, ischaemic muscle pain relieved by rest, which reduces  
104 physical function, walking capacity, balance, and quality of life and increases the risk of mortality  
105 from cardiovascular causes<sup>1-5</sup>. Patients with IC patients are at risk of disease progression to chronic  
106 limb threatening ischaemia(CLTI) and major adverse limb events (MALE) such as major lower limb  
107 amputations (MLLA), acute limb ischemia (ALI), or loss of untreated patency<sup>6,7</sup>.The goal of treatment  
108 is therefore to improve symptoms, physical function, and quality of life (QoL), while also reducing  
109 the risk of disease progression and limb loss, mortality and MACE.<sup>8</sup>

110 To achieve this, the National Institute for Health and Care Excellence (NICE) guideline 147<sup>9</sup> and the  
111 European society for vascular surgery (ESVS)<sup>10</sup> recommend supervised exercise therapy (SET) for 2-  
112 hours per week over a 3-month period, as the first-line treatment. Evidence shows that SET is  
113 significantly superior for improving walking performance, and therefore symptoms, when compared  
114 to home-based exercise and walking advice<sup>11</sup>. Further evidence also shows that SET is comparable to  
115 endovascular revascularisation for improving walking distance and importantly, QoL<sup>11</sup>. Given the  
116 positive effect that SET also has on cardiovascular risk factors,<sup>12,13</sup> it would be reasonable to assume  
117 that this leads to a potential benefit in morbidity, via a reduction in MACE and MALE, as well as a  
118 benefit in mortality. However, the evidence considering the long-term effects of SET on morbidity  
119 and mortality is lacking, with just one study considering the association between SET completion and  
120 mortality<sup>14,15</sup>.

121 Therefore, the aim of this study was to investigate whether completion of SET was associated with  
122 better cardiovascular outcomes compared to a group of patients with IC that did not complete SET

123 ~~using propensity score matching(PSM).Therefore, the aim of this study was to investigate the long-~~  
124 ~~term morbidity and mortality impact associated with successful completion of SET for the treatment~~  
125 ~~of IC.~~

126 Methods:

127 This study was conducted at a tertiary care referral vascular centre. The clinical, intra-operative and  
128 follow-up information were gathered, analysed and compared between patients who completed SET  
129 and patients who either declined or discontinued SET.

130 Patient selection:

131 We retrospectively analysed the data of consecutive patients with IC who were referred for SET  
132 between March 2015 and August 2016 (18 months). Patients who were referred but had CLTI, had  
133 undergone SET within the preceding 12 months, or had a recurrence of symptoms following previous  
134 revascularisation were excluded from this analysis. Patients who were referred for SET but were  
135 deemed unsuitable due to contraindications or the presence of significant co morbidities or missing  
136 data were also excluded. The diagnosis of IC was made clinically, and was further supported by a  
137 resting ankle brachial pressure index (ABPI) or toe -brachial pressure index, duplex ultrasound or  
138 cross-sectional imaging if required. Patients who declined SET were either discharged back to their  
139 general practitioner (GP), received regular follow-up or underwent a revascularisation procedure,  
140 depending on individual need.

141 Patients referred to supervised exercise therapy (SET) were initially assessed by physicians to identify  
142 any obvious contraindications such as severe frailty, unstable gait, and existing pulmonary and cardiac  
143 disorders (e.g., aortic stenosis, dyspnoea at rest). These contraindications were determined based on  
144 clinical judgment. Furthermore, patients who did not have any obvious contraindications to SET were  
145 then screened by the exercise physiologist prior to starting SET. This screening process aimed to  
146 identify any additional contraindications or factors that may affect the safety or effectiveness of SET  
147 for individual patients. It is important to note that all patients in our study underwent routine screening

148 at two levels (physician assessment and exercise physiologist screening) to ensure that only those who  
149 were suitable for SET were included.

150 Supervised exercise therapy:

151 Patients performed SET three times per week for 12 weeks comprising a total of 36 sessions. Missed  
152 sessions were made up at the end of the 12-week programme<sup>16</sup>. The programme was overseen by an  
153 exercise physiologist with support from undergraduate and postgraduate sports science students. SET  
154 sessions involved the completion of a circuit of six two-minute stations, separated by two-minute  
155 walking intervals. These were preceded by a warm-up and followed by a cool-down. The stations  
156 included step-ups, standing knee bends, sitting knee extensions, biceps curls, cycling, and heel raises  
157 (Figure 1). As the patient's exercise tolerance improved, an additional station was added each week  
158 from the seventh week and by the end of week 12, they completed two full circuits. Session length  
159 therefore began at 30, progressing up to 60 minutes. Patients were deemed to have successfully  
160 completed SET after accumulating 36 sessions. This circuit-based training program was designed  
161 based on previous recommendations that highlight the effectiveness of combining upper and lower  
162 limb ergometry, resistance exercise, and walking-based exercises to improve muscle strength and  
163 cardiorespiratory fitness. These interventions have been shown to elicit a more significant  
164 cardiorespiratory stimulus compared to walking alone.<sup>17-20</sup>

165 Outcome measures:

166 The study investigated the incidence and time-to CLTI, MALE, and MACE over a minimum of five  
167 years and up to seven years. CLTI was defined as ischaemic rest pain lasting for two or more weeks,  
168 non-healing wounds, or gangrene that was attributable to objectively proven arterial occlusive disease.  
169 MACE was defined as non-fatal stroke, nonfatal myocardial infarction (MI), or cardiovascular death  
170 (CVD)<sup>21</sup>. MALE was defined as ALI, untreated loss of patency, or MLLA.<sup>22</sup>

171 Statistical analyses:

172 Continuous data was assessed for a normality using the Shapiro-Wilk test and are presented as mean  $\pm$   
173 standard deviation or median and range or interquartile range as appropriate. Categorical data are



174 expressed as numbers and/or percentages. Time to event data is presented using Kaplan-Meier  
175 survival curves. Comparative hypothesis testing was performed using Chi-squared tests, t-tests or  
176 Mann Whitney U tests as appropriate, and log-rank tests. Statistical significance was set at  $p < .05$ .  
177 Serial univariable analysis and logistic regression was performed to identify the statistically  
178 significant clinical variables that were independent predictors of each outcome measure. This was  
179 confirmed by performing an independent variable importance analysis using the multilayer perceptron  
180 tool, which is a popular tool in machine learning and deep learning for pattern recognition.<sup>23</sup> The  
181 resulting statistically significant variables were used to guide 1:1 ~~propensity score matching (PSM)~~  
182 using the nearest neighbour method with a calliper of .2. The differences between these two matched  
183 groups were compared by using the Mann-Whitney U test, and categorical data were analysed using  
184 the Pearson's Chi-square test, the Fisher's exact test, or continuity correction where appropriate.  
185 Survival curves were obtained by the Kaplan-Meier method and a Cox proportional hazards  
186 regression was used to estimate the hazard ratio(HR) and 95% CI for the association between SET  
187 and the outcomes of interest. All statistical analyses were performed using Statistical Package for the  
188 Social Sciences (IBM Corp. 2020; Windows Version 27.0) and Medcalc (MedCalc Statistical  
189 Software version 19.2.6; MedCalc Software bv, Ostend, Belgium;)

190

191 Results:

192 Two-hundred and eighty-two patients presented to the vascular outpatient clinic with IC between  
193 March 2015 and August 2016 and were referred for SET. Sixteen patients were deemed unsuitable for  
194 SET due to advanced comorbidities, mobility problems and dementia. Two-hundred and sixty-six  
195 patients were deemed suitable and were offered SET, of which 83 (31%) attended and 183 (69%)  
196 declined. Of those that attended, 64 (77%) patients successfully completed SET, whilst 19 (23%)  
197 prematurely discontinued. Baseline characteristics of those who completed and those who declined or  
198 prematurely discontinued SET are presented in table 1a. The primary reasons for the low adoption of  
199 SET were related to location or travel (44.3%; n=81), individuals declining due to lack of  
200 interest/belief in the SET (39.3%; n=72), work/personal commitments resulting in a lack of time for

201 SET (12.6%; n=23), inability to participate due to musculoskeletal issues (2.2%; n=4), and patients  
202 already enrolled in a community exercise program (1.6%; n=3). Considering that nearly all patients  
203 who discontinued SET did so without attending at least 50% of the sessions, we deemed it appropriate  
204 to combine both groups, i.e., those who discontinued and those who declined SET, for the purpose of  
205 analysis.

206 Serial univariable and logistic regression analyses revealed that CLTI had the greatest number of  
207 statistically significant predictor variables compared to the other outcomes, and therefore, these  
208 significant predictors were used to guide PSM, which was performed to account for the independent  
209 association between these variables and outcome measures. Haemoglobin, self-reported claudication  
210 distance, ABPI, presence of ischaemic heart disease (IHD), neutrophil-to-lymphocyte ratio,  
211 compliance with smoking cessation and non-completion of supervised exercise therapy were found to  
212 be statistically significant predictors of CLTI based on serial univariable analyses. Logistic regression  
213 analysis performed using these variables indicated that haemoglobin, self-reported claudication  
214 distance, ABPI and the presence of IHD were significant predictors of CLTI. This was confirmed via  
215 an independent variable importance analysis (Figure 2). The multilayer perceptron(MLP) algorithm is  
216 employed to evaluate the relative contribution of independent variables in predicting CLTI. By  
217 assigning weights to each input variable based on their importance, the MLP algorithm provides  
218 valuable insights into the significance of each variable. This importance analysis helps identify the  
219 variables with the greatest impact on CLTI occurrence.

220 After PSM based on these variables, 49 patients were analysed in each cohort. There was no  
221 difference between groups with respect to haemoglobin (g/l) (130.9 ± 19.3 vs 138.6 ±  
222 18.8;  $p = .080$ ), IHD (59.2% vs 63.3%  $p = .56$ ), self-reported claudication distance (metres)  
223 ( $131 ± 19.4$  vs  $130 ± 18.9$ ;  $p = .81$ ) and ABPI ( $0.7 ± 0.1$  vs  $0.7 ± 0.2$ ;  $p = .29$ )(Table 1b). The Cox  
224 proportional hazards analysis revealed a significant association between completion of SET and  
225 progression to CLTI(HR: 0.091, 95% CI 0.04– 0.24;  $p < .001$ ), completion of SET and MACE(HR:  
226 0.52; 95% CI 0.28 – 0.99;  $p = .05$ ) and completion of SET and MALE( HR: 0.28, 95% CI 0.13 – 0.65;  
227  $p = .003$ ). The Kaplan-Meier curves demonstrated a consistent and statistically significant difference in

228 outcomes amongst those who completed SET, compared to those who did not complete SET (Figure  
229 3). The Harrell's C-index for all of these models were greater than .75 indicating good predictive  
230 accuracy.

231 To assess the adequacy of sample size, a post-hoc power analysis was conducted, revealing that a total  
232 of 48 events and a sample size of 36 patients in the SET completion cohort and 186 patients in the  
233 non-completion cohort were required to detect a significant association between SET and outcomes.  
234 This estimation followed the methodology outlined by Schoenfeld et al<sup>24</sup>, assuming a significance  
235 level of .05, 80% power, a 16% incidence of SET completion among referred patients<sup>25</sup>, a relative  
236 hazard of 3, a median survival of 12 years, and a planned follow-up of 7 years<sup>15,26,27</sup>.

237 Discussion:

238 This study demonstrates that completion of SET is associated with a reduced risk of ~~requiring~~  
239 ~~revascularisation and~~ experiencing MALE, MACE and progression to CLTI. To the best of our  
240 knowledge, this study represents one of the first evaluations of long-term outcomes following SET  
241 with a focus on cardiovascular morbidity and mortality in individuals with PAD. Whilst the data  
242 suggest a positive effect of SET, it is important to acknowledge that the patients in this cohort may  
243 differ in ways that have not been accounted for, and their outcomes may have been influenced by  
244 factors beyond SET. It is important to note that even with rigorous propensity score matching,  
245 confounding by indication cannot be completely adjusted for, as there may be unmeasured covariates  
246 that affect both the variable and outcome of interest. We also acknowledge that while this analysis  
247 provides important insights and suggests an association, the efficacy of SET for improving  
248 cardiovascular outcomes cannot be established. Nevertheless, these findings provide a strong rationale  
249 for increasing the delivery of SET and conducting further research to better understand its potential  
250 long-term benefits. Moving forward, efforts should be directed towards reducing SET barriers (such  
251 as the time commitment) to maximise patient engagement. By doing so, we may be able to optimise  
252 the effectiveness of SET and improve outcomes for a broader range of patients.

253

254 Currently, high quality evidence shows that SET provides an important benefit with respect to  
255 maximum walking distance (MWD), pain-free walking distance and QoL compared to home-based  
256 exercise therapy and walking advice<sup>14,28</sup>. Better SET compliance, measured by attendance at exercise  
257 sessions, is significantly associated with greater improvements in MWD and adherence to SET may  
258 imply better adherence of several factors in life, such as to smoking cessation, healthy diet and  
259 medication, resulting in better outcomes.<sup>29</sup> However, even patients at the lowest tercile of exercise  
260 attendance demonstrate a significant improvement in MWD<sup>30</sup>. Despite this evidence, and the  
261 guidance provided by NICE and the ESVS,<sup>9,10</sup> SET provision is not consistent in the UK, with less  
262 than 50% of vascular centres offering it and less than 25% of these adhering to the recommended  
263 exercise dose<sup>31</sup>. The low availability of SET in the UK can be attributed to various constraints faced in  
264 a centralized hub and spoke model. These constraints include running costs and a lack of resources  
265 and qualified personnel<sup>32-34</sup>. When SET is offered, patients may not want to participate due to a lack  
266 of availability near their home or the required time commitment, which contributes to the poor uptake  
267 rates seen.<sup>25,35</sup> Further research is needed to explore ways to address or minimise the constraints felt  
268 by patients and providers to improve the accessibility and acceptability of SET.

269 During the last two decades there has been a substantial increase in the number of studies comparing  
270 primary interventional therapy to SET. The results of these studies suggest that SET is comparable to  
271 primary percutaneous transluminal angioplasty (PTA) for improving in walking distance and  
272 QoL<sup>36,37,38</sup>. This suggests that the current first-line treatment strategy of SET is advocated. However,  
273 poor uptake and adherence to SET, poor patient fitness, and patient preference are cited as reasons for  
274 using a “PTA first” strategy in patients with IC<sup>39-41</sup>. Based on the results of the current study, even if  
275 a PTA first strategy is pursued due to these constraints, the integration of an exercise intervention may  
276 yield additional improvements in long-term cardiovascular outcomes, which may not occur with PTA  
277 alone.

278 Recent evidence has also demonstrated that SET produces a notable improvement in cardiovascular  
279 risk factors, such as cholesterol levels and resting and exercising blood pressure<sup>12,13</sup>. Interestingly, the  
280 greater the improvement in cardiovascular health, the greater the improvement in walking

281 performance.<sup>12</sup> Despite this evidence for a reduction in cardiovascular risk factors, there is limited  
282 data to support the reduction of long-term cardiovascular risk following SET.<sup>42,43</sup> The reduction in  
283 cardiovascular morbidity and mortality following SET demonstrated in this study could be  
284 attributable to these beneficial effects on cardiovascular risk factors.

285 Determining the percentage of outcomes that are directly associated with the completion of SET is  
286 difficult, given the presence of unmeasured confounding variables that may impact the findings, such  
287 as patient motivation. Even amongst highly motivated patients, uptake and adherence to SET can be  
288 difficult, underscoring the importance of offering alternative options to patients who wish to engage in  
289 SET but face barriers to compliance and uptake<sup>34</sup>. High-intensity interval training (HIIT) or remotely  
290 delivered supervised exercise interventions are alternatives that could offer promising benefits,  
291 specially tailored to the unique needs and conditions of patients who were previously unable to enrol  
292 in SET due to time or travel constraints.<sup>44,45</sup> Currently, a time efficient HIIT programme is being  
293 assessed as a potential alternative for SET, to reduce the time barrier faced by patients<sup>46</sup>. Early  
294 evidence has suggested that this HIIT programme appears to be feasible and well tolerated in patients  
295 with IC, which is to be confirmed via a proof-of-concept study<sup>46</sup>.

296

297 Other alternative approaches to delivering SET have been explored, including remote monitoring,  
298 videos, support groups, mobile-applications and trackers and virtual reality.<sup>44,47,48</sup> A smartphone-  
299 enabled home-based exercise program is feasible and effective in patients with symptomatic PAD, as  
300 is a community-based walking programme with training, monitoring and coaching components.<sup>47,49</sup>  
301 These alternative approaches to delivering SET have the potential to increase patient access and  
302 improve adherence. However, they are currently limited to small proof-of-concept studies. Further  
303 research is needed to explore their effectiveness in fully powered randomised controlled trials.

#### 304 **Limitations**

305 Although this study provides useful insights, its retrospective nature encompasses several inherent  
306 limitations, including unmeasurable confounding factors, potential biases, and the lack of blinding or

307 randomisation that can affect the objectivity of our analysis. The limitations associated with the  
308 retrospective nature of this study were addressed by enrolling consecutive patients over an eighteen-  
309 month period and conducting a meticulous PSM method with a 0.2 calliper. While there are many  
310 alternatives to 1:1 PSM such as mahalanobis distance matching, kernel matching and covariate  
311 matching, propensity score matching is considered the best approach due to its ability to balance  
312 covariates, flexibility in handling different types of covariates, interpretability, and the opportunity for  
313 sensitivity analysis.<sup>50-53</sup> Despite using rigorous propensity score matching, it is impossible to fully  
314 account for confounding by indication. This is because there might be unmeasured factors that impact  
315 both the variable being studied and the outcome of interest. In our study, we included statistically  
316 significant variables in the PSM to ensure that we were controlling for factors that had a proven  
317 association with the outcome. This approach was taken to minimize the risk of overfitting and to  
318 ensure the robustness of our findings. However, we acknowledge the potential for Type II errors and  
319 the possibility of missing relevant variables. The lack of differences observed in Table 1b after  
320 implementing PSM could potentially be attributed to a type II error. The use of inverse probability  
321 weighting (IPW) is a valid approach that can enhance the robustness of findings by retaining a larger  
322 sample size. However, we chose PSM for our study due to specific reasons. PSM allows us to best  
323 mimic a randomized controlled trial by matching patients who completed SET with control patients  
324 based on observed characteristics, reducing bias from confounding variables. While IPW could retain  
325 a larger sample size, it can introduce challenges such as sensitivity to model specification and  
326 unstable estimates with extreme weights. We believe PSM is more suitable for our study, considering  
327 these factors, although we acknowledge limitations such as potential bias from unobserved  
328 confounding and a reduced sample size. Additionally, it is important to acknowledge that although  
329 this analysis offers valuable insights and indicates a potential connection, we cannot definitively  
330 establish the effectiveness of SET in improving cardiovascular outcomes.

331 This study indicates an association between patients completing SET and better long-term clinical  
332 outcomes, such as slower disease progression, and a lower likelihood of experiencing MALE or  
333 MACE. However, due to the potential for unmeasured confounding, we cannot definitively conclude

334 that SET leads to an improvement in cardiovascular health or mitigates adverse long-term outcomes  
335 in IC. Rather, our findings suggest a potential association that warrants further investigation. Overall,  
336 these outcomes underscore the potential significance of SET in relation to cardiovascular health in IC  
337 patients. This study suggests that patients completing SET have better long-term clinical outcomes,  
338 such as slower disease progression, reduced intervention rates, and a lower likelihood of experiencing  
339 MALE or MACE. Overall, these outcomes highlight the critical significance of SET in improving  
340 cardiovascular health and its potential to mitigate adverse long-term outcomes in IC.

341 **Acknowledgements:** The authors gratefully acknowledge the invaluable contribution of Dr. Dror  
342 Rosentraub for his expertise and guidance in the application of statistical methods. The authors would  
343 also like to express their sincere gratitude to the academic vascular surgical unit for their invaluable  
344 support and collaboration throughout the course of this study. Their expertise and guidance have  
345 greatly contributed to the successful completion of this research.

346

347

348

349

350

351

352

353

354

355

356

357

358 References:

- 359 1. Criqui MH, Aboyans V. Epidemiology of peripheral artery disease. *Circ Res* [Internet]. 2015  
360 Apr 24 [cited 2023 May 1];116(9):1509–26. Available from:  
361 <https://pubmed.ncbi.nlm.nih.gov/25908725/>
- 362 2. Criqui MH, Langer RD, Fronek A, Feigelson HS, Klauber MR, McCann TJ, et al. Mortality  
363 over a period of 10 years in patients with peripheral arterial disease. *N Engl J Med* [Internet].  
364 1992 Feb 6 [cited 2023 May 1];326(6):381–6. Available from:  
365 <https://pubmed.ncbi.nlm.nih.gov/1729621/>
- 366 3. Pell JP. Impact of intermittent claudication on quality of life. *Eur J Vasc Endovasc Surg*. 1995  
367 May 1;9(4):469–72.
- 368 4. Gohil RA, Mockford KA, Mazari F, Khan J, Vanicek N, Chetter IC, et al. Balance impairment,  
369 physical ability, and its link with disease severity in patients with intermittent claudication.  
370 *Ann Vasc Surg* [Internet]. 2013 Jan 1 [cited 2023 May 9];27(1):68–74. Available from:  
371 <http://www.annalsofvascularsurgery.com/article/S0890509612003214/fulltext>
- 372 5. Meru A V., Mitra S, Thyagarajan B, Chugh A. Intermittent claudication: an overview.  
373 *Atherosclerosis* [Internet]. 2006 Aug [cited 2023 May 1];187(2):221–37. Available from:  
374 <https://pubmed.ncbi.nlm.nih.gov/16386260/>
- 375 6. Eid MA, Mehta K, Barnes JA, Wanken Z, Columbo JA, Stone DH, et al. The global burden of  
376 peripheral artery disease. *J Vasc Surg* [Internet]. 2023 Apr [cited 2023 Apr 3];77(4). Available  
377 from: <https://pubmed.ncbi.nlm.nih.gov/36565779/>
- 378 7. McDermott KM, Bose S, Keegan A, Hicks CW. Disparities in limb preservation and



- 379 associated socioeconomic burden among patients with diabetes and/or peripheral artery disease  
380 in the United States. *Semin Vasc Surg* [Internet]. 2023 Mar 1 [cited 2023 Apr 3];36(1).  
381 Available from: <https://pubmed.ncbi.nlm.nih.gov/36958896/>
- 382 8. Bevan GH, White Solaru KT. Evidence-Based Medical Management of Peripheral Artery  
383 Disease. *Arterioscler Thromb Vasc Biol*. 2020 Mar 1;40(3):541–53.
- 384 9. Overview | Peripheral arterial disease: diagnosis and management | Guidance | NICE  
385 [Internet]. [cited 2022 May 7]. Available from: <https://www.nice.org.uk/guidance/cg147>
- 386 10. Aboyans V, Ricco JB, Bartelink MLEL, Björck M, Brodmann M, Cohnert T, et al. 2017 ESC  
387 Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration  
388 with the European Society for Vascular Surgery (ESVS) Document covering atherosclerotic  
389 disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity  
390 arteries Endorsed by: the European Stroke Organization (ESO) The Task Force for the  
391 Diagnosis and Treatment of Peripheral Arterial Diseases of the European Society of  
392 Cardiology (ESC) and of the European Society for Vascul. *Eur Heart J* [Internet]. 2018 Mar 1  
393 [cited 2023 Apr 8];39(9):763–816. Available from:  
394 <https://academic.oup.com/eurheartj/article/39/9/763/4095038>
- 395 11. Murphy TP, Cutlip DE, Regensteiner JG, Mohler ER, Cohen DJ, Reynolds MR, et al.  
396 Supervised exercise, stent revascularization, or medical therapy for claudication due to  
397 aortoiliac peripheral artery disease: The CLEVER study. *J Am Coll Cardiol*. 2015 Mar  
398 17;65(10):999–1009.
- 399 12. Slysz JT, Tian L, Zhao L, Zhang D, McDermott MM. Effects of supervised exercise therapy  
400 on blood pressure and heart rate during exercise, and associations with improved walking  
401 performance in peripheral artery disease: Results of a randomized clinical trial. *J Vasc Surg*.  
402 2021 Nov 1;74(5):1589-1600.e4.
- 403 13. Jansen SCP, Hoorweg BBN, Hoeks SE, van den Houten MML, Scheltinga MRM, Teijink

- 404 JAW, et al. A systematic review and meta-analysis of the effects of supervised exercise  
405 therapy on modifiable cardiovascular risk factors in intermittent claudication. *J Vasc Surg*  
406 [Internet]. 2019 Apr 1 [cited 2023 May 16];69(4):1293-1308.e2. Available from:  
407 <https://pubmed.ncbi.nlm.nih.gov/30777692/>
- 408 14. Hageman D, Fokkenrood HJP, Gommans LNM, van den Houten MML, Teijink JAW.  
409 Supervised exercise therapy versus home-based exercise therapy versus walking advice for  
410 intermittent claudication. *Cochrane database Syst Rev* [Internet]. 2018 Apr 6 [cited 2023 Apr  
411 3];4(4). Available from: <https://pubmed.ncbi.nlm.nih.gov/29627967/>
- 412 15. Sakamoto S, Yokoyama N, Tamori Y, Akutsu K, Hashimoto H, Takeshita S. Patients with  
413 peripheral artery disease who complete 12-week supervised exercise training program show  
414 reduced cardiovascular mortality and morbidity. *Circ J* [Internet]. 2009 [cited 2023 Apr  
415 3];73(1):167–73. Available from: <https://pubmed.ncbi.nlm.nih.gov/19039192/>
- 416 16. Harwood AE, Totty JP, Pymer S, Huang C, Hitchman L, Carradice D, et al. Cardiovascular  
417 and musculoskeletal response to supervised exercise in patients with intermittent claudication.  
418 *J Vasc Surg* [Internet]. 2019 Jun 1 [cited 2023 May 16];69(6):1899-1908.e1. Available from:  
419 <https://pubmed.ncbi.nlm.nih.gov/30583899/>
- 420 17. Jansen SCP, Abaraogu UO, Lauret GJ, Fakhry F, Fokkenrood HJP, Teijink JAW. Modes of  
421 exercise training for intermittent claudication. *Cochrane Database Syst Rev* [Internet]. 2020  
422 Aug 23 [cited 2023 Aug 13];2020(8). Available from:  
423 <https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD009638.pub3/full>
- 424 18. Harwood AE, Pymer S, Ingle L, Doherty P, Chetter IC, Parmenter B, et al. Exercise training  
425 for intermittent claudication: a narrative review and summary of guidelines for practitioners.  
426 *BMJ open Sport Exerc Med* [Internet]. 2020 Nov 6 [cited 2023 Aug 13];6(1). Available from:  
427 <https://pubmed.ncbi.nlm.nih.gov/33262892/>
- 428 19. Mockford KA, Gohil RA, Mazari F, Khan JA, Vanicek N, Coughlin PA, et al. Effect of

- 429 supervised exercise on physical function and balance in patients with intermittent claudication.  
430 *Br J Surg*. 2014 Mar;101(4):356–62.
- 431 20. The Sport and Exercise Scientist n Issue 57 n Autumn 2018 n [@basesuk](http://www.bases.org.uk)  
432 @BASESUK bases\_uk BASESUK. [cited 2023 Aug 13]; Available from:  
433 [www.nice.org.uk/guidance/cg147](http://www.nice.org.uk/guidance/cg147)
- 434 21. Bianco M, Mottola FF, Cerrato E, Giordana F, Cinconze S, Baralis G, et al. Acute coronary  
435 syndrome in very elderly patients-a real-world experience. *Heart Vessels* [Internet]. 2023 Mar  
436 28 [cited 2023 Apr 3]; Available from: <https://pubmed.ncbi.nlm.nih.gov/36976424/>
- 437 22. Fashandi AZ, Mehaffey JH, Hawkins RB, Kron IL, Upchurch GR, Robinson WP. Major  
438 Adverse Limb Events and Major Adverse Cardiac Events after Contemporary Lower  
439 Extremity Bypass and Infrainguinal Endovascular Intervention in Patients with Claudication. *J*  
440 *Vasc Surg* [Internet]. 2018 Dec 1 [cited 2023 Apr 3];68(6):1817. Available from:  
441 [/pmc/articles/PMC6482457/](https://pubmed.ncbi.nlm.nih.gov/306482457/)
- 442 23. Idrissi J, Amine M. Multilayer Perceptron: Architecture Optimization and Training.
- 443 24. Schoenfeld DA. Sample-Size Formula for the Proportional-Hazards Regression Model.  
444 *Biometrics*. 1983 Jun;39(2):499.
- 445 25. Harwood AE, Smith GE, Cayton T, Broadbent E, Chetter IC. A systematic review of the  
446 uptake and adherence rates to supervised exercise programs in patients with intermittent  
447 claudication. *Ann Vasc Surg*. 2016 Jul 1;34:280–9.
- 448 26. Voci D, Fedeli U, Valerio L, Schievano E, Righini M, Kucher N, et al. Mortality rate related to  
449 peripheral arterial disease: A retrospective analysis of epidemiological data (years 2008–  
450 2019). *Nutr Metab Cardiovasc Dis*. 2023 Mar 1;33(3):516–22.
- 451 27. Klaphake S, Fakhry F, Rouwet E V., Van Der Laan L, Wever JJ, Teijink JA, et al. Long-term  
452 Follow-up of a Randomized Clinical Trial Comparing Endovascular Revascularization Plus

- 453 Supervised Exercise with Supervised Exercise only for Intermittent Claudication. *Ann Surg*  
454 [Internet]. 2022 Dec 1 [cited 2023 May 1];276(6):E1035–43. Available from:  
455 [https://journals.lww.com/annalsurgery/Fulltext/2022/12000/Long\\_term\\_Follow\\_up\\_of\\_a\\_R](https://journals.lww.com/annalsurgery/Fulltext/2022/12000/Long_term_Follow_up_of_a_Randomized_Clinical_Trial.71.aspx)  
456 [andomized\\_Clinical\\_Trial.71.aspx](https://journals.lww.com/annalsurgery/Fulltext/2022/12000/Long_term_Follow_up_of_a_Randomized_Clinical_Trial.71.aspx)
- 457 28. van den Houten MML, Hageman D, Gommans LNM, Kleijnen J, Scheltinga MRM, Teijink  
458 JAW. The Effect of Supervised Exercise, Home Based Exercise and Endovascular  
459 Revascularisation on Physical Activity in Patients With Intermittent Claudication: A Network  
460 Meta-analysis. *Eur J Vasc Endovasc Surg*. 2019 Sep 1;58(3):383–92.
- 461 29. Hammond MM, Tian L, Zhao L, Zhang D, McDermott MM. Attendance at Supervised  
462 Exercise Sessions and Walking Outcomes in Peripheral Artery Disease: Results From 2  
463 Randomized Clinical Trials. *J Am Hear Assoc Cardiovasc Cerebrovasc Dis* [Internet]. 2022  
464 Dec 12 [cited 2023 Apr 2];11(24):26136. Available from: [/pmc/articles/PMC9798808/](https://pubmed.ncbi.nlm.nih.gov/37111111/)
- 465 30. McDermott MMG, Criqui MH, Liu K, Guralnik JM, Greenland P, Martin GJ, et al. Lower  
466 ankle/brachial index, as calculated by averaging the dorsalis pedis and posterior tibial arterial  
467 pressures, and association with leg functioning in peripheral arterial disease. *J Vasc Surg*.  
468 2000;32(6):1164–71.
- 469 31. Harwood AE, Smith GE, Cayton T, Broadbent E, Chetter IC. A Systematic Review of the  
470 Uptake and Adherence Rates to Supervised Exercise Programs in Patients with Intermittent  
471 Claudication. *Ann Vasc Surg* [Internet]. 2016 Jul 1 [cited 2023 Jan 2];34:280–9. Available  
472 from: <https://pubmed.ncbi.nlm.nih.gov/27126713/>
- 473 32. Harwood AE, Smith GD, Broadbent E, Cayton TE, Carradice D, Chetter I. Access to  
474 supervised exercise services for peripheral vascular disease patients. *Bull R Coll Surg Engl*  
475 [Internet]. 2017 Jun [cited 2023 Apr 8];99(6):207–11. Available from:  
476 <https://doi.org/10.1308/rcsbull.2017.207>
- 477 33. Waddell A, Seed S, Broom DR, McGregor G, Birkett ST, Harwood AE. Safety of Home-based

- 478 Exercise for People with Intermittent Claudication: A Systematic Review. *J Vasc Surg*  
479 [Internet]. 2022 Apr 1 [cited 2023 Apr 8];75(4):1490. Available from:  
480 <http://www.jvascsurg.org/article/S0741521422000362/fulltext>
- 481 34. Harwood AE, Pymer S, Ibeggazene S, Ingle L, Caldow E, Birkett ST. Provision of exercise  
482 services in patients with peripheral artery disease in the United Kingdom. *Vascular*. 2022 Oct  
483 1;30(5):874–81.
- 484 35. Harwood AE, Hitchman LH, Ingle L, Doherty P, Chetter IC. Preferred exercise modalities in  
485 patients with intermittent claudication. *J Vasc Nurs* [Internet]. 2018 Jun 1 [cited 2023 May  
486 2];36(2):81–4. Available from: <https://pubmed.ncbi.nlm.nih.gov/29747787/>
- 487 36. Mazari FAK, Gulati S, Rahman MNA, Lee HLD, Mehta TA, McCollum PT, et al. Early  
488 outcomes from a randomized, controlled trial of supervised exercise, angioplasty, and  
489 combined therapy in intermittent claudication. *Ann Vasc Surg* [Internet]. 2010 Jan [cited 2023  
490 Apr 9];24(1):69–79. Available from: <https://pubmed.ncbi.nlm.nih.gov/19762206/>
- 491 37. Mazari FAK, Khan JA, Samuel N, Smith G, Carradice D, McCollum PC, et al. Long-term  
492 outcomes of a randomized clinical trial of supervised exercise, percutaneous transluminal  
493 angioplasty or combined treatment for patients with intermittent claudication due to  
494 femoropopliteal disease. *Br J Surg* [Internet]. 2017 Jan 1 [cited 2023 Apr 9];104(1):76–83.  
495 Available from: <https://pubmed.ncbi.nlm.nih.gov/27763685/>
- 496 38. Thanigaimani S, Phie J, Sharma C, Wong S, Ibrahim M, Huynh P, et al. Network meta-  
497 analysis comparing the outcomes of treatments for intermittent claudication tested in  
498 randomized controlled trials. *J Am Heart Assoc* [Internet]. 2021 May 4 [cited 2023 Apr  
499 3];10(9):19672. Available from:  
500 <https://www.ahajournals.org/doi/abs/10.1161/JAHA.120.019672>
- 501 39. Harwood AE, Broadbent E, Totty JP, Smith GE, Chetter IC. “Intermittent claudication a real  
502 pain in the calf”—Patient experience of diagnosis and treatment with a supervised exercise

- 503 program. *J Vasc Nurs*. 2017 Sep 1;35(3):131–5.
- 504 40. Vemulapalli S, Dolor RJ, Hasselblad V, Schmit K, Banks A, Heidenfelder B, et al. Supervised  
505 vs unsupervised exercise for intermittent claudication: A systematic review and meta-analysis.  
506 *Am Heart J*. 2015 Jun 1;169(6):924-937.e3.
- 507 41. Saratzis A, Paraskevopoulos I, Patel S, Donati T, Biasi L, Diamantopoulos A, et al. Supervised  
508 Exercise Therapy and Revascularization for Intermittent Claudication: Network Meta-Analysis  
509 of Randomized Controlled Trials. *JACC Cardiovasc Interv* [Internet]. 2019 Jun 24 [cited 2023  
510 Apr 3];12(12):1125–36. Available from: <https://pubmed.ncbi.nlm.nih.gov/31153838/>
- 511 42. Murphy TP, Cutlip DE, Regensteiner JG, Mohler ER, Cohen DJ, Reynolds MR, et al.  
512 Supervised exercise versus primary stenting for claudication resulting from aortoiliac  
513 peripheral artery disease: Six-month outcomes from the claudication: Exercise versus  
514 endoluminal revascularization (CLEVER) study. *Circulation*. 2012 Jan 3;125(1):130–9.
- 515 43. McDermott MM, Ferrucci L, Tian L, Guralnik JM, Lloyd-Jones D, Kibbe MR, et al. Effect of  
516 Granulocyte-Macrophage Colony-Stimulating Factor with or Without Supervised Exercise on  
517 Walking Performance in Patients with Peripheral Artery Disease: The PROPEL Randomized  
518 Clinical Trial. *JAMA - J Am Med Assoc*. 2017 Dec 5;318(21):2089–98.
- 519 44. Sivagangan P, Harwood AE, Stather PW. Patient and Healthcare Professional Priorities for a  
520 Mobile Phone Application for Patients With Peripheral Arterial Disease. *Cureus* [Internet].  
521 2023 Jan 20 [cited 2023 Apr 3];15(1). Available from:  
522 <https://pubmed.ncbi.nlm.nih.gov/36824553/>
- 523 45. Aalami OO, Lin J, Savage D, Ho V, Bertges D, Corriere M. Use of an app-based exercise  
524 therapy program including cognitive-behavioral techniques for the management of intermittent  
525 claudication. *J Vasc Surg* [Internet]. 2022 Dec 1 [cited 2023 Apr 3];76(6):1651-1656.e1.  
526 Available from: <https://pubmed.ncbi.nlm.nih.gov/35872328/>

- 527 46. Pymer S, Harwood A, Ibeggazene S, McGregor G, Huang C, Twiddy M, et al. High INtensity  
528 Interval Training In pATiEnts with intermittent claudication (INITIATE): protocol for a  
529 multicentre, proof-of-concept, prospective interventional study. *BMJ Open*. 2020 Jul  
530 6;10(7):e038825.
- 531 47. Harzand A, Vakili AA, Alrohaibani A, Abdelhamid SM, Gordon NF, Thiel J, et al. Rationale  
532 and design of a smartphone-enabled, home-based exercise program in patients with  
533 symptomatic peripheral arterial disease: The smart step randomized trial. *Clin Cardiol*  
534 [Internet]. 2020 Jun 1 [cited 2023 Apr 8];43(6):537–45. Available from:  
535 <https://onlinelibrary.wiley.com/doi/full/10.1002/clc.23362>
- 536 48. Persson AB, Buschmann EE, Lindhorst R, Troidl K, Langhoff R, Schulte KL, et al.  
537 Therapeutic arteriogenesis in peripheral arterial disease: combining intervention and passive  
538 training. <http://dx.doi.org/10.1024/0301-1526/a000092> [Internet]. 2013 Jan 7 [cited 2023 Apr  
539 9];40(3):177–87. Available from: [https://econtent.hogrefe.com/doi/10.1024/0301-](https://econtent.hogrefe.com/doi/10.1024/0301-1526/a000092)  
540 [1526/a000092](https://econtent.hogrefe.com/doi/10.1024/0301-1526/a000092)
- 541 49. Mays RJ, Hiatt WR, Casserly IP, Rogers RK, Main DS, Kohrt WM, et al. Community-based  
542 walking exercise for peripheral artery disease: An exploratory pilot study. *Vasc Med (United*  
543 *Kingdom)* [Internet]. 2015 Aug 10 [cited 2023 Apr 9];20(4):339–47. Available from:  
544 <https://journals.sagepub.com/doi/10.1177/1358863X15572725>
- 545 50. Austin PC. A critical appraisal of propensity-score matching in the medical literature between  
546 1996 and 2003. *Stat Med Stat Med* [Internet]. 2008 [cited 2023 Jul 2];27:2037–49. Available  
547 from: [www.interscience.wiley.com](http://www.interscience.wiley.com)
- 548 51. Stuart EA. Matching methods for causal inference: A review and a look forward. *Stat Sci*  
549 [Internet]. 2010 Feb 2 [cited 2023 Jul 2];25(1):1. Available from: [/pmc/articles/PMC2943670/](https://pubmed.ncbi.nlm.nih.gov/2943670/)
- 550 52. Caliendo M, Kopeinig S. Some Practical Guidance for the Implementation of Propensity Score  
551 Matching. 2005;

552 53. Amusa L, North D, Zewotir T. A tailored use of the mahalanobis distance matching for causal  
 553 effects estimation: A simulation study. Sci African. 2022 Jul 1;16:e01155.

554  
 555 Legends for figure:

556 Figure 1: Supervised Exercise Therapy Protocol: Outline of each session during weeks 1-6, with an  
 557 additional station added each week from week 7 until the patient had completed two full circuits. The  
 558 figure illustrates the progression of the supervised exercise therapy protocol used in the study.

559 Figure 2: Independent variable importance analysis using Multilayer perceptron to identify the most  
 560 significant predictors of chronic limb threatening ischemia to guide propensity score matching along  
 561 with multivariable and logistic regression analyses.

562 Figure 3: Number of cardiovascular events for patients who did and did not complete SET after  
 563 median follow up of 2164 days; IC: Intermittent Claudication; CLTI: Chronic limb threatening  
 564 ischemia; MALE: Major adverse limb events; MACE: Major adverse cardiovascular events ; SET:  
 565 Supervised exercise therapy

566 Figure 43: Survival curves obtained by the Kaplan-Meier method demonstrating time to chronic limb  
 567 threatening ischemia(a), time to first major adverse cardiovascular event(MACE)(b) and time to first  
 568 major adverse limb event(MALE)(c)

569 Table 1a: Baseline characteristics of both cohorts

Attribute	Patients who did not start SET n = 183	Patients who prematurely discontinued SET N = 19	Patients who completed SET n = 64	p value
Age (years ; Mean ± SD)	67.95 ± 10.4	70.1 ± 7.3	69.5 ± 7.8	.40
Male	119(65.7%)	12(63.2%)	44(68.8%)	.87
Diabetes Mellitus	54(29.5%)	4(21.1%)	29(45.3%)	.076



Hypertension	131(71.6%)	10(52.6%)	45(70.3%)	.17
Hyperlipidemia	82(44.8%)	6(31.5%)	30(46.8%)	.24
Ischaemic heart disease	101(55.8%)	11(57.9%)	28(43.8%)	.23
Cerebrovascular disease	25(13.7%)	4(21%)	8(12.5%)	.12
Atrial fibrillation	38(20.7%)	2(10.5%)	8(12.5%)	.18
Albumin (g/l; Mean $\pm$ SD)	36.9 $\pm$ 4.28	37.1 $\pm$ 3.3	35.2 $\pm$ 3.7	.16
Haemoglobin(g/l) Mean $\pm$ SD	132.73 $\pm$ 20.6	138.3 $\pm$ 19.0	136.5 $\pm$ 22.7	.16
Compliance with smoking cessation	45(24.9%)	5(26.3%)	22(34.0%)	.34
ABPI at presentation				
Right	0.79 $\pm$ 0.18	0.74 $\pm$ 0.19	0.80 $\pm$ 0.15	.41
Left	0.81 $\pm$ 0.20	0.82 $\pm$ 0.29	0.84 $\pm$ 0.15	.58
(Mean ,SD)				
Self-reported claudication distance(metres) (Mean ,SD)	77.5 $\pm$ 6.75	79.1 $\pm$ 7.5	79.4 $\pm$ 6.0	.11
No iliac disease	37(20.2%)	3(15.7%)	29(45.3%)	<u>.010</u>
Unilateral iliac disease	63(34.4%)	6(31.5%)	8(12.5%)	
Bilateral iliac disease	83(45.4%)	10(52.6%)	26(40.6%)	
No femoral disease	11(6.0%)	1(5.2%)	5(7.8%)	<u>.030</u>
Unilateral femoral disease	76(41.5%)	9(47.3%)	8(12.5%)	
Bilateral femoral disease	96(52.5%)	9(47.3%)	50(78.1%)	
No crural disease	87(47.5%)	10(52.6%)	38(59.3%)	.47
Unilateral crural disease	56(30.6%)	7(36.8%)	13(20.3%)	
	40(21.9%)	2(10.5%)	13(12.5%)	

Attribute	Non-Completion SET (n=49)	Completion SET (n=49)	P-value
Haemoglobin (g/l) Mean/SD	130.9 ± 19.3	138.6 ± 18.8	.08
Ischaemic heart disease	59.2%	63.3%	.56
Claudication distance (m) Mean/SD	131.1 ± 19.4	130.2 ± 18.9	.81
Ankle brachial pressure index Left Right	0.81 ± 0.16 0.71 ± 0.12	0.86 ± 0.15 0.64 ± 0.16	.11
Bilateral crural disease			

570

571 SD: Standard deviation; IQR: Interquartile range; SET: supervised exercise therapy ABPI: Ankle-  
572 brachial pressure index;

573

574

575

576 Table 1b: Impact of propensity score matching on significant confounders

577

578  
579  
580  
581  
582  
583  
584  
585  
586

<u>Attribute</u>	<u>Non Completion SET(n=49)</u>	<u>Completion SET (n=49)</u>	<u>P value</u>
<u>Haemoglobin (g/l) Mean/SD</u>	<u>130.9 ± 19.3</u>	<u>138.6 ± 18.8</u>	<u>.08</u>
<u>Ischaemic heart disease</u>	<u>59.2%</u>	<u>63.3%</u>	<u>.56</u>
<u>Claudication distance (m) Mean/SD</u>	<u>131.1 ± 19.4</u>	<u>130.2 ± 18.9</u>	<u>.81</u>
<u>Ankle-brachial pressure index</u> <u>Left</u> <u>Right</u>	<u>0.81 ± 0.16</u> <u>0.71 ± 0.12</u>	<u>0.86 ± 0.15</u> <u>0.64 ± 0.16</u>	<u>.11</u>

587  
588  
589

590 ~~Table 2: Seven year follow up data that suggest an association between completion of SET and~~  
591 ~~clinically important cardiovascular outcomes~~

592

593

Outcome	Non-Completion SET(n=49)	Completion-SET (n=49)	p-value
Progression to CLTI	31(63.3%)	5(10.2%)	$p < .001$
MALE	21(42.8%)	8(16.3%)	$p = .004$
MACE	26(53.1%)	15(30.6%)	$p = .025$

594

595 **IC: Intermittent Claudication; CLTI: Chronic limb threatening ischemia; MALE: Major adverse limb**  
596 **events; MACE: Major adverse cardiovascular events**

597

598

599

1 **Supervised Exercise Therapy for Intermittent Claudication: A Propensity Score Matched**  
 2 **Analysis of Retrospective Data on Long ~~term~~-Term Cardiovascular Outcomes**★

Formatted: Font: Bold

Formatted: Font: Bold

3 ~~Running-Short~~ title: Long-Term Outcomes Following Supervised Exercise Therapy ~~In~~-in Intermittent  
 4 Claudication

5 **Bharadhwaj Ravindhran**\*, **Arthur J.M. Lim**, **Thomas Kurian**, **Josephine Walshaw**,

Formatted: Font: Bold

6 **Louise H. Hitchman**,

Formatted: Font: Bold

7 **Ross Lathan**,

8 **George E. Smith**,

9 **Daniel Carradice**,

10 **Ian C. Chetter**,

11 **Sean Pymer**

12 <sup>+</sup>Academic Vascular Surgical Unit, ~~2<sup>nd</sup> Floor~~, Allam ~~diabetes~~-Diabetes ~~centre~~Centre, Hull Royal  
 13 Infirmary, ~~HU32JZHull, UK~~

14 \* Corresponding author: ~~-~~ **Bharadhwaj Ravindhran**

15 Academic Vascular Surgical Unit,

Formatted: Indent: Left: 0"

16 ~~2<sup>nd</sup> Floor~~, Allam diabetes centre,

Formatted: Not Superscript/ Subscript

17 Hull Royal Infirmary,

18 Hull HU3 2JZ, UK.

19 Bharadhwaj.Ravindhran@nhs.net (**Bharadhwaj Ravindhran**).

20 ★This paper was awarded the Norman Williams Prize for the best clinical research paper and is  
 21 shortlisted for the BJS Best Manuscript Prize at the Annual Meeting of the Surgical Research Society  
 22 in 2023 at Nottingham, UK.

Formatted: Line spacing: Multiple 1.08 li

23 ~~Word counts~~

24 ~~Abstract: 285~~

25 ~~What this paper adds: 37~~

26 ~~The text body: 2932~~

27 ~~Number of tables and figures: 2 tables and 4 figures~~

28

29 **WHAT THIS PAPER ADDS:**

31 This study contributes to the current body of literature by conducting an initial assessment of long-  
32 term outcomes in patients with intermittent claudication (~~IC~~) who underwent supervised exercise  
33 therapy (SET), with a focus on cardiovascular morbidity and mortality.- The results indicate that  
34 completing SET is associated with a decreased risk of major adverse limb events, major adverse  
35 cardiovascular events, and progression to chronic limb-threatening ischaemia based on this  
36 retrospective propensity score matched analysis of patients who completed, discontinued, or declined  
37 SET.

38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53

54

55

56 **Abstract:**

57 **Objective:** This study aimed to explore the long-term outcomes of patients with intermittent  
58 claudication (IC) who completed supervised exercise therapy (SET) ~~versus vs.~~ those who declined or  
59 prematurely discontinued SET, focusing on the incidence of chronic limb-threatening ischaemia  
60 (CLTI), revascularisation, major adverse limb events (MALE), and major adverse  
61 cardiovascular events (MACE).

Formatted: Font: Bold

Formatted: Font: Italic

62 ~~Methods: Design:~~ Retrospective registry analysis of consecutive patients with IC who were referred  
63 for SET between March 2015 and August 2016 and followed up for a minimum of five years.

Formatted: Font: Bold

64 ~~Methods:~~ Serial univariable analysis and logistic regression ~~was were~~ performed to identify the  
65 statistically significant clinical variables that were independent predictors of each outcome measure.  
66 The resulting statistically significant variables were used to guide 1:1 propensity score matching  
67 (PSM) using the nearest neighbour method with a calliper of 0.2. ~~A~~ Cox proportional hazards  
68 regression was used to estimate the hazard ratio (HR) and 95% confidence interval (CI) for the  
69 association between SET and the outcomes of interest.

70 **Results:** Two hundred and sixty-six patients were referred to SET between March 2015 and August

Formatted: Font: Bold

71 2016. Of these, 64 patients completed SET and 202 patients did not. After PSM, 49 patients were  
72 analysed in each cohort. The Cox proportional hazards analysis revealed a significant association

73 between completion of SET and revascularisation requirement (~~HR:HR~~ 0.46 95% CI 0.25 – 0.84; ~~p~~

Formatted: Font: Italic

74 ~~p =~~ .011), completion of SET and progression to CLTI (~~HR:HR~~ 0.091, 95% CI 0.04 – 0.24; ~~p~~

Formatted: Font: Italic

75 ~~p <~~ .001), completion of SET and MACE (~~HR:HR~~ 0.52; 95% CI 0.28 – 0.99; ~~p =~~ .05) and

76 completion of SET and MALE (~~HR:HR~~ 0.28, 95% CI 0.13 – 0.65; ~~p =~~ .003). The Harrell's C-

77 index for all of these models were greater than 0.75, indicating good predictive accuracy.

78 **Conclusion:** Completion of SET is associated with better outcomes in patients who completed SET  
79 compared to patients who declined or discontinued SET with respect to clinically important  
80 cardiovascular outcomes over ~~7~~seven years.

Formatted: Font: Bold

81 **Key-words:** Exercise therapy, Intermittent claudication, Ischaemia, ~~outcome~~Outcome assessment,  
82 ~~propensity~~Propensity score, ~~ischemia~~, ~~exercise therapy~~; ~~resistance~~Resistance training

Formatted: Font: Bold

83  
84  
85  
86  
87  
88  
89  
90  
91  
92  
93  
94  
95  
96  
97



## **INTRODUCTION**

Formatted: Font: Bold

Intermittent claudication (IC) is an ambulatory, ischaemic muscle pain relieved by rest, which reduces physical function, walking capacity, balance, and quality of life and increases the risk of mortality from cardiovascular causes.<sup>1-5</sup> Patients with IC ~~patients~~ are at risk of disease progression to chronic limb threatening ischaemia (CLTI) and major adverse limb events (MALE) such as major lower limb amputations (MLLA), acute limb ~~ischem~~ischaemia (ALI), or loss of untreated patency.<sup>6,7</sup> The goal of treatment is therefore to improve symptoms, physical function, and quality of life (QoL), while also reducing the risk of disease progression and limb loss, mortality and MACE.<sup>8</sup>

To achieve this, the National Institute for Health and Care Excellence (NICE) guideline 147<sup>9</sup> and the European ~~society~~ Society for ~~vascular~~ Vascular surgery Surgery (ESVS)<sup>10</sup> recommend supervised exercise therapy (SET) for ~~2~~ two hours per week over a ~~three~~ 3-month period, as the first-line treatment. Evidence shows that SET is significantly superior for improving walking performance, and therefore symptoms, when compared ~~to~~ with home-based exercise and walking advice.<sup>11</sup> Further evidence also shows that SET is ~~comparable~~ similar to endovascular revascularisation for improving walking distance and, importantly, QoL.<sup>11</sup> Given the positive effect that SET also has on cardiovascular risk factors,<sup>12,13</sup> it would be reasonable to assume that this leads to a potential benefit in morbidity, via a reduction in MACE and MALE, as well as a benefit in mortality. However, the evidence considering the long-term effects of SET on morbidity and mortality is lacking, with just one study considering the association between SET completion and mortality.<sup>14,15</sup>

Formatted: Indent: First line: 0.5"

Therefore, the aim of this study was to investigate whether completion of SET was associated with better cardiovascular outcomes compared ~~to~~ with a group of patients with IC ~~that~~ who did not complete SET using propensity score matching (PSM).

## **MATERIALS AND METHODS**

Formatted: Font: Bold

This study was conducted at a tertiary care referral vascular centre. The clinical, intra-operative and follow-up information were gathered, analysed, and compared between patients who completed SET and patients who either declined or discontinued SET.

124 ***Patient selection:***

Formatted: Font: Bold, Italic

125 ~~We retrospectively analysed the~~ The data of consecutive patients with IC who were referred for SET  
126 between March 2015 and August 2016 (18 months) ~~were retrospectively analysed~~. Patients who were  
127 referred but had CLTI, had undergone SET within the preceding 12 months, or had a recurrence of  
128 symptoms following previous revascularisation were excluded from this analysis. ~~Patients who were~~  
129 referred for SET but were deemed unsuitable due to contraindications or the presence of significant co  
130 morbidities or missing data were also excluded. The diagnosis of IC was made clinically, and was  
131 further supported by a resting ~~ankle-ankle~~-brachial pressure index (ABPI) or toe-~~brachial~~ pressure  
132 index, duplex ultrasound, or cross-sectional imaging if required. Patients who declined SET were  
133 either discharged back to their general practitioner ~~(GP)~~, received regular follow-up or underwent a  
134 revascularisation procedure, depending on individual need.

135 Patients referred to ~~supervised exercise therapy (SET)~~ were initially assessed by physicians to  
136 identify any obvious contraindications such as severe frailty, unstable gait, and existing pulmonary  
137 and cardiac disorders (e.g., aortic stenosis, dyspnoea at rest). These contraindications were determined  
138 based on clinical judgement. Furthermore, patients who did not have any obvious contraindications to  
139 SET were then screened by the exercise physiologist prior to starting SET. This screening process  
140 aimed to identify any additional contraindications or factors that may affect the safety or effectiveness  
141 of SET for individual patients. It is important to note that all patients in ~~our~~ the study underwent  
142 routine screening at two levels (physician assessment and exercise physiologist screening) to ensure  
143 that only those who were suitable for SET were included.

Formatted: Indent: First line: 0.5"

144 ***Supervised exercise therapy:***

Formatted: Font: Bold, Italic

145 Patients performed SET three times per week for 12 weeks comprising a total of 36 sessions. Missed  
146 sessions were made up at the end of the 12-week programme<sup>16</sup>. The programme was overseen by an  
147 exercise physiologist with support from undergraduate and postgraduate sports science students. SET  
148 sessions involved the completion of a circuit of six two-minute stations, separated by two-minute  
149 walking intervals. These were preceded by a warm-up and followed by a cool-down. The stations

150 included step-ups, standing knee bends, sitting knee extensions, biceps curls, cycling, and heel raises  
151 (Figure Fig. 1). As the patient's exercise tolerance improved, an additional station was added  
152 each week from the seventh week and by the end of week 12, they completed two full circuits.  
153 Session length therefore began at 30, progressing up to 60 minutes. Patients were deemed to have  
154 successfully completed SET after accumulating 36 sessions. This circuit-based training programme  
155 was designed based on previous recommendations that highlight the effectiveness of combining upper  
156 and lower limb ergometry, resistance exercise, and walking-based exercises to improve muscle  
157 strength and cardiorespiratory fitness. These interventions have been shown to elicit a more  
158 significant cardiorespiratory stimulus compared to walking alone.<sup>17-20</sup>

Formatted: Highlight

#### 159 ***Outcome measures***

Formatted: Font: Bold, Italic

160 The study investigated the incidence and time to CLTI, MALE, and MACE over a minimum of five  
161 years and up to seven years. CLTI was defined as ischaemic rest pain lasting for two or more weeks,  
162 non-healing wounds, or gangrene that was attributable to objectively proven arterial occlusive disease.  
163 MACE was defined as non-fatal stroke, non-fatal myocardial infarction (MI), or cardiovascular death  
164 (CVD).<sup>21</sup> MALE was defined as ALL, untreated loss of patency, or MLLA.<sup>22</sup>

#### 165 ***Statistical analyses***

Formatted: Font: Bold, Italic

166 Continuous data was assessed for a normality using the Shapiro-Wilk test and are presented as  
167 mean ± standard deviation or median and range or interquartile range as appropriate. Categorical data  
168 are expressed as numbers and/or percentages. Time to event data is presented using Kaplan-Meier  
169 survival curves. Comparative hypothesis testing was performed using Chi-squared tests, t-tests or  
170 Mann-Whitney U tests as appropriate, and log-rank tests. Statistical significance was set at  $p < .05$ .  
171 Serial univariable analysis and logistic regression was performed to identify the statistically  
172 significant clinical variables that were independent predictors of each outcome measure. This was  
173 confirmed by performing an independent variable importance analysis using the multilayer perceptron  
174 tool, which is a popular tool in machine learning and deep learning for pattern recognition.<sup>23</sup> The  
175 resulting statistically significant variables were used to guide 1:1 PSM using the nearest neighbour

Formatted: Font color: Text 1

176 method with a calliper of 0.2. -The differences between these two matched groups were compared by  
177 using the Mann–Whitney U test, and categorical data were analysed using the Pearson’s ~~Chi-~~  
178 square test, ~~the~~ Fisher’s exact test, or continuity correction where appropriate. Survival curves were  
179 obtained by the Kaplan–Meier method and a Cox proportional hazards regression was used to  
180 estimate the hazard ratio (HR) and 95% ~~confidence interval (CI)~~ for the association between SET and  
181 the outcomes of interest. All statistical analyses were performed using Statistical Package for the  
182 Social Sciences (IBM Corp. 2020; Windows Version 27.0) and Medcalc (MedCalc Statistical  
183 Software version 19.2.6; MedCalc Software bv, Ostend, Belgium);  
184

## 185 **RESULTS:**

186 Two-hundred and eighty-two patients presented to the vascular outpatient clinic with IC between  
187 March 2015 and August 2016 and were referred for SET. Sixteen patients were deemed unsuitable for  
188 SET due to advanced comorbidities, mobility problems, and dementia. Two-hundred and sixty-six  
189 patients were deemed suitable and were offered SET, of which 83 (31%) attended and 183 (69%)  
190 declined. Of those that attended, 64 (77%) patients successfully completed SET, ~~whilst while~~ 19  
191 (23%) prematurely discontinued. Baseline characteristics of those who completed and those who  
192 declined or prematurely discontinued SET are presented in ~~table-Table 1a~~. The primary reasons for  
193 the low adoption of SET were related to location or travel (44.3%; ~~n = 81~~), individuals declining due  
194 to lack of interest/belief in the SET (39.3%; ~~n = n=72~~), work/personal commitments resulting in a lack  
195 of time for SET (12.6%; ~~n = n=23~~), inability to participate due to musculoskeletal issues (2.2%;  
196 ~~n = n=4~~), and patients already enrolled in a community exercise programme (1.6%; ~~n = n=3~~).  
197 Considering that nearly all patients who discontinued SET did so without attending at least 50% of the  
198 sessions, ~~we deemed~~ it ~~was deemed~~ appropriate to combine both groups, i.e., those who discontinued  
199 and those who declined SET, for the purpose of analysis.

200 Serial univariable and logistic regression analyses revealed that CLTI had the greatest number  
201 of statistically significant predictor variables ~~compared to~~ ~~than~~ the other outcomes, and, therefore,

Formatted: Font: Bold

Formatted: Font color: Text 1, Highlight

Formatted: Font color: Text 1

Formatted: Font: Italic

Formatted: Indent: First line: 0.5"

202 these significant predictors were used to guide PSM, which was performed to account for the  
203 independent association between these variables and outcome measures. Haemoglobin, self-reported  
204 claudication distance, ABPI, presence of ischaemic heart disease (IHD), neutrophil-to-lymphocyte  
205 ratio, compliance with smoking cessation and non-completion of supervised exercise therapy (SET)  
206 were found to be statistically significant predictors of CLTI based on serial univariable analyses.  
207 Logistic regression analysis performed using these variables indicated that haemoglobin, self-  
208 reported claudication distance, ABPI and the presence of IHD were significant predictors of CLTI.  
209 This was confirmed via an independent variable importance analysis (Figure Fig. 2). The multilayer  
210 perceptron (MLP) algorithm is employed to evaluate the relative contribution of independent  
211 variables in predicting CLTI. By assigning weights to each input variable based on their importance,  
212 the MLP algorithm provides valuable insights into the significant of each variable. This importance  
213 analysis helps identify the variables with the greatest impact on CLTI occurrence.

Formatted: Highlight

214 After PSM based on these variables, 49 patients were analysed in each cohort. There was no  
215 difference between groups with respect to haemoglobin (g/dL) ( $130.9 \pm 19.3$  vs.  $138.6 \pm 18.8$ ;  $p = p =$   
216  $.080$ ), IHD ( $59.2\%$  vs.  $63.3\%$   $p = p = .56$ ), self-reported claudication distance (metres) ( $131 \pm 19.4$   
217 vs.  $130 \pm 18.9$ ;  $p = p = .81$ ), and ABPI ( $0.7 \pm 0.1$  vs.  $0.7 \pm 0.2$ ;  $p = p = .29$ ) (Table 4b2). The Cox  
218 proportional hazards analysis revealed a significant association between completion of SET and  
219 progression to CLTI (HR:HR 0.091, 95% CI 0.04 – 0.24;  $p < p < .001$ ), completion of SET and  
220 MACE (HR:HR 0.52; 95% CI 0.28 – 0.99;  $p = p = .050$ ) and completion of SET and MALE (HR:HR  
221 0.28, 95% CI 0.13 – 0.65;  $p = p = .003$ ). The Kaplan–Meier curves demonstrated a consistent and  
222 statistically significant difference in outcomes amongst those who completed SET, compared to with  
223 those who did not complete SET (Figure Fig. 3). The Harrell’s C-index for all of these models were  
224 greater than 0.75 indicating good predictive accuracy.

Formatted: Font: Italic

Formatted: Highlight

Formatted: Highlight

225 To assess the adequacy of sample size, a post-hoc power analysis was conducted, revealing  
226 that a total of 48 events and a sample size of 36 patients in the SET completion cohort and 186  
227 patients in the non-completion cohort were required to detect a significant association between SET  
228 and outcomes. This estimation followed the methodology outlined by Schoenfeld *et al.*<sup>24</sup>, assuming a

Formatted: Font: Italic

Formatted: Font: Italic

229 significance level of .05, 80% power, a 16% incidence of SET completion among referred patients,<sup>25</sup>  
230 a relative hazard of 3, a median survival of 12 years, and a planned follow-up of 7-seven years (Fig.  
231 4).<sup>15,26,27</sup>

Commented [ACG1]: AQ: please check the citation inserted for Figure 4

Formatted: Highlight

## 232 **DISCUSSION:**

Formatted: Font: Bold

233 This study demonstrates that completion of SET is associated with a reduced risk of experiencing  
234 MALE, MACE<sub>2</sub> and progression to CLTI. ~~To the best of our knowledge,~~†This study is thought to  
235 represents one of the first evaluations of long-term outcomes following SET with a focus on  
236 cardiovascular morbidity and mortality in individuals with PADperipheral arterial disease. ~~Whilst~~  
237 While the data suggest a positive effect of SET, it is important to acknowledge that the patients in this  
238 cohort may differ in ways that have not been accounted for, and their outcomes may have been  
239 influenced by factors beyond SET. It is important to note that even with rigorous propensity score  
240 matchingPSM, confounding by indication cannot be completely adjusted for, as there may be  
241 unmeasured covariates that affect both the variable and outcome of interest. ~~We also acknowledge~~  
242 ~~that while~~†Although this analysis provides important insights and suggests an association, the  
243 efficacy of SET for improving cardiovascular outcomes cannot be established. Nevertheless, these  
244 findings provide a strong rationale for increasing the delivery of SET and conducting further research  
245 to better understand its potential long-term benefits. Moving forward, efforts should be directed  
246 towards reducing SET barriers (such as the time commitment) to maximise patient engagement. By  
247 doing so, ~~we-it~~ may be able to optimise the effectiveness of SET and improve outcomes for a broader  
248 range of patients.

249

250 Currently, high quality evidence shows that SET provides an important benefit with respect to  
251 maximum walking distance (MWD), pain-free walking distance—and QoL compared to home-based  
252 exercise therapy and walking advice.<sup>14,28</sup> Better SET compliance, measured by attendance at exercise  
253 sessions, is significantly associated with greater improvements in MWD and adherence to SET may  
254 imply better adherence of several factors in life, such as to smoking cessation, healthy diet and

Formatted: Indent: First line: 0.5"

255 medication, resulting in better outcomes.<sup>29</sup> However, even patients at the lowest tercile of exercise  
256 attendance demonstrate a significant improvement in MWD.<sup>30</sup> Despite this evidence, and the  
257 guidance provided by NICE and the ESVS,<sup>9,10</sup> SET provision is not consistent in the UK, with less  
258 than 50% of vascular centres offering it and less than 25% of these adhering to the recommended  
259 exercise dose.<sup>31</sup> The low availability of SET in the UK can be attributed to various constraints faced  
260 in a centralized hub and spoke model. These constraints include running costs and a lack of  
261 resources and qualified personnel.<sup>32-34</sup> When SET is offered, patients may not want to participate due  
262 to a lack of availability near their home or the required time commitment, which contributes to the  
263 poor uptake rates seen.<sup>25,35</sup> Further research is needed to explore ways to address or minimise the  
264 constraints felt by patients and providers to improve the accessibility and acceptability of SET.

265 During the last two decades there has been a substantial increase in the number of studies  
266 comparing primary interventional therapy to SET. The results of these studies suggest that SET is  
267 comparable to primary percutaneous transluminal angioplasty (PTA) for improving in walking  
268 distance and QoL.<sup>36,37,38</sup> This suggests that the current first-line treatment strategy of SET is  
269 advocated. However, poor uptake and adherence to SET, poor patient fitness, and patient preference  
270 are cited as reasons for using a “PTA first” strategy in patients with IC.<sup>39-41</sup> Based on the results of  
271 the current study, even if a PTA first strategy is pursued due to these constraints, the integration of an  
272 exercise intervention may yield additional improvements in long-term cardiovascular outcomes,  
273 which may not occur with PTA alone.

274 Recent evidence has also demonstrated that SET produces a notable improvement in  
275 cardiovascular risk factors, such as cholesterol levels and resting and exercising blood pressure.<sup>12,13</sup>  
276 Interestingly, the greater the improvement in cardiovascular health, the greater the improvement in  
277 walking performance.<sup>12</sup> Despite this evidence for a reduction in cardiovascular risk factors, there is  
278 limited data to support the reduction of long-term cardiovascular risk following SET.<sup>42,43</sup> The  
279 reduction in cardiovascular morbidity and mortality following SET demonstrated in this study could  
280 be attributable to these beneficial effects on cardiovascular risk factors.

281 Determining the percentage of outcomes that are directly associated with the completion of  
282 SET is difficult, given the presence of unmeasured confounding variables that may impact the  
283 findings, such as patient motivation. Even amongst highly motivated patients, uptake and adherence  
284 to SET can be difficult, underscoring the importance of offering alternative options to patients who  
285 wish to engage in SET but face barriers to compliance and uptake.<sup>34</sup> High-intensity interval training  
286 (HIIT) or remotely delivered supervised exercise interventions are alternatives that could offer  
287 promising benefits, specially tailored to the unique needs and conditions of patients who were  
288 previously unable to enrol in SET due to time or travel constraints.<sup>44,45</sup> Currently, a time efficient  
289 HIIT programme is being assessed as a potential alternative for SET, to reduce the time barrier faced  
290 by patients.<sup>46</sup> Early evidence has suggested that this HIIT programme appears to be feasible and well  
291 tolerated in patients with IC, which is to be confirmed via a proof-of-concept study.<sup>46</sup>

292  
293 Other alternative approaches to delivering SET have been explored, including remote  
294 monitoring, videos, support groups, mobile-applications and trackers and virtual reality.<sup>44,47,48</sup> A  
295 smartphone-enabled home-based exercise programme is feasible and effective in patients with  
296 symptomatic peripheral arterial disease (PAD), as is a community-based walking programme with  
297 training, monitoring and coaching components.<sup>47,49</sup> These alternative approaches to delivering SET  
298 have the potential to increase patient access and improve adherence. However, they are currently  
299 limited to small proof-of-concept studies. Further research is needed to explore their effectiveness in  
300 fully powered randomised controlled trials.

### 301 *Limitations*

302 Although this study provides useful insights, its retrospective nature encompasses several inherent  
303 limitations, including unmeasurable confounding factors, potential biases, and the lack of blinding or  
304 randomisation that can affect the objectivity of ~~our~~ the analysis. The limitations associated with the  
305 retrospective nature of this study were addressed by enrolling consecutive patients over an  
306 ~~eighteen~~ 18-month period and conducting a meticulous PSM method with a 0.2 calliper. While there

Formatted: Font: Italic



307 are many alternatives to 1:1 PSM such as mahalanobis distance matching, kernel matching, and  
308 covariate matching. ~~propensity score matching~~ PSM is considered the best approach due to its ability  
309 to balance covariates, flexibility in handling different types of covariates, interpretability, and the  
310 opportunity for sensitivity analysis.<sup>50-53</sup> Despite using rigorous ~~propensity score matching~~ PSM, it is  
311 impossible to fully account for confounding by indication. This is because there might be unmeasured  
312 factors that impact both the variable being studied and the outcome of interest. In ~~our the current~~  
313 study, ~~we included~~ statistically significant variables were included in the PSM to ensure that ~~we were~~  
314 ~~controlling for~~ factors that had a proven association with the outcome were controlled for. This  
315 approach was taken to ~~minimize~~ minimise the risk of overfitting and to ensure the robustness of ~~our~~  
316 the findings. However, ~~we acknowledge there is~~ potential for ~~Type-type~~ II errors and the possibility of  
317 missing relevant variables. The lack of differences observed in Table 1b after implementing PSM  
318 could potentially be attributed to a type II error. ~~The~~ use of inverse probability weighting (~~IPW~~) is a  
319 valid approach that can enhance the robustness of findings by retaining a larger sample size. However,  
320 ~~we chose~~ PSM was chosen for ~~our the~~ study due to specific reasons. PSM allows ~~us one~~ to best  
321 mimic a randomized ~~ised~~ controlled trial by matching patients who completed SET with control  
322 patients based on observed characteristics, reducing bias from confounding variables. While inverse  
323 probability weighting ~~IPW~~ could retain a larger sample size, it can introduce challenges such as  
324 sensitivity to model specification and unstable estimates with extreme weights. ~~We believe~~ PSM is  
325 believed to be more suitable for ~~our this~~ study, considering these factors, although ~~we~~  
326 ~~acknowledgethere are~~ limitations, such as potential bias from unobserved confounding and a reduced  
327 sample size. Additionally, it is important to acknowledge that although this analysis offers valuable  
328 insights and indicates a potential connection, ~~we cannot definitively establish~~ the effectiveness of SET  
329 in improving cardiovascular outcomes cannot be definitively established.

330 This study indicates an association between patients completing SET and better long-term  
331 clinical outcomes, such as slower disease progression, and a lower likelihood of experiencing MALE  
332 or MACE. However, due to the potential for unmeasured confounding, ~~we cannot definitively~~  
333 ~~conclude~~ that SET leads to an improvement in cardiovascular health or mitigates adverse long-term

Formatted: Font color: Text 1

334 outcomes in IC ~~cannot be definitively concluded~~. Rather, ~~our~~ findings suggest a potential  
335 association that warrants further investigation. Overall, these outcomes underscore the potential  
336 significance of SET in relation to cardiovascular health in ~~patients with IC~~ ~~patients~~.

### 337 **CONFLICT OF INTEREST**

Formatted: Font: Bold

338 None.

### 339 **FUNDING**

340 None.

### 341 **ACKNOWLEDGEMENTS**

342 ~~±~~The authors gratefully acknowledge the invaluable contribution of Dr. Dror Rosentraub for his  
343 expertise and guidance in the application of statistical methods. The authors would also like to express  
344 their sincere gratitude to the academic vascular surgical unit for their invaluable support and  
345 collaboration throughout the course of this study. Their expertise and guidance have greatly  
346 contributed to the successful completion of this research.

347

### 348 **REFERENCES:**

Formatted: Font: Bold

349 1. Criqui MH, Aboyans V. Epidemiology of peripheral artery disease. *Circ Res* ~~[Internet]~~. 2015

Formatted: Font: Italic

350 ~~Apr 24 [cited 2023 May 1];~~ **116**(9):1509–26. Available from:

Formatted: Font: Bold

351 ~~<https://pubmed.ncbi.nlm.nih.gov/25908725/>~~

352 2. Criqui MH, Langer RD, Fronck A, Feigelson HS, Klauber MR, McCann TJ, et al. Mortality

353 over a period of 10 years in patients with peripheral arterial disease. *N Engl J Med* ~~[Internet]~~.

Formatted: Font: Italic

354 1992; ~~Feb 6 [cited 2023 May 1];~~ **326**(6):381–6. Available from:

Formatted: Font: Bold

355 ~~<https://pubmed.ncbi.nlm.nih.gov/1729621/>~~

356 3. Pell JP. Impact of intermittent claudication on quality of life. *Eur J Vasc Endovasc Surg*. 1995  
357 ~~May 1~~; ~~9~~(4):469–72.

Formatted: Font: Italic

Formatted: Font: Bold

358 4. Gohil RA, Mockford KA, Mazari F, Khan J, Vanicek N, Chetter IC, et al. Balance impairment,  
359 physical ability, and its link with disease severity in patients with intermittent claudication.

360 *Ann Vasc Surg* [~~Internet~~]. 2013 ~~Jan 1~~ [~~cited 2023 May 9~~]; ~~27~~(1):68–74. Available from:  
361 ~~http://www.annalsofvascularsurgery.com/article/S0890509612003214/fulltext~~

Formatted: Font: Italic

Formatted: Font: Bold

362 5. Meru A-V, Mitra S, Thyagarajan B, Chugh A. Intermittent claudication: an overview.

363 *Atherosclerosis* [~~Internet~~]. 2006 ~~Aug~~ [~~cited 2023 May 11~~]; ~~187~~(2):221–37. Available from:  
364 ~~https://pubmed.ncbi.nlm.nih.gov/16386260/~~

Formatted: Font: Italic

Formatted: Font: Bold

365 6. Eid MA, Mehta K, Barnes JA, Wanken Z, Columbo JA, Stone DH, et al. The global burden of  
366 peripheral artery disease. *J Vasc Surg* [~~Internet~~]. 2023 ~~Apr~~ [~~cited 2023 Apr 3~~]; ~~77~~(4):1119–26.

367 Available from: ~~https://pubmed.ncbi.nlm.nih.gov/36565779/~~

Formatted: Font: Italic

Formatted: Font: Bold

368 7. McDermott KM, Bose S, Keegan A, Hicks CW. Disparities in limb preservation and  
369 associated socioeconomic burden among patients with diabetes and/or peripheral artery disease  
370 in the United States. *Semin Vasc Surg* [~~Internet~~]. 2023 ~~Mar 1~~ [~~cited 2023 Apr 3~~]; ~~36~~(1):39–48.

371 Available from: ~~https://pubmed.ncbi.nlm.nih.gov/36958896/~~

Formatted: Font: Italic

372 8. Bevan GH, White Solaru KT. Evidence-based medical management of peripheral artery  
373 disease. *Arterioscler Thromb Vasc Biol*. 2020 ~~Mar 1~~; ~~40~~(3):541–53.

Formatted: Font: Italic

Formatted: Font: Bold

374 9. NICE. Overview. Peripheral arterial disease: diagnosis and management. Guidance. NICE  
375 [~~Internet~~]. [~~cited 2022 May 7~~]. Available from: ~~https://www.nice.org.uk/guidance/cg147~~  
376 [~~Accessed 22 November 2023~~].

377 10. Aboyans V, Ricco JB, Bartelink MLEL, Björck M, Brodmann M, Cohnert T, et al. Editor's  
378 Choice – 2017 ESC guidelines on the diagnosis and treatment of peripheral arterial diseases, in  
379 collaboration with the European Society for Vascular Surgery (ESVS). Document covering

Commented [ACG2]: AQ: Ref. 10 has been updated to the EJVES version of the joint guideline

Formatted: Font color: Text 1

Formatted: Font color: Text 1

380 atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower  
381 extremity arteries. Endorsed by: the European Stroke Organization (ESO) The Task Force for  
382 the Diagnosis and Treatment of Peripheral Arterial Diseases of the European Society of  
383 Cardiology (ESC) and of the European Society for Vascu. *Eur Heart J*. *Eur J Vasc Endovasc*  
384 *Surg* [Internet]. 2018 Mar 1 [cited 2023 Apr 8]; **39**(9):763–816305–68. Available from:  
385 <https://academic.oup.com/eurheartj/article/39/9/763/4095038>

Formatted: Font: Italic, Font color: Text 1

Formatted: Font color: Text 1

Formatted: Font: Bold, Font color: Text 1

Formatted: Font color: Text 1

386 11. Murphy TP, Cutlip DE, Regensteiner JG, Mohler ER, Cohen DJ, Reynolds MR, et al.  
387 Supervised exercise, stent revascularization, or medical therapy for claudication due to  
388 aortoiliac peripheral artery disease: ~~The the~~ CLEVER study. *J Am Coll Cardiol*. 2015 Mar  
389 ~~17~~; **65**(10):999–1009.

Formatted: Font: Italic

Formatted: Font: Bold

390 12. Slysz JT, Tian L, Zhao L, Zhang D, McDermott MM. Effects of supervised exercise therapy  
391 on blood pressure and heart rate during exercise, and associations with improved walking  
392 performance in peripheral artery disease: ~~Results results~~ of a randomized clinical trial. *J Vasc*  
393 *Surg*. 2021 Nov 1; **74**(5):1589–1600. ~~e4~~.

Formatted: Font: Italic

Formatted: Font: Bold

394 13. Jansen SCP, Hoorweg BBN, Hoeks SE, van den Houten MML, Scheltinga MRM, Teijink  
395 JAW, et al. A systematic review and meta-analysis of the effects of supervised exercise  
396 therapy on modifiable cardiovascular risk factors in intermittent claudication. *J Vasc Surg*  
397 [Internet]. 2019 Apr 1 [cited 2023 May 16]; **69**(4):1293–1308. ~~e2~~. Available from:  
398 <https://pubmed.ncbi.nlm.nih.gov/30777692/>

Formatted: Font: Italic

Formatted: Font: Bold

399 14. Hageman D, Fokkenrood HJP, Gommans LNM, van den Houten MML, Teijink JAW.  
400 Supervised exercise therapy versus home-based exercise therapy versus walking advice for  
401 intermittent claudication. *Cochrane database-Database Syst Rev* [Internet]. 2018 Apr 6 [cited  
402 2023 Apr 3]; **4**:CD005263(4). Available from: <https://pubmed.ncbi.nlm.nih.gov/29627967/>

Formatted: Font: Italic

Formatted: Font: Bold

Formatted: Font: (Default) Times New Roman, Font color: Auto, Pattern: Clear

403 15. Sakamoto S, Yokoyama N, Tamori Y, Akutsu K, Hashimoto H, Takeshita S. Patients with  
404 peripheral artery disease who complete 12-week supervised exercise training program show

405 reduced cardiovascular mortality and morbidity. *Circ J* [Internet]. 2009 [cited 2023 Apr  
406 3];73(1):167–73. Available from: <https://pubmed.ncbi.nlm.nih.gov/19039192/>

Formatted: Font: Italic

Formatted: Font: Bold

407 16. Harwood AE, Totty JP, Pymmer S, Huang C, Hitchman L, Carradice D, et al. Cardiovascular  
408 and musculoskeletal response to supervised exercise in patients with intermittent claudication.

409 *J Vasc Surg* [Internet]. 2019 Jun 1 [cited 2023 May 16];69(6):1899–1908.e1. Available from:  
410 <https://pubmed.ncbi.nlm.nih.gov/30583899/>

Formatted: Font: Italic

Formatted: Font: Bold

411 17. Jansen SCP, Abaraogu UO, Lauret GJ, Fakhry F, Fokkenrood HJP, Tejjink JAW. Modes of  
412 exercise training for intermittent claudication. *Cochrane Database Syst Rev* [Internet]. 2020

413 Aug 23 [cited 2023 Aug 13];2020(8):CD009638). Available from:

414 <https://www.cochranelibrary.com/edsr/doi/10.1002/14651858.CD009638.pub3/full>

Formatted: Font: Italic

Formatted: Font: Bold

Formatted: Font: (Default) Times New Roman, Font color: Auto, Pattern: Clear

415 18. Harwood AE, Pymmer S, Ingle L, Doherty P, Chetter IC, Parmenter B, et al. Exercise training  
416 for intermittent claudication: a narrative review and summary of guidelines for practitioners.

417 *BMJ open Sport Exerc Med* [Internet]. 2020 Nov 6 [cited 2023 Aug 13];6(1). Available

418 from: e000897. <https://pubmed.ncbi.nlm.nih.gov/33262892/>

Formatted: Font: Italic

Formatted: Font: Bold

Formatted: Font: (Default) Times New Roman, Font color: Auto, Pattern: Clear

419 19. Mockford KA, Gohil RA, Mazari F, Khan JA, Vanicek N, Coughlin PA, et al. Effect of  
420 supervised exercise on physical function and balance in patients with intermittent claudication.

421 *Br J Surg*. 2014 Mar;101(4):356–62.

Formatted: Font: Italic

Formatted: Font: Bold

422 20. [British Association of Sport and Exercise Sciences. The BASES Expert Statement on](#)  
423 [Exercise Training for People with Intermittent Claudication due to Peripheral Arterial Disease. The](#)  
424 [Sport and Exercise Scientist n Issue 57 n Autumn 2018 n www.bases.org.uk @basesuk @BASESUK](#)  
425 [bases\\_uk BASESUK. \[cited 2023 Aug 13\]. Available from:](#)

Formatted: Normal (Web), Indent: Left: 0", First line: 0", Space Before: 0 pt, After: 0 pt, Widow/Orphan control, Adjust space between Latin and Asian text, Adjust space between Asian text and numbers

Formatted: Font: (Default) Times New Roman, 11 pt

Formatted: Font: (Default) Times New Roman, 11 pt, Font color: Auto

Formatted: Font: 11 pt

Formatted: Font: 11 pt

Formatted: Font: 11 pt, Font color: Auto

426 [https://www.bases.org.uk/imgs/autumn\\_2018\\_7601\\_bas\\_expert\\_statement\\_v2\\_569.pdf](https://www.bases.org.uk/imgs/autumn_2018_7601_bas_expert_statement_v2_569.pdf),

427 [Accessed 23 November 2023]. [www.nice.org.uk/guidance/eg147](http://www.nice.org.uk/guidance/eg147),

Commented [ACG3]: AQ: Please ref. 20: I've updated it according to the new link you sent

428 21. Bianco M, Mottola FF, Cerrato E, Giordana F, Cinconze S, Baralis G, et al. Acute coronary

Formatted: Font: 11 pt, Font color: Auto

Formatted: Font: 11 pt

429 syndrome in very elderly patients-a real-world experience. *Heart Vessels* ~~[Internet].~~  
430 2023;**38**:1019–27. Mar 28 [cited 2023 Apr 3]; Available from:  
431 <https://pubmed.ncbi.nlm.nih.gov/36976424/>

432 22. Fashandi AZ, Mehaffey JH, Hawkins RB, Kron IL, Upchurch GR, Robinson WP. Major  
433 adverse limb events and major adverse cardiac events after contemporary lower extremity  
434 bypass and infrainguinal endovascular intervention in patients with claudication. *J Vasc Surg*  
435 ~~[Internet].~~ 2018 Dec 1 [cited 2023 Apr 3];**68**(6):1817. Available from:  
436 [/pmc/articles/PMC6482457/](https://pubmed.ncbi.nlm.nih.gov/306482457/)

437 23. Idrissi J, Amine M. Multilayer perceptron: architecture optimization and training.

438 24. ~~schoenfeld-Schoenfeld~~ DA. ~~sample~~Sample-size formula for the proportional-hazards  
439 regression model. *Biometrics*. 1983 Jun;**39**(2):499.

440 25. Harwood AE, Smith GE, Cayton T, Broadbent E, Chetter IC. A systematic review of the  
441 uptake and adherence rates to supervised exercise programs in patients with intermittent  
442 claudication. *Ann Vasc Surg*. 2016 Jul 1;**34**:280–9.

443 26. Voci D, Fedeli U, Valerio L, Schievano E, Righini M, Kucher N, et al. Mortality rate related to  
444 peripheral arterial disease: ~~A~~a retrospective analysis of epidemiological data (years 2008–  
445 2019). *Nutr Metab Cardiovasc Dis*. 2023 Mar 1;**33**(3):516–22.

446 27. Klaphake S, Fakhry F, Rouwet E V., Van Der Laan L, Wever JJ, Teijink JA, et al. Long-term  
447 follow-up of a randomized clinical trial comparing endovascular revascularization plus  
448 supervised exercise with supervised exercise only for intermittent claudication. *Ann Surg*  
449 ~~[Internet].~~ 2022 Dec 1 [cited 2023 May 1];**276**(6):E1035–43. Available from:  
450 [https://journals.lww.com/annalsurgery/Fulltext/2022/12000/Long\\_term\\_Follow\\_up\\_of\\_a\\_R](https://journals.lww.com/annalsurgery/Fulltext/2022/12000/Long_term_Follow_up_of_a_Randomized_Clinical_Trial.71.aspx)  
451 [andomized\\_Clinical\\_Trial.71.aspx](https://journals.lww.com/annalsurgery/Fulltext/2022/12000/Long_term_Follow_up_of_a_Randomized_Clinical_Trial.71.aspx)

452 28. van den Houten MML, Hageman D, Gommans LNM, Kleijnen J, Scheltinga MRM, Teijink

Formatted: Font: Italic

Formatted: Font: Bold

Formatted: Font: Italic

Formatted: Font: Bold

Formatted: Font: Italic

Formatted: Font: Bold

Formatted: Font: Italic

Formatted: Font: Bold

Formatted: Font: Italic

Formatted: Font: Bold

Formatted: Font: Italic

Formatted: Font: Bold

- 453 JAW. The effect of supervised exercise, home based exercise and endovascular  
454 revascularisation on physical activity in patients with intermittent claudication: a network  
455 meta-analysis. *Eur J Vasc Endovasc Surg*. 2019-Sep 1;58(3):383–92.
- 456 29. Hammond MM, Tian L, Zhao L, Zhang D, McDermott MM. Attendance at supervised  
457 exercise sessions and walking outcomes in peripheral artery disease: results from 2  
458 randomized clinical trials. *J Am Hear Assoc Cardiovasc Cerebrovasc Dis [Internet]*. 2022-Dec  
459 12 [cited 2023-Apr 2];11(24):26136. Available from: [pmc/articles/PMC9798808/](https://pubmed.ncbi.nlm.nih.gov/39798808/)
- 460 30. McDermott MMG, Criqui MH, Liu K, Guralnik JM, Greenland P, Martin GJ, et al. Lower  
461 ankle/brachial index, as calculated by averaging the dorsalis pedis and posterior tibial arterial  
462 pressures, and association with leg functioning in peripheral arterial disease. *J Vasc Surg*.  
463 2000;32(6):1164–71.
- 464 31. Harwood AE, Smith GE, Cayton T, Broadbent E, Chetter IC. A Systematic review of the  
465 uptake and adherence rates to supervised exercise programs in patients with intermittent  
466 claudication. *Ann Vasc Surg [Internet]*. 2016-Jul 1 [cited 2023-Jan 2];34:280–9. Available  
467 from: <https://pubmed.ncbi.nlm.nih.gov/27126713/>
- 468 32. Harwood AE, Smith GD, Broadbent E, Cayton TE, Carradice D, Chetter I. Access to  
469 supervised exercise services for peripheral vascular disease patients. *Bull R Coll Surg Engl*  
470 [Internet]. 2017-Jun [cited 2023-Apr 8];99(6):207–11. Available from:  
471 <https://doi.org/10.1308/resbull.2017.207>
- 472 33. Waddell A, Seed S, Broom DR, McGregor G, Birkett ST, Harwood AE. Safety of home-based  
473 exercise for people with intermittent claudication: a systematic review. *J Vasc Surg [Internet]*.  
474 2022-Apr 1 [cited 2023-Apr 8];75(4):1490. Available from:  
475 <http://www.jvasesurg.org/article/S0741521422000362/fulltext>
- 476 34. Harwood AE, Pymer S, Ibeggazene S, Ingle L, Caldow E, Birkett ST. Provision of exercise  
477 services in patients with peripheral artery disease in the United Kingdom. *Vascular*. 2022-Oct

Formatted: Font: Italic

Formatted: Font: Bold

Formatted: Font: Italic

Formatted: Font: Bold

Formatted: Font: Italic

Formatted: Font: Bold

Formatted: Font: Italic

Formatted: Font: Bold

Formatted: Font: Italic

Formatted: Font: Bold

Formatted: Font: Italic

Formatted: Font: Bold

Formatted: Font: Italic

478 1;30(5):874–81.

Formatted: Font: Bold

479 35. Harwood AE, Hitchman LH, Ingle L, Doherty P, Chetter IC. Preferred exercise modalities in  
480 patients with intermittent claudication. *J Vasc Nurs* [Internet]. 2018 Jun 1 [cited 2023 May

Formatted: Font: Italic

481 2];36(2):81–4. Available from: <https://pubmed.ncbi.nlm.nih.gov/29747787/>

Formatted: Font: Bold

482 36. Mazari FAK, Gulati S, Rahman MNA, Lee HLD, Mehta TA, McCollum PT, et al. Early  
483 outcomes from a randomized, controlled trial of supervised exercise, angioplasty, and  
484 combined therapy in intermittent claudication. *Ann Vasc Surg* [Internet]. 2010 Jan [cited 2023

Formatted: Font: Italic

485 Apr 9];24(1):69–79. Available from: <https://pubmed.ncbi.nlm.nih.gov/19762206/>

Formatted: Font: Bold

486 37. Mazari FAK, Khan JA, Samuel N, Smith G, Carradice D, McCollum PC, et al. Long-term  
487 outcomes of a randomized clinical trial of supervised exercise, percutaneous transluminal  
488 angioplasty or combined treatment for patients with intermittent claudication due to

489 femoropopliteal disease. *Br J Surg* [Internet]. 2017 Jan 1 [cited 2023 Apr 9];104(1):76–83.

Formatted: Font: Italic

490 Available from: <https://pubmed.ncbi.nlm.nih.gov/27763685/>

Formatted: Font: Bold

491 38. Thanigaimani S, Phie J, Sharma C, Wong S, Ibrahim M, Huynh P, et al. Network meta-  
492 analysis comparing the outcomes of treatments for intermittent claudication tested in

493 randomized controlled trials. *J Am Heart Assoc* [Internet]. 2021 May 4 [cited 2023 Apr

Formatted: Font: Italic

494 3];10(9):19672. Available from:

Formatted: Font: Bold

495 <https://www.ahajournals.org/doi/abs/10.1161/JAHA.120.019672>

496 39. Harwood AE, Broadbent E, Totty JP, Smith GE, Chetter IC. “Intermittent claudication a real  
497 pain in the calf”—Patient experience of diagnosis and treatment with a supervised exercise  
498 program. *J Vasc Nurs*. 2017 Sep 1;35(3):131–5.

Formatted: Font: Italic

Formatted: Font: Bold

499 40. Vemulapalli S, Dolor RJ, Hasselblad V, Schmit K, Banks A, Heidenfelder B, et al. Supervised  
500 vs unsupervised exercise for intermittent claudication: A systematic review and meta-  
501 analysis. *Am Heart J*. 2015 Jun 1;169(6):924–937.e3.

Formatted: Font: Italic

Formatted: Font: Bold



- 502 41. Saratzis A, Paraskevopoulos I, Patel S, Donati T, Biasi L, Diamantopoulos A, et al. Supervised  
503 exercise therapy and revascularization for intermittent claudication: network meta-analysis of  
504 randomized controlled trials. *JACC Cardiovasc Interv* [~~Internet~~]. 2019 Jun 24 [cited 2023 Apr  
505 3]; ~~12~~(12):1125–36. Available from: <https://pubmed.ncbi.nlm.nih.gov/31153838/>
- 506 42. Murphy TP, Cutlip DE, Regensteiner JG, Mohler ER, Cohen DJ, Reynolds MR, et al.  
507 Supervised exercise versus primary stenting for claudication resulting from aortoiliac  
508 peripheral artery disease: Six-month outcomes from the claudication: Exercise versus  
509 endoluminal revascularization (CLEVER) study. *Circulation*. 2012 Jan 3; ~~125~~(1):130–9.
- 510 43. McDermott MM, Ferrucci L, Tian L, Guralnik JM, Lloyd-Jones D, Kibbe MR, et al. Effect of  
511 granulocyte-macrophage colony-stimulating factor with or without supervised exercise on  
512 walking performance in patients with peripheral artery disease: ~~The~~ the PROPEL randomized  
513 clinical trial. *JAMA – J Am Med Assoc*. 2017 Dec 5; ~~318~~(21):2089–98.
- 514 44. Sivagangan P, Harwood AE, Stather PW. Patient and healthcare professional priorities for a  
515 mobile phone application for patients with peripheral arterial ~~Disease~~disease. *Cureus*  
516 [~~Internet~~]. 2023 Jan 20 [cited 2023 Apr 3]; ~~15~~(1):e33993. Available from:  
517 <https://pubmed.ncbi.nlm.nih.gov/36824553/>
- 518 45. Aalami OO, Lin J, Savage D, Ho V, Bertges D, Corriere M. Use of an app-based exercise  
519 therapy program including cognitive-behavioral techniques for the management of intermittent  
520 claudication. *J Vasc Surg* [~~Internet~~]. 2022 Dec 1 [cited 2023 Apr 3]; ~~76~~(6):1651–1656. ~~e1~~  
521 Available from: <https://pubmed.ncbi.nlm.nih.gov/35872328/>
- 522 46. Pymer S, Harwood A, Ibeggazene S, McGregor G, Huang C, Twiddy M, et al. High INtensity  
523 Interval Training In pATiEnts with intermittent claudication (INITIATE): protocol for a  
524 multicentre, proof-of-concept, prospective interventional study. *BMJ Open*. 2020 Jul  
525 ~~6~~; ~~10~~(7):e038825.
- 526 47. Harzand A, Vakili AA, Alrohaibani A, Abdelhamid SM, Gordon NF, Thiel J, et al. Rationale

Formatted: Font: Italic

Formatted: Font: Bold

Formatted: Font: Italic

Formatted: Font: Bold

Formatted: Font: Italic

Formatted: Font: Bold

Formatted: Font: Italic

Formatted: Font: Bold

Formatted: Font: (Default) Times New Roman, Font color: Auto, Pattern: Clear

Formatted: Font: Italic

Formatted: Font: Bold

Formatted: Font: Italic

Formatted: Font: Bold

- 527 and design of a smartphone-enabled, home-based exercise program in patients with  
 528 symptomatic peripheral arterial disease: The smart step randomized trial. *Clin Cardiol*  
 529 ~~[Internet]. 2020 Jun 1 [cited 2023 Apr 8];43(6):537–45. Available from:~~  
 530 ~~https://onlinelibrary.wiley.com/doi/full/10.1002/ele.23362~~
- 531 48. Persson AB, Buschmann EE, Lindhorst R, Troidl K, Langhoff R, Schulte KL, et al.  
 532 Therapeutic arteriogenesis in peripheral arterial disease: combining intervention and passive  
 533 training. ~~http://dx.doi.org/10.1024/0301-1526/a000092 [Internet]. 2013 Jan 7 [cited 2023 Apr~~  
 534 ~~9];Vasa 2011;40(3):177–87. Available from: https://econtent.hogrefe.com/doi/10.1024/0301-~~  
 535 ~~1526/a000092~~
- 536 49. Mays RJ, Hiatt WR, Casserly IP, Rogers RK, Main DS, Kohrt WM, et al. Community-based  
 537 walking exercise for peripheral artery disease: ~~An an~~ exploratory pilot study. *Vasc Med*  
 538 ~~(United Kingdom) [Internet]. 2015 Aug 10 [cited 2023 Apr 9];20(4):339–47. Available from:~~  
 539 ~~https://journals.sagepub.com/doi/10.1177/1358863X15572725~~
- 540 50. Austin PC. A critical appraisal of propensity-score matching in the medical literature between  
 541 1996 and 2003. *Stat Med Stat Med* ~~[Internet]. 2008 [cited 2023 Jul 2];27:2037–49. Available~~  
 542 ~~from: www.interscience.wiley.com~~
- 543 51. Stuart EA. Matching methods for causal inference: ~~A a~~ review and a look forward. *Stat Sci*  
 544 ~~[Internet]. 2010 Feb 2 [cited 2023 Jul 2];25(1):1–21. Available from:~~  
 545 ~~/pmc/articles/PMC2943670/~~
- 546 52. Caliendo M, Kopeinig S. Some practical guidance for the implementation of propensity score  
 547 matching. *J Econ Surv* 2008;22:31–72. 2005;
- 548 53. Amusa L, North D, Zewotir T. A tailored use of the mahalanobis distance matching for causal  
 549 effects estimation: A simulation study. *Sci African*. 2022 Jul 1;16:e01155.

Formatted: Font: Italic

Formatted: Font: Italic

Formatted: Font: Bold

Formatted: Font: Italic

Formatted: Font: Bold

Formatted: Font: Italic

Formatted: Font: Bold

Formatted: Font: Italic

Formatted: Font: Bold

Formatted: Font: (Default) Times New Roman, Font color: Auto, Pattern: Clear

Formatted: Font: Italic

Formatted: Font: Bold

Formatted: Font: Bold

551 **Legends for figure:**

552 **Figure 1:** Supervised exercise therapy protocol. Outline of each session during weeks 1–6, with an  
553 additional station added each week from week 7 until the patient had completed two full circuits. The  
554 figure illustrates the progression of the supervised exercise therapy protocol used in the study.

555 **Figure 2:** Independent variable importance analysis using ~~Multilayer-multilayer~~ perceptron to  
556 identify the most significant predictors of chronic limb threatening ischaemia to guide propensity  
557 score matching along with multivariable and logistic regression analyses. SET = supervised exercise  
558 therapy.

559 **Figure 3:** Number of cardiovascular events for patients who did and did not complete supervised  
560 exercise therapy (SET) after median follow up of 2.164 days; IC: Intermittent Claudication;  
561 CLTI = Chronic-chronic limb threatening ischemia; MALE = Major-major adverse limb events;  
562 MACE = Major-major adverse cardiovascular events; SET: Supervised exercise therapy.

563 **Figure 4:** Cumulative Kaplan–Meier estimate of survival curves obtained by the Kaplan–Meier  
564 method demonstrating (A) time to chronic limb threatening ischaemia(a), (B) time to first major  
565 adverse cardiovascular event (MACE)(b) and (C) time to first major adverse limb event (MALE)(c)

566 **Table 1a: Baseline characteristics of both cohorts**

**Table 1. Baseline characteristics of both cohorts.**

Attribute	Patients who did not start SET (n = 183)	Patients who prematurely discontinued SET (N, n = 19)	Patients who completed SET (n = 64)	p value
Age (years; Mean ± SD)	67.95 ± 10.4	70.1 ± 7.3	69.5 ± 7.8	.40
Male	119 (65.7%)	12 (63.2%)	44 (68.8%)	.87
Diabetes Mellitus	54 (29.5%)	4 (21.1%)	29 (45.3%)	.076

Formatted: Font: Bold

Formatted: Font color: Text 1

Formatted: Font color: Red

Formatted: Font: Bold

Formatted: Font: Bold, Font color: Text 1

Formatted: Font color: Text 1

Formatted: Font: (Default) Times New Roman

Formatted: Font color: Text 1

Formatted: Line spacing: Double

Formatted: Font: Bold

Formatted Table

Formatted: Font: Bold

Formatted: Font: Bold, Italic

Formatted: Font: Bold

Formatted: Font: Bold, Italic

Formatted: Font: Bold

Formatted: Font: Bold, Italic

Formatted: Font: Bold

Hypertension	131_(71.6%)	10_(52.6%)	45_(70.3%)	.17
Hyperlipidaemia	82_(44.8%)	6_(31.5%)	30_(46.8%)	.24
Ischaemic heart disease	101_(55.8%)	11_(57.9%)	28_(43.8%)	.23
Cerebrovascular disease	25_(13.7%)	4_(21%)	8_(12.5%)	.12
Atrial fibrillation	38_(20.7%)	2_(10.5%)	8_(12.5%)	.18
Albumin ( $\leftarrow$ g/L; Mean $\pm$ SD)	36.9 $\pm$ 4.28	37.1 $\pm$ 3.3	35.2 $\pm$ 3.7	.16
Haemoglobin ( $\leftarrow$ g/L) Mean $\pm$ SD	132.73 $\pm$ 20.6	138.3 $\pm$ 19.0	136.5 $\pm$ 22.7	.16
Compliance with smoking cessation	45_(24.9%)	5_(26.3%)	22_(34.0%)	.34
<i><u>ABPI at presentation</u></i>				
<u>Right</u>	<u>0.79 <math>\pm</math> 0.18</u>	<u>0.74 <math>\pm</math> 0.19</u>	<u>0.80 <math>\pm</math> 0.15</u>	<u>.41</u>
<u>ABPI at presentation</u>				
<u>Right</u>	<u>0.79 <math>\pm</math> 0.18</u>	<u>0.74 <math>\pm</math> 0.19</u>	<u>0.80 <math>\pm</math> 0.15</u>	<u>.41</u>
Left	0.81 $\pm$ 0.20	0.82 $\pm$ 0.29	0.84 $\pm$ 0.15	.58
(Mean, SD)				
Self-reported claudication distance (metres) m				
(Mean, SD)	77.5 $\pm$ 6.75	79.1 $\pm$ 7.5	79.4 $\pm$ 6.0	.11
<u>No iliac disease</u>	<u>37 (20.2)</u>	<u>3 (15.7)</u>	<u>29 (45.3)</u>	
<u>No iliac disease</u>	<u>37(20.2%)</u>	<u>3(15.7%)</u>	<u>29(45.3%)</u>	
Unilateral iliac disease	63_(34.4%)	6_(31.5%)	8_(12.5%)	.010
Bilateral iliac disease	83_(45.4%)	10_(52.6%)	26_(40.6%)	

Formatted: Font: Italic

Formatted: Font: Not Bold, Italic

Formatted: Font color: Auto

Formatted: Font color: Auto

Formatted: Font color: Auto

Formatted: Font: Not Bold, Font color: Auto

Formatted: Font color: Auto

Formatted: Font color: Auto

Formatted: Font color: Auto

Formatted Table

Formatted: No underline

<u>Bilateral iliac disease</u>	<u>83 (45.4)</u>	<u>10 (52.6)</u>	<u>26 (40.6)</u>	
<u>No femoral disease</u>	<u>11 (6.0)</u>	<u>1 (5.2)</u>	<u>5 (7.8)</u>	
<b>No femoral disease</b>	<b>11(6.0%)</b>	<b>1(5.2%)</b>	<b>5(7.8%)</b>	
Unilateral- femoral disease	76 (41.5%)	9 (47.3%)	8 (12.5%)	.030
<b>Bilateral femoral disease</b>	<b>96(52.5%)</b>	<b>9(47.3%)</b>	<b>50(78.1%)</b>	
<u>Bilateral femoral disease</u>	<u>96 (52.5)</u>	<u>9 (47.3)</u>	<u>50 (78.1)</u>	
<u>No crural disease</u>	<u>87 (47.5)</u>	<u>10 (52.6)</u>	<u>38 (59.3)</u>	
<u>Unilateral crural disease</u>	<u>56 (30.6)</u>	<u>7 (36.8)</u>	<u>13 (20.3)</u>	
<b>No crural disease</b>	<b>87(47.5%)</b>	<b>10(52.6%)</b>	<b>38(59.3%)</b>	
<b>Unilateral crural disease</b>	<b>56(30.6%)</b>	<b>7(36.8%)</b>	<b>13(20.3%)</b>	.47
Bilateral crural disease	40 (21.9%)	2 (10.5%)	13 (12.5%)	

Formatted: Font: Not Bold, Font color: Auto

Formatted: Font color: Auto

Formatted: Font color: Auto

Formatted: Font color: Auto

Formatted Table

Formatted: No underline

Formatted: Font: Bold, No underline

Formatted: Font: Not Bold, Font color: Auto

Formatted: Font color: Auto

Formatted: Font color: Auto

Formatted: Font color: Auto

Formatted: Font: Not Bold, Font color: Auto

Formatted: Font color: Auto

Formatted: Font color: Auto

Formatted: Font color: Auto

Formatted Table

Formatted: Font: Italic

567 -Data are presented as mean  $\pm$  SD or *n* (%).

568 SD: = Standard standard deviation; IQR: = Interquartile-interquartile range; SET: = supervised

569 exercise therapy; ABPI: = Ankle-brachial pressure index.

570

571

572

573 Table 1b: Impact of propensity score matching on significant confounders

574



**Formatted:** Space Before: 12 pt, After: 12 pt, Line spacing: Double

[Click here to view linked References](#)

1 Title: Supervised Exercise Therapy for Intermittent Claudication: A Propensity Score Matched  
2 Analysis of Retrospective Data on Long term Cardiovascular Outcomes  
3 Running title: Long-term outcomes following supervised exercise therapy in intermittent claudication  
4 Authors: Bharadhwaj Ravindhran,  
5 Arthur JM Lim  
6 Thomas Kurian  
7 Josephine Walshaw  
8 Louise H Hitchman  
9 Ross Lathan  
10 George E Smith  
11 Daniel Carradice  
12 Ian C Chetter  
13 Sean Pymer  
14 <sup>1</sup> Academic Vascular Surgical Unit, 2<sup>nd</sup> Floor, Allam diabetes centre, Hull Royal Infirmary, HU32JZ  
15 Corresponding author: Bharadhwaj Ravindhran  
16 Academic Vascular Surgical Unit  
17 2<sup>nd</sup> Floor, Allam diabetes centre  
18 Hull Royal Infirmary  
19 Hull HU32JZ  
20 Bharadhwaj.Ravindhran@nhs.net  
21 This paper was awarded the Norman Williams Prize for the best clinical research paper and is  
22 shortlisted for the BJS Best Manuscript Prize at the Annual Meeting of the Surgical Research Society  
23 in 2023 at Nottingham, UK.  
24  
25 Word counts  
26 Abstract: 285  
27 What this paper adds: 37  
28 The text body: 2932  
29 Number of tables and figures: 2 tables and 4 figures  
30



31 **What this paper adds:**

32 This study contributes to the current body of literature by conducting an initial assessment of long-  
33 term outcomes in patients with intermittent claudication (IC) who underwent supervised exercise  
34 therapy (SET), with a focus on cardiovascular morbidity and mortality.. The results indicate that  
35 completing SET is associated with a decreased risk of major adverse limb events, major adverse  
36 cardiovascular events, and progression to chronic limb-threatening ischemia based on this  
37 retrospective propensity score matched analysis of patients who completed, discontinued or declined  
38 SET.

39

40

41

42

43

44

45

46

47

48

49

50

51

52

53

54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65  
66  
67  
68  
69  
70  
71  
72  
73  
74  
75  
76  
77  
78

**Abstract:**

Objective: This study aimed to explore the long-term outcomes of patients with intermittent claudication (IC) who completed supervised exercise therapy (SET) versus those who declined or prematurely discontinued SET, focusing on the incidence of chronic limb-threatening ischemia (CLTI), revascularization, major adverse limb events (MALE), and major adverse cardiovascular events (MACE).

Design: Retrospective registry analysis of consecutive patients with IC who were referred for SET between March 2015 and August 2016 and followed up for a minimum of five years.

Methods: Serial univariable analysis and logistic regression was performed to identify the statistically significant clinical variables that were independent predictors of each outcome measure. The resulting statistically significant variables were used to guide 1:1 propensity score matching (PSM) using the nearest neighbour method with a calliper of .2. A Cox proportional hazards regression was used to estimate the hazard ratio(HR) and 95% CI for the association between SET and the outcomes of interest.

Results: Two hundred and sixty-six patients were referred to SET between March 2015 and August 2016. Of these, 64 patients completed SET and 202 patients did not. After PSM, 49 patients were analysed in each cohort. The Cox proportional hazards analysis revealed a significant association between completion of SET and revascularisation requirement( HR: 0.46 95% CI 0.25 – 0.84; p =.011), completion of SET and progression to CLTI(HR: 0.091, 95% CI 0.04 – 0.24; p <.001), completion of SET and MACE(HR: 0.52; 95% CI 0.28 – 0.99; p =.05) and completion of SET and MALE( HR: 0.28, 95% CI 0.13 – 0.65; p =.003). The Harrell’s C-index for all of these models were greater than .75 indicating good predictive accuracy.

79 Conclusion: Completion of SET is associated with better outcomes in patients who completed SET  
80 compared to patients who declined or discontinued SET with respect to clinically important  
81 cardiovascular outcomes over 7 years.

82 Key words: Intermittent claudication, outcome assessment, propensity score, ischemia, exercise  
83 therapy; resistance training

84

85

86

87

88

89

90

91

92

93

94

95

96

97

98

99 Introduction:

100 Intermittent claudication (IC) is an ambulatory, ischaemic muscle pain relieved by rest, which reduces  
101 physical function, walking capacity, balance, and quality of life and increases the risk of mortality  
102 from cardiovascular causes<sup>1-5</sup>. Patients with IC patients are at risk of disease progression to chronic  
103 limb threatening ischaemia (CLTI) and major adverse limb events (MALE) such as major lower limb  
104 amputations (MLLA), acute limb ischemia (ALI), or loss of untreated patency<sup>6,7</sup>. The goal of treatment  
105 is therefore to improve symptoms, physical function, and quality of life (QoL), while also reducing  
106 the risk of disease progression and limb loss, mortality and MACE.<sup>8</sup>

107 To achieve this, the National Institute for Health and Care Excellence (NICE) guideline 147<sup>9</sup> and the  
108 European society for vascular surgery (ESVS)<sup>10</sup> recommend supervised exercise therapy (SET) for 2-  
109 hours per week over a 3-month period, as the first-line treatment. Evidence shows that SET is  
110 significantly superior for improving walking performance, and therefore symptoms, when compared  
111 to home-based exercise and walking advice<sup>11</sup>. Further evidence also shows that SET is comparable to  
112 endovascular revascularisation for improving walking distance and importantly, QoL<sup>11</sup>. Given the  
113 positive effect that SET also has on cardiovascular risk factors,<sup>12,13</sup> it would be reasonable to assume  
114 that this leads to a potential benefit in morbidity, via a reduction in MACE and MALE, as well as a  
115 benefit in mortality. However, the evidence considering the long-term effects of SET on morbidity  
116 and mortality is lacking, with just one study considering the association between SET completion and  
117 mortality<sup>14,15</sup>.

118 Therefore, the aim of this study was to investigate whether completion of SET was associated with  
119 better cardiovascular outcomes compared to a group of patients with IC that did not complete SET  
120 using propensity score matching (PSM). Methods:

121 This study was conducted at a tertiary care referral vascular centre. The clinical, intra-operative and  
122 follow-up information were gathered, analysed and compared between patients who completed SET  
123 and patients who either declined or discontinued SET.

124 Patient selection:

125 We retrospectively analysed the data of consecutive patients with IC who were referred for SET  
126 between March 2015 and August 2016 (18 months). Patients who were referred but had CLTI, had  
127 undergone SET within the preceding 12 months, or had a recurrence of symptoms following previous  
128 revascularisation were excluded from this analysis. Patients who were referred for SET but were  
129 deemed unsuitable due to contraindications or the presence of significant co morbidities or missing  
130 data were also excluded. The diagnosis of IC was made clinically, and was further supported by a  
131 resting ankle brachial pressure index (ABPI) or toe -brachial pressure index, duplex ultrasound or  
132 cross-sectional imaging if required. Patients who declined SET were either discharged back to their  
133 general practitioner (GP), received regular follow-up or underwent a revascularisation procedure,  
134 depending on individual need.

135 Patients referred to supervised exercise therapy (SET) were initially assessed by physicians to identify  
136 any obvious contraindications such as severe frailty, unstable gait, and existing pulmonary and cardiac  
137 disorders (e.g., aortic stenosis, dyspnoea at rest). These contraindications were determined based on  
138 clinical judgment. Furthermore, patients who did not have any obvious contraindications to SET were  
139 then screened by the exercise physiologist prior to starting SET. This screening process aimed to  
140 identify any additional contraindications or factors that may affect the safety or effectiveness of SET  
141 for individual patients. It is important to note that all patients in our study underwent routine screening  
142 at two levels (physician assessment and exercise physiologist screening) to ensure that only those who  
143 were suitable for SET were included.

144 Supervised exercise therapy:

145 Patients performed SET three times per week for 12 weeks comprising a total of 36 sessions. Missed  
146 sessions were made up at the end of the 12-week programme<sup>16</sup>. The programme was overseen by an  
147 exercise physiologist with support from undergraduate and postgraduate sports science students. SET  
148 sessions involved the completion of a circuit of six two-minute stations, separated by two-minute  
149 walking intervals. These were preceded by a warm-up and followed by a cool-down. The stations  
150 included step-ups, standing knee bends, sitting knee extensions, biceps curls, cycling, and heel raises  
151 (Figure 1). As the patient's exercise tolerance improved, an additional station was added each week

152 from the seventh week and by the end of week 12, they completed two full circuits. Session length  
153 therefore began at 30, progressing up to 60 minutes. Patients were deemed to have successfully  
154 completed SET after accumulating 36 sessions. This circuit-based training program was designed  
155 based on previous recommendations that highlight the effectiveness of combining upper and lower  
156 limb ergometry, resistance exercise, and walking-based exercises to improve muscle strength and  
157 cardiorespiratory fitness. These interventions have been shown to elicit a more significant  
158 cardiorespiratory stimulus compared to walking alone.<sup>17–20</sup>

159 Outcome measures:

160 The study investigated the incidence and time-to CLTI, MALE, and MACE over a minimum of five  
161 years and up to seven years. CLTI was defined as ischaemic rest pain lasting for two or more weeks,  
162 non-healing wounds, or gangrene that was attributable to objectively proven arterial occlusive disease.  
163 MACE was defined as non-fatal stroke, nonfatal myocardial infarction (MI), or cardiovascular death  
164 (CVD)<sup>21</sup>. MALE was defined as ALI, untreated loss of patency, or MLLA.<sup>22</sup>

165 Statistical analyses:

166 Continuous data was assessed for a normality using the Shapiro-Wilk test and are presented as mean  $\pm$   
167 standard deviation or median and range or interquartile range as appropriate. Categorical data are  
168 expressed as numbers and/or percentages. Time to event data is presented using Kaplan-Meier  
169 survival curves. Comparative hypothesis testing was performed using Chi-squared tests, t-tests or  
170 Mann Whitney U tests as appropriate, and log-rank tests. Statistical significance was set at  $p < .05$ .  
171 Serial univariable analysis and logistic regression was performed to identify the statistically  
172 significant clinical variables that were independent predictors of each outcome measure. This was  
173 confirmed by performing an independent variable importance analysis using the multilayer perceptron  
174 tool, which is a popular tool in machine learning and deep learning for pattern recognition.<sup>23</sup> The  
175 resulting statistically significant variables were used to guide 1:1 PSM using the nearest neighbour  
176 method with a calliper of .2. The differences between these two matched groups were compared by  
177 using the Mann–Whitney U test, and categorical data were analysed using the Pearson’s Chi-square

178 test, the Fisher's exact test, or continuity correction where appropriate. Survival curves were obtained  
179 by the Kaplan-Meier method and a Cox proportional hazards regression was used to estimate the  
180 hazard ratio(HR) and 95% CI for the association between SET and the outcomes of interest. All  
181 statistical analyses were performed using Statistical Package for the Social Sciences (IBM Corp.  
182 2020; Windows Version 27.0) and Medcalc (MedCalc Statistical Software version 19.2.6; MedCalc  
183 Software bv, Ostend, Belgium;)

184

185 Results:

186 Two-hundred and eighty-two patients presented to the vascular outpatient clinic with IC between  
187 March 2015 and August 2016 and were referred for SET. Sixteen patients were deemed unsuitable for  
188 SET due to advanced comorbidities, mobility problems and dementia. Two-hundred and sixty-six  
189 patients were deemed suitable and were offered SET, of which 83 (31%) attended and 183 (69%)  
190 declined. Of those that attended, 64 (77%) patients successfully completed SET, whilst 19 (23%)  
191 prematurely discontinued. Baseline characteristics of those who completed and those who declined or  
192 prematurely discontinued SET are presented in table 1a. The primary reasons for the low adoption of  
193 SET were related to location or travel (44.3%; n=81), individuals declining due to lack of  
194 interest/belief in the SET (39.3%; n=72), work/personal commitments resulting in a lack of time for  
195 SET (12.6%; n=23), inability to participate due to musculoskeletal issues (2.2%; n=4), and patients  
196 already enrolled in a community exercise program (1.6%; n=3). Considering that nearly all patients  
197 who discontinued SET did so without attending at least 50% of the sessions, we deemed it appropriate  
198 to combine both groups, i.e., those who discontinued and those who declined SET, for the purpose of  
199 analysis.

200 Serial univariable and logistic regression analyses revealed that CLTI had the greatest number of  
201 statistically significant predictor variables compared to the other outcomes, and therefore, these  
202 significant predictors were used to guide PSM, which was performed to account for the independent  
203 association between these variables and outcome measures. Haemoglobin, self-reported claudication

204 distance, ABPI, presence of ischaemic heart disease (IHD), neutrophil-to-lymphocyte ratio,  
205 compliance with smoking cessation and non-completion of supervised exercise therapy were found to  
206 be statistically significant predictors of CLTI based on serial univariable analyses. Logistic regression  
207 analysis performed using these variables indicated that haemoglobin, self-reported claudication  
208 distance, ABPI and the presence of IHD were significant predictors of CLTI. This was confirmed via  
209 an independent variable importance analysis (Figure 2). The multilayer perceptron(MLP) algorithm is  
210 employed to evaluate the relative contribution of independent variables in predicting CLTI. By  
211 assigning weights to each input variable based on their importance, the MLP algorithm provides  
212 valuable insights into the significant of each variable. This importance analysis helps identify the  
213 variables with the greatest impact on CLTI occurrence.

214 After PSM based on these variables, 49 patients were analysed in each cohort. There was no  
215 difference between groups with respect to haemoglobin (g/l) ( $130.9 \pm 19.3$  vs  $138.6 \pm 18.8$ ;  $p = .080$ ),  
216 IHD (59.2% vs 63.3%  $p = .56$ ), self-reported claudication distance (metres) ( $131 \pm 19.4$  vs  $130 \pm 18.9$ ;  
217  $p = .81$ ) and ABPI ( $0.7 \pm 0.1$  vs  $0.7 \pm 0.2$ ;  $p = .29$ )(Table 1b). The Cox proportional hazards analysis  
218 revealed a significant association between completion of SET and progression to CLTI(HR: 0.091,  
219 95% CI 0.04– 0.24;  $p < .001$ ), completion of SET and MACE(HR: 0.52; 95% CI 0.28 – 0.99;  $p = .05$ )  
220 and completion of SET and MALE( HR: 0.28, 95% CI 0.13 – 0.65;  $p = .003$ ). The Kaplan-Meier  
221 curves demonstrated a consistent and statistically significant difference in outcomes amongst those  
222 who completed SET, compared to those who did not complete SET (Figure 3). The Harrell's C-index  
223 for all of these models were greater than .75 indicating good predictive accuracy.

224 To assess the adequacy of sample size, a post-hoc power analysis was conducted, revealing that a total  
225 of 48 events and a sample size of 36 patients in the SET completion cohort and 186 patients in the  
226 non-completion cohort were required to detect a significant association between SET and outcomes.  
227 This estimation followed the methodology outlined by Schoenfeld et al<sup>24</sup>, assuming a significance  
228 level of .05, 80% power, a 16% incidence of SET completion among referred patients<sup>25</sup>, a relative  
229 hazard of 3, a median survival of 12 years, and a planned follow-up of 7 years<sup>15,26,27</sup>.

230 Discussion:



231 This study demonstrates that completion of SET is associated with a reduced risk of experiencing  
232 MALE, MACE and progression to CLTI. To the best of our knowledge, this study represents one of  
233 the first evaluations of long-term outcomes following SET with a focus on cardiovascular morbidity  
234 and mortality in individuals with PAD. Whilst the data suggest a positive effect of SET, it is important  
235 to acknowledge that the patients in this cohort may differ in ways that have not been accounted for,  
236 and their outcomes may have been influenced by factors beyond SET. It is important to note that even  
237 with rigorous propensity score matching, confounding by indication cannot be completely adjusted  
238 for, as there may be unmeasured covariates that affect both the variable and outcome of interest. We  
239 also acknowledge that while this analysis provides important insights and suggests an association, the  
240 efficacy of SET for improving cardiovascular outcomes cannot be established. Nevertheless, these  
241 findings provide a strong rationale for increasing the delivery of SET and conducting further research  
242 to better understand its potential long-term benefits. Moving forward, efforts should be directed  
243 towards reducing SET barriers (such as the time commitment) to maximise patient engagement. By  
244 doing so, we may be able to optimise the effectiveness of SET and improve outcomes for a broader  
245 range of patients.

246

247 Currently, high quality evidence shows that SET provides an important benefit with respect to  
248 maximum walking distance (MWD), pain-free walking distance and QoL compared to home-based  
249 exercise therapy and walking advice<sup>14,28</sup>. Better SET compliance, measured by attendance at exercise  
250 sessions, is significantly associated with greater improvements in MWD and adherence to SET may  
251 imply better adherence of several factors in life, such as to smoking cessation, healthy diet and  
252 medication, resulting in better outcomes.<sup>29</sup> However, even patients at the lowest tercile of exercise  
253 attendance demonstrate a significant improvement in MWD<sup>30</sup>. Despite this evidence, and the  
254 guidance provided by NICE and the ESVS,<sup>9,10</sup> SET provision is not consistent in the UK, with less  
255 than 50% of vascular centres offering it and less than 25% of these adhering to the recommended  
256 exercise dose<sup>31</sup>. The low availability of SET in the UK can be attributed to various constraints faced in  
257 a centralized hub and spoke model. These constraints include running costs and a lack of resources

258 and qualified personnel<sup>32–34</sup>. When SET is offered, patients may not want to participate due to a lack  
259 of availability near their home or the required time commitment, which contributes to the poor uptake  
260 rates seen.<sup>25,35</sup> Further research is needed to explore ways to address or minimise the constraints felt  
261 by patients and providers to improve the accessibility and acceptability of SET.

262 During the last two decades there has been a substantial increase in the number of studies comparing  
263 primary interventional therapy to SET. The results of these studies suggest that SET is comparable to  
264 primary percutaneous transluminal angioplasty (PTA) for improving in walking distance and  
265 QoL<sup>36,37,38</sup>. This suggests that the current first-line treatment strategy of SET is advocated. However,  
266 poor uptake and adherence to SET, poor patient fitness, and patient preference are cited as reasons for  
267 using a “PTA first” strategy in patients with IC<sup>39–41</sup>. Based on the results of the current study, even if  
268 a PTA first strategy is pursued due to these constraints, the integration of an exercise intervention may  
269 yield additional improvements in long-term cardiovascular outcomes, which may not occur with PTA  
270 alone.

271 Recent evidence has also demonstrated that SET produces a notable improvement in cardiovascular  
272 risk factors, such as cholesterol levels and resting and exercising blood pressure<sup>12,13</sup>. Interestingly, the  
273 greater the improvement in cardiovascular health, the greater the improvement in walking  
274 performance.<sup>12</sup> Despite this evidence for a reduction in cardiovascular risk factors, there is limited  
275 data to support the reduction of long-term cardiovascular risk following SET.<sup>42,43</sup> The reduction in  
276 cardiovascular morbidity and mortality following SET demonstrated in this study could be  
277 attributable to these beneficial effects on cardiovascular risk factors.

278 Determining the percentage of outcomes that are directly associated with the completion of SET is  
279 difficult, given the presence of unmeasured confounding variables that may impact the findings, such  
280 as patient motivation. Even amongst highly motivated patients, uptake and adherence to SET can be  
281 difficult, underscoring the importance of offering alternative options to patients who wish to engage in  
282 SET but face barriers to compliance and uptake<sup>34</sup>. High-intensity interval training (HIIT) or remotely  
283 delivered supervised exercise interventions are alternatives that could offer promising benefits,  
284 specially tailored to the unique needs and conditions of patients who were previously unable to enrol

285 in SET due to time or travel constraints.<sup>44,45</sup> Currently, a time efficient HIIT programme is being  
286 assessed as a potential alternative for SET, to reduce the time barrier faced by patients<sup>46</sup>. Early  
287 evidence has suggested that this HIIT programme appears to be feasible and well tolerated in patients  
288 with IC, which is to be confirmed via a proof-of-concept study<sup>46</sup>.

289

290 Other alternative approaches to delivering SET have been explored, including remote monitoring,  
291 videos, support groups, mobile-applications and trackers and virtual reality.<sup>44,47,48</sup> A smartphone-  
292 enabled home-based exercise program is feasible and effective in patients with symptomatic PAD, as  
293 is a community-based walking programme with training, monitoring and coaching components.<sup>47,49</sup>  
294 These alternative approaches to delivering SET have the potential to increase patient access and  
295 improve adherence. However, they are currently limited to small proof-of-concept studies. Further  
296 research is needed to explore their effectiveness in fully powered randomised controlled trials.

## 297 **Limitations**

298 Although this study provides useful insights, its retrospective nature encompasses several inherent  
299 limitations, including unmeasurable confounding factors, potential biases, and the lack of blinding or  
300 randomisation that can affect the objectivity of our analysis. The limitations associated with the  
301 retrospective nature of this study were addressed by enrolling consecutive patients over an eighteen-  
302 month period and conducting a meticulous PSM method with a 0.2 calliper. While there are many  
303 alternatives to 1:1 PSM such as mahalanobis distance matching, kernel matching and covariate  
304 matching, propensity score matching is considered the best approach due to its ability to balance  
305 covariates, flexibility in handling different types of covariates, interpretability, and the opportunity for  
306 sensitivity analysis.<sup>50-53</sup> Despite using rigorous propensity score matching, it is impossible to fully  
307 account for confounding by indication. This is because there might be unmeasured factors that impact  
308 both the variable being studied and the outcome of interest. In our study, we included statistically  
309 significant variables in the PSM to ensure that we were controlling for factors that had a proven  
310 association with the outcome. This approach was taken to minimize the risk of overfitting and to

311 ensure the robustness of our findings. However, we acknowledge the potential for Type II errors and  
312 the possibility of missing relevant variables. The lack of differences observed in Table 1b after  
313 implementing PSM could potentially be attributed to a type II error. The use of inverse probability  
314 weighting (IPW) is a valid approach that can enhance the robustness of findings by retaining a larger  
315 sample size. However, we chose PSM for our study due to specific reasons. PSM allows us to best  
316 mimic a randomized controlled trial by matching patients who completed SET with control patients  
317 based on observed characteristics, reducing bias from confounding variables. While IPW could retain  
318 a larger sample size, it can introduce challenges such as sensitivity to model specification and  
319 unstable estimates with extreme weights. We believe PSM is more suitable for our study, considering  
320 these factors, although we acknowledge limitations such as potential bias from unobserved  
321 confounding and a reduced sample size. Additionally, it is important to acknowledge that although  
322 this analysis offers valuable insights and indicates a potential connection, we cannot definitively  
323 establish the effectiveness of SET in improving cardiovascular outcomes.

324 This study indicates an association between patients completing SET and better long-term clinical  
325 outcomes, such as slower disease progression, and a lower likelihood of experiencing MALE or  
326 MACE. However, due to the potential for unmeasured confounding, we cannot definitively conclude  
327 that SET leads to an improvement in cardiovascular health or mitigates adverse long-term outcomes  
328 in IC. Rather, our findings suggest a potential association that warrants further investigation. Overall,  
329 these outcomes underscore the potential significance of SET in relation to cardiovascular health in IC  
330 patients.

331 **Acknowledgements:** The authors gratefully acknowledge the invaluable contribution of Dr. Dror  
332 Rosentraub for his expertise and guidance in the application of statistical methods. The authors would  
333 also like to express their sincere gratitude to the academic vascular surgical unit for their invaluable  
334 support and collaboration throughout the course of this study. Their expertise and guidance have  
335 greatly contributed to the successful completion of this research.

336

337 References:

- 338 1. Criqui MH, Aboyans V. Epidemiology of peripheral artery disease. *Circ Res* [Internet]. 2015  
339 Apr 24 [cited 2023 May 1];116(9):1509–26. Available from:  
340 <https://pubmed.ncbi.nlm.nih.gov/25908725/>
- 341 2. Criqui MH, Langer RD, Fronek A, Feigelson HS, Klauber MR, McCann TJ, et al. Mortality  
342 over a period of 10 years in patients with peripheral arterial disease. *N Engl J Med* [Internet].  
343 1992 Feb 6 [cited 2023 May 1];326(6):381–6. Available from:  
344 <https://pubmed.ncbi.nlm.nih.gov/1729621/>
- 345 3. Pell JP. Impact of intermittent claudication on quality of life. *Eur J Vasc Endovasc Surg*. 1995  
346 May 1;9(4):469–72.
- 347 4. Gohil RA, Mockford KA, Mazari F, Khan J, Vanicek N, Chetter IC, et al. Balance impairment,  
348 physical ability, and its link with disease severity in patients with intermittent claudication.  
349 *Ann Vasc Surg* [Internet]. 2013 Jan 1 [cited 2023 May 9];27(1):68–74. Available from:  
350 <http://www.annalsofvascularsurgery.com/article/S0890509612003214/fulltext>
- 351 5. Meru A V., Mitra S, Thyagarajan B, Chugh A. Intermittent claudication: an overview.  
352 *Atherosclerosis* [Internet]. 2006 Aug [cited 2023 May 1];187(2):221–37. Available from:  
353 <https://pubmed.ncbi.nlm.nih.gov/16386260/>
- 354 6. Eid MA, Mehta K, Barnes JA, Wanken Z, Columbo JA, Stone DH, et al. The global burden of  
355 peripheral artery disease. *J Vasc Surg* [Internet]. 2023 Apr [cited 2023 Apr 3];77(4). Available  
356 from: <https://pubmed.ncbi.nlm.nih.gov/36565779/>
- 357 7. McDermott KM, Bose S, Keegan A, Hicks CW. Disparities in limb preservation and  
358 associated socioeconomic burden among patients with diabetes and/or peripheral artery disease  
359 in the United States. *Semin Vasc Surg* [Internet]. 2023 Mar 1 [cited 2023 Apr 3];36(1).  
360 Available from: <https://pubmed.ncbi.nlm.nih.gov/36958896/>

- 361 8. Bevan GH, White Solaru KT. Evidence-Based Medical Management of Peripheral Artery  
362 Disease. *Arterioscler Thromb Vasc Biol.* 2020 Mar 1;40(3):541–53.
- 363 9. Overview | Peripheral arterial disease: diagnosis and management | Guidance | NICE  
364 [Internet]. [cited 2022 May 7]. Available from: <https://www.nice.org.uk/guidance/cg147>
- 365 10. Aboyans V, Ricco JB, Bartelink MLEL, Björck M, Brodmann M, Cohnert T, et al. 2017 ESC  
366 Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration  
367 with the European Society for Vascular Surgery (ESVS) Document covering atherosclerotic  
368 disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity  
369 arteries Endorsed by: the European Stroke Organization (ESO) The Task Force for the  
370 Diagnosis and Treatment of Peripheral Arterial Diseases of the European Society of  
371 Cardiology (ESC) and of the European Society for Vascul. *Eur Heart J* [Internet]. 2018 Mar 1  
372 [cited 2023 Apr 8];39(9):763–816. Available from:  
373 <https://academic.oup.com/eurheartj/article/39/9/763/4095038>
- 374 11. Murphy TP, Cutlip DE, Regensteiner JG, Mohler ER, Cohen DJ, Reynolds MR, et al.  
375 Supervised exercise, stent revascularization, or medical therapy for claudication due to  
376 aortoiliac peripheral artery disease: The CLEVER study. *J Am Coll Cardiol.* 2015 Mar  
377 17;65(10):999–1009.
- 378 12. Slysz JT, Tian L, Zhao L, Zhang D, McDermott MM. Effects of supervised exercise therapy  
379 on blood pressure and heart rate during exercise, and associations with improved walking  
380 performance in peripheral artery disease: Results of a randomized clinical trial. *J Vasc Surg.*  
381 2021 Nov 1;74(5):1589-1600.e4.
- 382 13. Jansen SCP, Hoorweg BBN, Hoeks SE, van den Houten MML, Scheltinga MRM, Teijink  
383 JAW, et al. A systematic review and meta-analysis of the effects of supervised exercise  
384 therapy on modifiable cardiovascular risk factors in intermittent claudication. *J Vasc Surg*  
385 [Internet]. 2019 Apr 1 [cited 2023 May 16];69(4):1293-1308.e2. Available from:

- 386 <https://pubmed.ncbi.nlm.nih.gov/30777692/>
- 387 14. Hageman D, Fokkenrood HJP, Gommans LNM, van den Houten MML, Teijink JAW.  
388 Supervised exercise therapy versus home-based exercise therapy versus walking advice for  
389 intermittent claudication. *Cochrane database Syst Rev* [Internet]. 2018 Apr 6 [cited 2023 Apr  
390 3];4(4). Available from: <https://pubmed.ncbi.nlm.nih.gov/29627967/>
- 391 15. Sakamoto S, Yokoyama N, Tamori Y, Akutsu K, Hashimoto H, Takeshita S. Patients with  
392 peripheral artery disease who complete 12-week supervised exercise training program show  
393 reduced cardiovascular mortality and morbidity. *Circ J* [Internet]. 2009 [cited 2023 Apr  
394 3];73(1):167–73. Available from: <https://pubmed.ncbi.nlm.nih.gov/19039192/>
- 395 16. Harwood AE, Totty JP, Pymer S, Huang C, Hitchman L, Carradice D, et al. Cardiovascular  
396 and musculoskeletal response to supervised exercise in patients with intermittent claudication.  
397 *J Vasc Surg* [Internet]. 2019 Jun 1 [cited 2023 May 16];69(6):1899-1908.e1. Available from:  
398 <https://pubmed.ncbi.nlm.nih.gov/30583899/>
- 399 17. Jansen SCP, Abaraogu UO, Lauret GJ, Fakhry F, Fokkenrood HJP, Teijink JAW. Modes of  
400 exercise training for intermittent claudication. *Cochrane Database Syst Rev* [Internet]. 2020  
401 Aug 23 [cited 2023 Aug 13];2020(8). Available from:  
402 <https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD009638.pub3/full>
- 403 18. Harwood AE, Pymer S, Ingle L, Doherty P, Chetter IC, Parmenter B, et al. Exercise training  
404 for intermittent claudication: a narrative review and summary of guidelines for practitioners.  
405 *BMJ open Sport Exerc Med* [Internet]. 2020 Nov 6 [cited 2023 Aug 13];6(1). Available from:  
406 <https://pubmed.ncbi.nlm.nih.gov/33262892/>
- 407 19. Mockford KA, Gohil RA, Mazari F, Khan JA, Vanicek N, Coughlin PA, et al. Effect of  
408 supervised exercise on physical function and balance in patients with intermittent claudication.  
409 *Br J Surg*. 2014 Mar;101(4):356–62.

- 410 20. The Sport and Exercise Scientist n Issue 57 n Autumn 2018 n [www.bases.org.uk](http://www.bases.org.uk) @basesuk  
411 @BASESUK bases\_uk BASESUK. [cited 2023 Aug 13]; Available from:  
412 [www.nice.org.uk/guidance/cg147](http://www.nice.org.uk/guidance/cg147)
- 413 21. Bianco M, Mottola FF, Cerrato E, Giordana F, Cinconze S, Baralis G, et al. Acute coronary  
414 syndrome in very elderly patients-a real-world experience. *Heart Vessels* [Internet]. 2023 Mar  
415 28 [cited 2023 Apr 3]; Available from: <https://pubmed.ncbi.nlm.nih.gov/36976424/>
- 416 22. Fashandi AZ, Mehaffey JH, Hawkins RB, Kron IL, Upchurch GR, Robinson WP. Major  
417 Adverse Limb Events and Major Adverse Cardiac Events after Contemporary Lower  
418 Extremity Bypass and Infrainguinal Endovascular Intervention in Patients with Claudication. *J*  
419 *Vasc Surg* [Internet]. 2018 Dec 1 [cited 2023 Apr 3];68(6):1817. Available from:  
420 [/pmc/articles/PMC6482457/](https://pubmed.ncbi.nlm.nih.gov/306482457/)
- 421 23. Idrissi J, Amine M. Multilayer Perceptron: Architecture Optimization and Training.
- 422 24. Schoenfeld DA. Sample-Size Formula for the Proportional-Hazards Regression Model.  
423 *Biometrics*. 1983 Jun;39(2):499.
- 424 25. Harwood AE, Smith GE, Cayton T, Broadbent E, Chetter IC. A systematic review of the  
425 uptake and adherence rates to supervised exercise programs in patients with intermittent  
426 claudication. *Ann Vasc Surg*. 2016 Jul 1;34:280–9.
- 427 26. Voci D, Fedeli U, Valerio L, Schievano E, Righini M, Kucher N, et al. Mortality rate related to  
428 peripheral arterial disease: A retrospective analysis of epidemiological data (years 2008–  
429 2019). *Nutr Metab Cardiovasc Dis*. 2023 Mar 1;33(3):516–22.
- 430 27. Klaphake S, Fakhry F, Rouwet E V., Van Der Laan L, Wever JJ, Teijink JA, et al. Long-term  
431 Follow-up of a Randomized Clinical Trial Comparing Endovascular Revascularization Plus  
432 Supervised Exercise with Supervised Exercise only for Intermittent Claudication. *Ann Surg*  
433 [Internet]. 2022 Dec 1 [cited 2023 May 1];276(6):E1035–43. Available from:



- 434 [https://journals.lww.com/annalsofsurgery/Fulltext/2022/12000/Long\\_term\\_Follow\\_up\\_of\\_a\\_R](https://journals.lww.com/annalsofsurgery/Fulltext/2022/12000/Long_term_Follow_up_of_a_R)  
435 [andomized\\_Clinical\\_Trial.71.aspx](https://journals.lww.com/annalsofsurgery/Fulltext/2022/12000/Long_term_Follow_up_of_a_R)
- 436 28. van den Houten MML, Hageman D, Gommans LNM, Kleijnen J, Scheltinga MRM, Teijink  
437 JAW. The Effect of Supervised Exercise, Home Based Exercise and Endovascular  
438 Revascularisation on Physical Activity in Patients With Intermittent Claudication: A Network  
439 Meta-analysis. *Eur J Vasc Endovasc Surg*. 2019 Sep 1;58(3):383–92.
- 440 29. Hammond MM, Tian L, Zhao L, Zhang D, McDermott MM. Attendance at Supervised  
441 Exercise Sessions and Walking Outcomes in Peripheral Artery Disease: Results From 2  
442 Randomized Clinical Trials. *J Am Hear Assoc Cardiovasc Cerebrovasc Dis* [Internet]. 2022  
443 Dec 12 [cited 2023 Apr 2];11(24):26136. Available from: [/pmc/articles/PMC9798808/](https://pubmed.ncbi.nlm.nih.gov/39798808/)
- 444 30. McDermott MMG, Criqui MH, Liu K, Guralnik JM, Greenland P, Martin GJ, et al. Lower  
445 ankle/brachial index, as calculated by averaging the dorsalis pedis and posterior tibial arterial  
446 pressures, and association with leg functioning in peripheral arterial disease. *J Vasc Surg*.  
447 2000;32(6):1164–71.
- 448 31. Harwood AE, Smith GE, Cayton T, Broadbent E, Chetter IC. A Systematic Review of the  
449 Uptake and Adherence Rates to Supervised Exercise Programs in Patients with Intermittent  
450 Claudication. *Ann Vasc Surg* [Internet]. 2016 Jul 1 [cited 2023 Jan 2];34:280–9. Available  
451 from: <https://pubmed.ncbi.nlm.nih.gov/27126713/>
- 452 32. Harwood AE, Smith GD, Broadbent E, Cayton TE, Carradice D, Chetter I. Access to  
453 supervised exercise services for peripheral vascular disease patients. *Bull R Coll Surg Engl*  
454 [Internet]. 2017 Jun [cited 2023 Apr 8];99(6):207–11. Available from:  
455 <https://doi.org/10.1308/rcsbull.2017.207>
- 456 33. Waddell A, Seed S, Broom DR, McGregor G, Birkett ST, Harwood AE. Safety of Home-based  
457 Exercise for People with Intermittent Claudication: A Systematic Review. *J Vasc Surg*  
458 [Internet]. 2022 Apr 1 [cited 2023 Apr 8];75(4):1490. Available from:

- 459 <http://www.jvascsurg.org/article/S0741521422000362/fulltext>
- 460 34. Harwood AE, Pymmer S, Ibeggazene S, Ingle L, Caldow E, Birkett ST. Provision of exercise  
461 services in patients with peripheral artery disease in the United Kingdom. *Vascular*. 2022 Oct  
462 1;30(5):874–81.
- 463 35. Harwood AE, Hitchman LH, Ingle L, Doherty P, Chetter IC. Preferred exercise modalities in  
464 patients with intermittent claudication. *J Vasc Nurs* [Internet]. 2018 Jun 1 [cited 2023 May  
465 2];36(2):81–4. Available from: <https://pubmed.ncbi.nlm.nih.gov/29747787/>
- 466 36. Mazari FAK, Gulati S, Rahman MNA, Lee HLD, Mehta TA, McCollum PT, et al. Early  
467 outcomes from a randomized, controlled trial of supervised exercise, angioplasty, and  
468 combined therapy in intermittent claudication. *Ann Vasc Surg* [Internet]. 2010 Jan [cited 2023  
469 Apr 9];24(1):69–79. Available from: <https://pubmed.ncbi.nlm.nih.gov/19762206/>
- 470 37. Mazari FAK, Khan JA, Samuel N, Smith G, Carradice D, McCollum PC, et al. Long-term  
471 outcomes of a randomized clinical trial of supervised exercise, percutaneous transluminal  
472 angioplasty or combined treatment for patients with intermittent claudication due to  
473 femoropopliteal disease. *Br J Surg* [Internet]. 2017 Jan 1 [cited 2023 Apr 9];104(1):76–83.  
474 Available from: <https://pubmed.ncbi.nlm.nih.gov/27763685/>
- 475 38. Thanigaimani S, Phie J, Sharma C, Wong S, Ibrahim M, Huynh P, et al. Network meta-  
476 analysis comparing the outcomes of treatments for intermittent claudication tested in  
477 randomized controlled trials. *J Am Heart Assoc* [Internet]. 2021 May 4 [cited 2023 Apr  
478 3];10(9):19672. Available from:  
479 <https://www.ahajournals.org/doi/abs/10.1161/JAHA.120.019672>
- 480 39. Harwood AE, Broadbent E, Totty JP, Smith GE, Chetter IC. “Intermittent claudication a real  
481 pain in the calf”—Patient experience of diagnosis and treatment with a supervised exercise  
482 program. *J Vasc Nurs*. 2017 Sep 1;35(3):131–5.

- 483 40. Vemulapalli S, Dolor RJ, Hasselblad V, Schmit K, Banks A, Heidenfelder B, et al. Supervised  
484 vs unsupervised exercise for intermittent claudication: A systematic review and meta-analysis.  
485 *Am Heart J*. 2015 Jun 1;169(6):924-937.e3.
- 486 41. Saratzis A, Paraskevopoulos I, Patel S, Donati T, Biasi L, Diamantopoulos A, et al. Supervised  
487 Exercise Therapy and Revascularization for Intermittent Claudication: Network Meta-Analysis  
488 of Randomized Controlled Trials. *JACC Cardiovasc Interv* [Internet]. 2019 Jun 24 [cited 2023  
489 Apr 3];12(12):1125–36. Available from: <https://pubmed.ncbi.nlm.nih.gov/31153838/>
- 490 42. Murphy TP, Cutlip DE, Regensteiner JG, Mohler ER, Cohen DJ, Reynolds MR, et al.  
491 Supervised exercise versus primary stenting for claudication resulting from aortoiliac  
492 peripheral artery disease: Six-month outcomes from the claudication: Exercise versus  
493 endoluminal revascularization (CLEVER) study. *Circulation*. 2012 Jan 3;125(1):130–9.
- 494 43. McDermott MM, Ferrucci L, Tian L, Guralnik JM, Lloyd-Jones D, Kibbe MR, et al. Effect of  
495 Granulocyte-Macrophage Colony-Stimulating Factor with or Without Supervised Exercise on  
496 Walking Performance in Patients with Peripheral Artery Disease: The PROPEL Randomized  
497 Clinical Trial. *JAMA - J Am Med Assoc*. 2017 Dec 5;318(21):2089–98.
- 498 44. Sivagangan P, Harwood AE, Stather PW. Patient and Healthcare Professional Priorities for a  
499 Mobile Phone Application for Patients With Peripheral Arterial Disease. *Cureus* [Internet].  
500 2023 Jan 20 [cited 2023 Apr 3];15(1). Available from:  
501 <https://pubmed.ncbi.nlm.nih.gov/36824553/>
- 502 45. Aalami OO, Lin J, Savage D, Ho V, Bertges D, Corriere M. Use of an app-based exercise  
503 therapy program including cognitive-behavioral techniques for the management of intermittent  
504 claudication. *J Vasc Surg* [Internet]. 2022 Dec 1 [cited 2023 Apr 3];76(6):1651-1656.e1.  
505 Available from: <https://pubmed.ncbi.nlm.nih.gov/35872328/>
- 506 46. Pymer S, Harwood A, Ibeggazene S, McGregor G, Huang C, Twiddy M, et al. High INTensity  
507 Interval Training In pATiEnts with intermittent claudication (INITIATE): protocol for a

- 508 multicentre, proof-of-concept, prospective interventional study. *BMJ Open*. 2020 Jul  
509 6;10(7):e038825.
- 510 47. Harzand A, Vakili AA, Alrohaibani A, Abdelhamid SM, Gordon NF, Thiel J, et al. Rationale  
511 and design of a smartphone-enabled, home-based exercise program in patients with  
512 symptomatic peripheral arterial disease: The smart step randomized trial. *Clin Cardiol*  
513 [Internet]. 2020 Jun 1 [cited 2023 Apr 8];43(6):537–45. Available from:  
514 <https://onlinelibrary.wiley.com/doi/full/10.1002/clc.23362>
- 515 48. Persson AB, Buschmann EE, Lindhorst R, Troidl K, Langhoff R, Schulte KL, et al.  
516 Therapeutic arteriogenesis in peripheral arterial disease: combining intervention and passive  
517 training. <http://dx.doi.org/10.1024/0301-1526/a000092> [Internet]. 2013 Jan 7 [cited 2023 Apr  
518 9];40(3):177–87. Available from: [https://econtent.hogrefe.com/doi/10.1024/0301-  
519 1526/a000092](https://econtent.hogrefe.com/doi/10.1024/0301-1526/a000092)
- 520 49. Mays RJ, Hiatt WR, Casserly IP, Rogers RK, Main DS, Kohrt WM, et al. Community-based  
521 walking exercise for peripheral artery disease: An exploratory pilot study. *Vasc Med (United  
522 Kingdom)* [Internet]. 2015 Aug 10 [cited 2023 Apr 9];20(4):339–47. Available from:  
523 <https://journals.sagepub.com/doi/10.1177/1358863X15572725>
- 524 50. Austin PC. A critical appraisal of propensity-score matching in the medical literature between  
525 1996 and 2003. *Stat Med Stat Med* [Internet]. 2008 [cited 2023 Jul 2];27:2037–49. Available  
526 from: [www.interscience.wiley.com](http://www.interscience.wiley.com)
- 527 51. Stuart EA. Matching methods for causal inference: A review and a look forward. *Stat Sci*  
528 [Internet]. 2010 Feb 2 [cited 2023 Jul 2];25(1):1. Available from: [/pmc/articles/PMC2943670/](https://pubmed.ncbi.nlm.nih.gov/2943670/)
- 529 52. Caliendo M, Kopeinig S. Some Practical Guidance for the Implementation of Propensity Score  
530 Matching. 2005;
- 531 53. Amusa L, North D, Zewotir T. A tailored use of the mahalanobis distance matching for causal

532 effects estimation: A simulation study. Sci African. 2022 Jul 1;16:e01155.

533

534 Legends for figure:

535 Figure 1: Supervised Exercise Therapy Protocol: Outline of each session during weeks 1-6, with an  
536 additional station added each week from week 7 until the patient had completed two full circuits. The  
537 figure illustrates the progression of the supervised exercise therapy protocol used in the study.

538 Figure 2: Independent variable importance analysis using Multilayer perceptron to identify the most  
539 significant predictors of chronic limb threatening ischemia to guide propensity score matching along  
540 with multivariable and logistic regression analyses.

541 Figure 3: Number of cardiovascular events for patients who did and did not complete SET after  
542 median follow up of 2164 days; IC: Intermittent Claudication; CLTI: Chronic limb threatening  
543 ischemia; MALE: Major adverse limb events; MACE: Major adverse cardiovascular events ; SET:  
544 Supervised exercise therapy

545 Figure 4: Survival curves obtained by the Kaplan-Meier method demonstrating time to chronic limb  
546 threatening ischemia(a), time to first major adverse cardiovascular event(MACE)(b) and time to first  
547 major adverse limb event(MALE)(c)

548 Table 1a: Baseline characteristics of both cohorts

Attribute	Patients who did not start SET n = 183	Patients who prematurely discontinued SET N = 19	Patients who completed SET n = 64	p value
Age (years ; Mean $\pm$ SD)	67.95 $\pm$ 10.4	70.1 $\pm$ 7.3	69.5 $\pm$ 7.8	.40
Male	119(65.7%)	12(63.2%)	44(68.8%)	.87
Diabetes Mellitus	54(29.5%)	4(21.1%)	29(45.3%)	.076
Hypertension	131(71.6%)	10(52.6%)	45(70.3%)	.17

Hyperlipidemia	82(44.8%)	6(31.5%)	30(46.8%)	.24
Ischaemic heart disease	101(55.8%)	11(57.9%)	28(43.8%)	.23
Cerebrovascular disease	25(13.7%)	4(21%)	8(12.5%)	.12
Atrial fibrillation	38(20.7%)	2(10.5%)	8(12.5%)	.18
Albumin (g/l; Mean ± SD)	36.9 ± 4.28	37.1 ± 3.3	35.2 ± 3.7	.16
Haemoglobin(g/l) Mean ± SD	132.73 ± 20.6	138.3 ± 19.0	136.5 ± 22.7	.16
Compliance with smoking cessation	45(24.9%)	5(26.3%)	22(34.0%)	.34
ABPI at presentation				
Right	0.79 ± 0.18	0.74 ± 0.19	0.80 ± 0.15	.41
Left	0.81 ± 0.20	0.82 ± 0.29	0.84 ± 0.15	.58
(Mean ,SD)				
Self-reported claudication distance(metres)	77.5 ± 6.75	79.1 ± 7.5	79.4 ± 6.0	.11
(Mean ,SD)				
No iliac disease	37(20.2%)	3(15.7%)	29(45.3%)	<u>.010</u>
Unilateral iliac disease	63(34.4%)	6(31.5%)	8(12.5%)	
Bilateral iliac disease	83(45.4%)	10(52.6%)	26(40.6%)	
No femoral disease	11(6.0%)	1(5.2%)	5(7.8%)	<u>.030</u>
Unilateral femoral disease	76(41.5%)	9(47.3%)	8(12.5%)	
Bilateral femoral disease	96(52.5%)	9(47.3%)	50(78.1%)	
No crural disease	87(47.5%)	10(52.6%)	38(59.3%)	.47
Unilateral crural disease	56(30.6%)	7(36.8%)	13(20.3%)	
Bilateral crural disease	40(21.9%)	2(10.5%)	13(12.5%)	

550 SD: Standard deviation; IQR: Interquartile range; SET: supervised exercise therapy ABPI: Ankle-  
551 brachial pressure index;

552

553

554

555 Table 1b: Impact of propensity score matching on significant confounders

556

Attribute	Non Completion SET(n=49)	Completion SET (n=49)	P value
Haemoglobin (g/l) Mean/SD	130.9 ± 19.3	138.6 ± 18.8	<u>.08</u>
Ischaemic heart disease	59.2%	63.3%	<u>.56</u>
Claudication distance (m) Mean/SD	131.1 ± 19.4	130.2 ± 18.9	<u>.81</u>
Ankle-brachial pressure index Left Right	0.81 ± 0.16 0.71 ± 0.12	0.86 ± 0.15 0.64 ± 0.16	<u>.11</u>

557

558

559

560

561

562

563

564

565

566

[Click here to view linked References](#)

1 **Supervised Exercise Therapy for Intermittent Claudication: A Propensity Score Matched**  
2 **Analysis of Retrospective Data on Long Term Cardiovascular Outcomes**★

3 Short title: Long Term Outcomes Following Supervised Exercise Therapy in Intermittent Claudication

4 **Bharadhwaj Ravindhran \***, Arthur J.M. Lim, Thomas Kurian, Josephine Walshaw, Louise H.  
5 **Hitchman, Ross Lathan, George E. Smith, Daniel Carradice, Ian C. Chetter, Sean Pymer**

6 Academic Vascular Surgical Unit, Allam Diabetes Centre, Hull Royal Infirmary, Hull, UK

7 \* Corresponding author. Academic Vascular Surgical Unit, 2nd Floor, Allam diabetes centre, Hull  
8 Royal Infirmary, Hull HU3 2JZ, UK.

9 Bharadhwaj.Ravindhran@nhs.net (Bharadhwaj Ravindhran).

10 ★This paper was awarded the Norman Williams Prize for the best clinical research paper and is  
11 shortlisted for the BJS Best Manuscript Prize at the Annual Meeting of the Surgical Research Society  
12 in 2023 at Nottingham, UK.

13 **WHAT THIS PAPER ADDS**

14 This study contributes to the current body of literature by conducting an initial assessment of long  
15 term outcomes in patients with intermittent claudication who underwent supervised exercise therapy  
16 (SET), with a focus on cardiovascular morbidity and mortality. The results indicate that completing  
17 SET is associated with a decreased risk of major adverse limb events, major adverse cardiovascular  
18 events, and progression to chronic limb threatening ischaemia based on this retrospective propensity  
19 score matched analysis of patients who completed, discontinued, or declined SET.

20 **Objective:** This study aimed to explore the long term outcomes of patients with intermittent  
21 claudication (IC) who completed supervised exercise therapy (SET) vs. those who declined or  
22 prematurely discontinued SET, focusing on the incidence of chronic limb threatening ischaemia  
23 (CLTI), revascularisation, major adverse limb events (MALE), and major adverse cardiovascular  
24 events (MACE).

25 **Methods:** Retrospective registry analysis of consecutive patients with IC who were referred for SET  
26 between March 2015 and August 2016 and followed up for a minimum of five years. Serial  
27 univariable analysis and logistic regression were performed to identify the statistically significant  
28 clinical variables that were independent predictors of each outcome measure. The resulting  
29 statistically significant variables were used to guide 1:1 propensity score matching (PSM) using the  
30 nearest neighbour method with a calliper of 0.2. Cox proportional hazards regression was used to



31 estimate the hazard ratio (HR) and 95% confidence interval (CI) for the association between SET and  
32 the outcomes of interest.

33 **Results:** Two hundred and sixty-six patients were referred to SET between March 2015 and August  
34 2016. Of these, 64 patients completed SET and 202 patients did not. After PSM, 49 patients were  
35 analysed in each cohort. The Cox proportional hazards analysis revealed a significant association  
36 between completion of SET and revascularisation requirement (HR 0.46 95% CI 0.25 – 0.84;  
37  $p = .011$ ), completion of SET and progression to CLTI (HR 0.091, 95% CI 0.04 – 0.24;  $p < .001$ ),  
38 completion of SET and MACE (HR 0.52; 95% CI 0.28 – 0.99;  $p = .05$ ) and completion of SET and  
39 MALE (HR 0.28, 95% CI 0.13 – 0.65;  $p = .003$ ). The Harrell's C index for all of these models were  
40 greater than 0.75, indicating good predictive accuracy.

41 **Conclusion:** Completion of SET is associated with better outcomes in patients who completed SET  
42 compared to patients who declined or discontinued SET with respect to clinically important  
43 cardiovascular outcomes over seven years.

44 **Keywords:** Exercise therapy, Intermittent claudication, Ischaemia, Outcome assessment, Propensity  
45 score, Resistance training

## 46 INTRODUCTION

47 Intermittent claudication (IC) is an ambulatory, ischaemic muscle pain relieved by rest, which reduces  
48 physical function, walking capacity, balance, and quality of life and increases the risk of mortality  
49 from cardiovascular causes.<sup>1-5</sup> Patients with IC are at risk of disease progression to chronic limb  
50 threatening ischaemia (CLTI) and major adverse limb events (MALE) such as major lower limb  
51 amputation (MLLA), acute limb ischaemia (ALI), or loss of untreated patency.<sup>6,7</sup> The goal of  
52 treatment is therefore to improve symptoms, physical function, and quality of life (QoL), while also  
53 reducing the risk of disease progression and limb loss, mortality and MACE.<sup>8</sup>

54 To achieve this, the National Institute for Health and Care Excellence (NICE) guideline 147<sup>9</sup>  
55 and the European Society for Vascular Surgery (ESVS)<sup>10</sup> recommend supervised exercise therapy

56 (SET) for two hours per week over a three month period as the first line treatment. Evidence shows  
57 that SET is significantly superior for improving walking performance, and therefore symptoms, when  
58 compared with home based exercise and walking advice.<sup>11</sup> Further evidence also shows that SET is  
59 similar to endovascular revascularisation for improving walking distance and, importantly, QoL.<sup>11</sup>  
60 Given the positive effect that SET also has on cardiovascular risk factors,<sup>12,13</sup> it would be reasonable  
61 to assume that this leads to a potential benefit in morbidity, via a reduction in MACE and MALE, as  
62 well as a benefit in mortality. However, the evidence considering the long term effects of SET on  
63 morbidity and mortality is lacking, with just one study considering the association between SET  
64 completion and mortality.<sup>14,15</sup>

65 Therefore, the aim of this study was to investigate whether completion of SET was associated  
66 with better cardiovascular outcomes compared with a group of patients with IC who did not complete  
67 SET using propensity score matching (PSM).

## 68 **MATERIALS AND METHODS**

69 This study was conducted at a tertiary care referral vascular centre. The clinical, intra-operative and  
70 follow up information were gathered, analysed, and compared between patients who completed SET  
71 and patients who either declined or discontinued SET.

### 72 *Patient selection*

73 The data of consecutive patients with IC who were referred for SET between March 2015 and August  
74 2016 (18 months) were retrospectively analysed. Patients who were referred but had CLTI, had  
75 undergone SET within the preceding 12 months, or had a recurrence of symptoms following previous  
76 revascularisation were excluded from this analysis. Patients who were referred for SET but were  
77 deemed unsuitable due to contraindications or the presence of significant comorbidities or missing  
78 data were also excluded. The diagnosis of IC was made clinically, and was further supported by a  
79 resting ankle-brachial pressure index (ABPI) or toe-brachial pressure index, duplex ultrasound, or  
80 cross-sectional imaging if required. Patients who declined SET were either discharged back to their

81 general practitioner, received regular follow up or underwent a revascularisation procedure,  
82 depending on individual need.

83 Patients referred to SET were initially assessed by physicians to identify any obvious  
84 contraindications such as severe frailty, unstable gait, and existing pulmonary and cardiac disorders  
85 (e.g., aortic stenosis, dyspnoea at rest). These contraindications were determined based on clinical  
86 judgement. Furthermore, patients who did not have any obvious contraindications to SET were then  
87 screened by the exercise physiologist prior to starting SET. This screening process aimed to identify  
88 any additional contraindications or factors that may affect the safety or effectiveness of SET for  
89 individual patients. It is important to note that all patients in the study underwent routine screening at  
90 two levels (physician assessment and exercise physiologist screening) to ensure that only those who  
91 were suitable for SET were included.

#### 92 *Supervised exercise therapy*

93 Patients performed SET three times per week for 12 weeks comprising a total of 36 sessions. Missed  
94 sessions were made up at the end of the 12 week programme.<sup>16</sup> The programme was overseen by an  
95 exercise physiologist with support from undergraduate and postgraduate sports science students. SET  
96 sessions involved the completion of a circuit of six two minute stations, separated by two minute  
97 walking intervals. These were preceded by a warm up and followed by a cool down. The stations  
98 included step ups, standing knee bends, sitting knee extensions, biceps curls, cycling, and heel raises  
99 (Fig. 1). As the patient's exercise tolerance improved, an additional station was added each week from  
100 the seventh week and by the end of week 12, they completed two full circuits. Session length  
101 therefore began at 30, progressing up to 60 minutes. Patients were deemed to have successfully  
102 completed SET after accumulating 36 sessions. This circuit based training programme was designed  
103 based on previous recommendations that highlight the effectiveness of combining upper and lower  
104 limb ergometry, resistance exercise, and walking based exercises to improve muscle strength and  
105 cardiorespiratory fitness. These interventions have been shown to elicit a more significant  
106 cardiorespiratory stimulus than walking alone.<sup>17-20</sup>

107 ***Outcome measures***

108 The study investigated the incidence and time to CLTI, MALE, and MACE over a minimum of five  
109 years and up to seven years. CLTI was defined as ischaemic rest pain lasting for two or more weeks,  
110 non-healing wounds, or gangrene that was attributable to objectively proven arterial occlusive disease.  
111 MACE was defined as non-fatal stroke, non-fatal myocardial infarction, or cardiovascular death.<sup>21</sup>  
112 MALE was defined as ALI, untreated loss of patency, or MLLA.<sup>22</sup>

113 ***Statistical analyses***

114 Continuous data were assessed for a normality using the Shapiro–Wilk test and are presented as mean  
115 ± standard deviation or median and range or interquartile range as appropriate. Categorical data are  
116 expressed as numbers and/or percentages. Time to event data is presented using Kaplan–Meier  
117 survival curves. Comparative hypothesis testing was performed using chi-squared tests, t-tests or  
118 Mann–Whitney U tests as appropriate, and log rank tests. Statistical significance was set at  $p < .05$ .  
119 Serial univariable analysis and logistic regression was performed to identify the statistically  
120 significant clinical variables that were independent predictors of each outcome measure. This was  
121 confirmed by performing an independent variable importance analysis using the multilayer perceptron  
122 tool, which is a popular tool in machine learning and deep learning for pattern recognition.<sup>23</sup> The  
123 resulting statistically significant variables were used to guide 1:1 PSM using the nearest neighbour  
124 method with a calliper of 0.2. The differences between these two matched groups were compared by  
125 using the Mann–Whitney U test, and categorical data were analysed using the Pearson’s chi square  
126 test, Fisher’s exact test, or continuity correction where appropriate. Survival curves were obtained by  
127 the Kaplan–Meier method and a Cox proportional hazards regression was used to estimate the hazard  
128 ratio (HR) and 95% confidence interval (CI) for the association between SET and the outcomes of  
129 interest. All statistical analyses were performed using Statistical Package for the Social Sciences  
130 (IBM Corp. 2020; Windows Version 27.0) and Medcalc (MedCalc Statistical Software version 19.2.6;  
131 MedCalc Software bv, Ostend, Belgium)

132 **RESULTS**

133 Two hundred and eighty-two patients presented to the vascular outpatient clinic with IC between  
134 March 2015 and August 2016 and were referred for SET. Sixteen patients were deemed unsuitable for  
135 SET due to advanced comorbidities, mobility problems, and dementia. Two hundred and sixty-six  
136 patients were deemed suitable and were offered SET, of which 83 (31%) attended and 183 (69%)  
137 declined. Of those that attended, 64 (77%) patients successfully completed SET, while 19 (23%)  
138 prematurely discontinued. Baseline characteristics of those who completed and those who declined or  
139 prematurely discontinued SET are presented in [Table 1](#). The primary reasons for the low adoption of  
140 SET were related to location or travel (44.3%;  $n = 81$ ), individuals declining due to lack of  
141 interest/belief in the SET (39.3%;  $n = 72$ ), work/personal commitments resulting in a lack of time for  
142 SET (12.6%;  $n = 23$ ), inability to participate due to musculoskeletal issues (2.2%;  $n = 4$ ), and patients  
143 already enrolled in a community exercise programme (1.6%;  $n = 3$ ). Considering that nearly all  
144 patients who discontinued SET did so without attending at least 50% of the sessions, it was deemed  
145 appropriate to combine both groups, i.e., those who discontinued and those who declined SET, for the  
146 purpose of analysis.

147 Serial univariable and logistic regression analyses revealed that CLTI had the greatest number  
148 of statistically significant predictor variables than the other outcomes, and, therefore, these significant  
149 predictors were used to guide PSM, which was performed to account for the independent association  
150 between these variables and outcome measures. Haemoglobin, self reported claudication distance,  
151 ABPI, presence of ischaemic heart disease (IHD), neutrophil to lymphocyte ratio, compliance with  
152 smoking cessation and non-completion of SET were found to be statistically significant predictors of  
153 CLTI based on serial univariable analyses. Logistic regression analysis performed using these  
154 variables indicated that haemoglobin, self reported claudication distance, ABPI and the presence of  
155 IHD were significant predictors of CLTI. This was confirmed via an independent variable importance  
156 analysis ([Fig. 2](#)). The multilayer perceptron (MLP) algorithm is employed to evaluate the relative  
157 contribution of independent variables in predicting CLTI. By assigning weights to each input variable  
158 based on their importance, the MLP algorithm provides valuable insights into the significant of each

159 variable. This importance analysis helps identify the variables with the greatest impact on CLTI  
160 occurrence.

161 After PSM based on these variables, 49 patients were analysed in each cohort. There was no  
162 difference between groups with respect to haemoglobin (g/L) ( $130.9 \pm 19.3$  vs.  $138.6 \pm 18.8$ ;  
163  $p = .080$ ), IHD (59.2% vs. 63.3%  $p = .56$ ), self reported claudication distance (metres) ( $131 \pm 19.4$   
164 vs.  $130 \pm 18.9$ ;  $p = .81$ ), and ABPI ( $0.7 \pm 0.1$  vs.  $0.7 \pm 0.2$ ;  $p = .29$ ) (Table 2). The Cox proportional  
165 hazards analysis revealed a significant association between completion of SET and progression to  
166 CLTI (HR 0.091, 95% CI 0.04 – 0.24;  $p < .001$ ), completion of SET and MACE (HR 0.52; 95% CI  
167 0.28 – 0.99;  $p = .050$ ) and completion of SET and MALE (HR 0.28, 95% CI 0.13 – 0.65;  $p = .003$ ).  
168 The Kaplan–Meier curves demonstrated a consistent and statistically significant difference in  
169 outcomes among those who completed SET, compared with those who did not complete SET (Fig. 3).  
170 The Harrell’s C index for all of these models were greater than 0.75 indicating good predictive  
171 accuracy.

172 To assess the adequacy of sample size, a *post hoc* power analysis was conducted, revealing  
173 that a total of 48 events and a sample size of 36 patients in the SET completion cohort and 186  
174 patients in the non-completion cohort were required to detect a significant association between SET  
175 and outcomes. This estimation followed the methodology outlined by Schoenfeld *et al.*,<sup>24</sup> assuming a  
176 significance level of .05, 80% power, a 16% incidence of SET completion among referred patients,<sup>25</sup> a  
177 relative hazard of 3, a median survival of 12 years, and a planned follow up of seven years (Fig.  
178 4).<sup>1,5,26,27</sup>

## 179 DISCUSSION

180 This study demonstrates that completion of SET is associated with a reduced risk of experiencing  
181 MALE, MACE, and progression to CLTI. This study is thought to represent one of the first  
182 evaluations of long term outcomes following SET with a focus on cardiovascular morbidity and  
183 mortality in individuals with peripheral arterial disease. While the data suggest a positive effect of  
184 SET, it is important to acknowledge that the patients in this cohort may differ in ways that have not

Commented [ACG1]: AQ: please check the citation inserted for Figure 4

185 been accounted for, and their outcomes may have been influenced by factors beyond SET. It is  
186 important to note that even with rigorous PSM, confounding by indication cannot be completely  
187 adjusted for, as there may be unmeasured covariates that affect both the variable and outcome of  
188 interest. Although this analysis provides important insights and suggests an association, the efficacy  
189 of SET for improving cardiovascular outcomes cannot be established. Nevertheless, these findings  
190 provide a strong rationale for increasing the delivery of SET and conducting further research to better  
191 understand its potential long term benefits. Moving forward, efforts should be directed towards  
192 reducing SET barriers (such as the time commitment) to maximise patient engagement. By doing so,  
193 it may be able to optimise the effectiveness of SET and improve outcomes for a broader range of  
194 patients.

195         Currently, high quality evidence shows that SET provides an important benefit with respect to  
196 maximum walking distance (MWD), pain free walking distance and QoL compared to home-based  
197 exercise therapy and walking advice.<sup>14,28</sup> Better SET compliance, measured by attendance at exercise  
198 sessions, is significantly associated with greater improvements in MWD and adherence to SET may  
199 imply better adherence of several factors in life, such as to smoking cessation, healthy diet and  
200 medication, resulting in better outcomes.<sup>29</sup> However, even patients at the lowest tercile of exercise  
201 attendance demonstrate a significant improvement in MWD.<sup>30</sup> Despite this evidence, and the guidance  
202 provided by NICE and the ESVS,<sup>9,10</sup> SET provision is not consistent in the UK, with less than 50% of  
203 vascular centres offering it and less than 25% of these adhering to the recommended exercise dose.<sup>31</sup>  
204 The low availability of SET in the UK can be attributed to various constraints faced in a centralised  
205 hub and spoke model. These constraints include running costs and a lack of resources and qualified  
206 personnel.<sup>32-34</sup> When SET is offered, patients may not want to participate due to a lack of availability  
207 near their home or the required time commitment, which contributes to the poor uptake rates seen.<sup>25,35</sup>  
208 Further research is needed to explore ways to address or minimise the constraints felt by patients and  
209 providers to improve the accessibility and acceptability of SET.

210         During the last two decades there has been a substantial increase in the number of studies  
211 comparing primary interventional therapy to SET. The results of these studies suggest that SET is

212 comparable to primary percutaneous transluminal angioplasty (PTA) for improving in walking  
213 distance and QoL.<sup>36-38</sup> This suggests that the current first line treatment strategy of SET is advocated.  
214 However, poor uptake and adherence to SET, poor patient fitness, and patient preference are cited as  
215 reasons for using a “PTA first” strategy in patients with IC.<sup>39-41</sup> Based on the results of the current  
216 study, even if a PTA first strategy is pursued due to these constraints, the integration of an exercise  
217 intervention may yield additional improvements in long term cardiovascular outcomes, which may not  
218 occur with PTA alone.

219         Recent evidence has also demonstrated that SET produces a notable improvement in  
220 cardiovascular risk factors, such as cholesterol levels and resting and exercising blood pressure.<sup>12,13</sup>  
221 Interestingly, the greater the improvement in cardiovascular health, the greater the improvement in  
222 walking performance.<sup>12</sup> Despite this evidence for a reduction in cardiovascular risk factors, there is  
223 limited data to support the reduction of long term cardiovascular risk following SET.<sup>42,43</sup> The  
224 reduction in cardiovascular morbidity and mortality following SET demonstrated in this study could  
225 be attributable to these beneficial effects on cardiovascular risk factors.

226         Determining the percentage of outcomes that are directly associated with the completion of  
227 SET is difficult, given the presence of unmeasured confounding variables that may impact the  
228 findings, such as patient motivation. Even amongst highly motivated patients, uptake and adherence  
229 to SET can be difficult, underscoring the importance of offering alternative options to patients who  
230 wish to engage in SET but face barriers to compliance and uptake.<sup>34</sup> High intensity interval training  
231 (HIIT) or remotely delivered supervised exercise interventions are alternatives that could offer  
232 promising benefits, specially tailored to the unique needs and conditions of patients who were  
233 previously unable to enrol in SET due to time or travel constraints.<sup>44,45</sup> Currently, a time efficient  
234 HIIT programme is being assessed as a potential alternative for SET, to reduce the time barrier faced  
235 by patients.<sup>46</sup> Early evidence has suggested that this HIIT programme appears to be feasible and well  
236 tolerated in patients with IC, which is to be confirmed via a proof of concept study.<sup>46</sup>

237         Other alternative approaches to delivering SET have been explored, including remote  
238 monitoring, videos, support groups, mobile applications and trackers and virtual reality.<sup>44,47,48</sup> A



239 smartphone enabled home based exercise programme is feasible and effective in patients with  
240 symptomatic peripheral arterial disease, as is a community based walking programme with training,  
241 monitoring, and coaching components.<sup>47,49</sup> These alternative approaches to delivering SET have the  
242 potential to increase patient access and improve adherence. However, they are currently limited to  
243 small proof of concept studies. Further research is needed to explore their effectiveness in fully  
244 powered randomised controlled trials.

#### 245 *Limitations*

246 Although this study provides useful insights, its retrospective nature encompasses several inherent  
247 limitations, including unmeasurable confounding factors, potential biases, and the lack of blinding or  
248 randomisation that can affect the objectivity of the analysis. The limitations associated with the  
249 retrospective nature of this study were addressed by enrolling consecutive patients over an 18 month  
250 period and conducting a meticulous PSM method with a 0.2 calliper. While there are many  
251 alternatives to 1:1 PSM such as mahalanobis distance matching, kernel matching, and covariate  
252 matching, PSM is considered the best approach due to its ability to balance covariates, flexibility in  
253 handling different types of covariates, interpretability, and the opportunity for sensitivity analysis.<sup>50-53</sup>  
254 Despite using rigorous PSM, it is impossible to fully account for confounding by indication. This is  
255 because there might be unmeasured factors that impact both the variable being studied and the  
256 outcome of interest. In the current study, statistically significant variables were included in the PSM  
257 to ensure that factors that had a proven association with the outcome were controlled for. This  
258 approach was taken to minimise the risk of overfitting and to ensure the robustness of the findings.  
259 However, there is potential for type II errors and the possibility of missing relevant variables. The lack  
260 of differences observed in Table 1 after implementing PSM could potentially be attributed to a type II  
261 error. The use of inverse probability weighting is a valid approach that can enhance the robustness of  
262 findings by retaining a larger sample size. However, PSM was chosen for the study due to specific  
263 reasons. PSM allows one to best mimic a randomised controlled trial by matching patients who  
264 completed SET with control patients based on observed characteristics, reducing bias from  
265 confounding variables. While inverse probability weighting could retain a larger sample size, it can

266 introduce challenges such as sensitivity to model specification and unstable estimates with extreme  
267 weights. PSM is believed to be more suitable for this study, considering these factors, although there  
268 are limitations, such as potential bias from unobserved confounding and a reduced sample size.  
269 Additionally, it is important to acknowledge that although this analysis offers valuable insights and  
270 indicates a potential connection, the effectiveness of SET in improving cardiovascular outcomes  
271 cannot be definitively established.

272           This study indicates an association between patients completing SET and better long term  
273 clinical outcomes, such as slower disease progression, and a lower likelihood of experiencing MALE  
274 or MACE. However, due to the potential for unmeasured confounding, that SET leads to an  
275 improvement in cardiovascular health or mitigates adverse long term outcomes in IC cannot be  
276 definitively concluded. Rather, the findings suggest a potential association that warrants further  
277 investigation. Overall, these outcomes underscore the potential significance of SET in relation to  
278 cardiovascular health in patients with IC.

#### 279 **CONFLICT OF INTEREST**

280 None.

#### 281 **FUNDING**

282 None.

#### 283 **ACKNOWLEDGEMENTS**

284 The authors gratefully acknowledge the invaluable contribution of Dr Dror Rosentraub for his  
285 expertise and guidance in the application of statistical methods. The authors would also like to express  
286 their sincere gratitude to the academic vascular surgical unit for their invaluable support and  
287 collaboration throughout the course of this study. Their expertise and guidance have greatly  
288 contributed to the successful completion of this research.

#### 289 **REFERENCES**

- 290 1. Criqui MH, Aboyans V. Epidemiology of peripheral artery disease. *Circ Res* 2015;**116**:1509–  
291 26.
- 292 2. Criqui MH, Langer RD, Fronck A, Feigelson HS, Klauber MR, McCann TJ, et al. Mortality  
293 over a period of 10 years in patients with peripheral arterial disease. *N Engl J Med*  
294 1992;**326**:381–6.
- 295 3. Pell JP. Impact of intermittent claudication on quality of life. *Eur J Vasc Endovasc Surg*  
296 1995;**9**:469–72.
- 297 4. Gohil RA, Mockford KA, Mazari F, Khan J, Vanicek N, Chetter IC, et al. Balance impairment,  
298 physical ability, and its link with disease severity in patients with intermittent claudication.  
299 *Ann Vasc Surg* 2013;**27**:68–74.
- 300 5. Meru AV, Mitra S, Thyagarajan B, Chugh A. Intermittent claudication: an overview.  
301 *Atherosclerosis* 2006;**187**:221–37.
- 302 6. Eid MA, Mehta K, Barnes JA, Wanken Z, Columbo JA, Stone DH, et al. The global burden of  
303 peripheral artery disease. *J Vasc Surg* 2023;**77**:1119–26.
- 304 7. McDermott KM, Bose S, Keegan A, Hicks CW. Disparities in limb preservation and  
305 associated socioeconomic burden among patients with diabetes and/or peripheral artery disease  
306 in the United States. *Semin Vasc Surg* 2023;**36**:39–48.
- 307 8. Bevan GH, White Solaru KT. Evidence-based medical management of peripheral artery  
308 disease. *Arterioscler Thromb Vasc Biol* 2020;**40**:541–53.
- 309 9. NICE. Overview. Peripheral arterial disease: diagnosis and management. Guidance [cited 2022  
310 May 7]. Available at: <https://www.nice.org.uk/guidance/cg147> [Accessed 22 November 2023].
- 311 10. Aboyans V, Ricco JB, Bartelink MLEL, Björck M, Brodmann M, Cohnert T, et al. Editor’s  
312 Choice – 2017 ESC guidelines on the diagnosis and treatment of peripheral arterial diseases, in

**Commented [ACG2]:** AQ: Ref. 10 has been updated to the EJVES version of the joint guideline

- 313 collaboration with the European Society for Vascular Surgery (ESVS). *Eur J Vasc Endovasc*  
314 *Surg* 2018;**39**:305–68.
- 315 11. Murphy TP, Cutlip DE, Regensteiner JG, Mohler ER, Cohen DJ, Reynolds MR, et al.  
316 Supervised exercise, stent revascularization, or medical therapy for claudication due to  
317 aortoiliac peripheral artery disease: the CLEVER study. *J Am Coll Cardiol* 2015;**65**:999–1009.
- 318 12. Slysz JT, Tian L, Zhao L, Zhang D, McDermott MM. Effects of supervised exercise therapy  
319 on blood pressure and heart rate during exercise, and associations with improved walking  
320 performance in peripheral artery disease: results of a randomized clinical trial. *J Vasc Surg*  
321 2021;**74**:1589–600.
- 322 13. Jansen SCP, Hoorweg BBN, Hoeks SE, van den Houten MML, Scheltinga MRM, Tejjink  
323 JAW, et al. A systematic review and meta-analysis of the effects of supervised exercise  
324 therapy on modifiable cardiovascular risk factors in intermittent claudication. *J Vasc Surg*  
325 2019;**69**:1293–308.
- 326 14. Hageman D, Fokkenrood HJP, Gommans LNM, van den Houten MML, Tejjink JAW.  
327 Supervised exercise therapy versus home-based exercise therapy versus walking advice for  
328 intermittent claudication. *Cochrane Database Syst Rev* 2018;**4**:CD005263.
- 329 15. Sakamoto S, Yokoyama N, Tamori Y, Akutsu K, Hashimoto H, Takeshita S. Patients with  
330 peripheral artery disease who complete 12-week supervised exercise training program show  
331 reduced cardiovascular mortality and morbidity. *Circ J* 2009;**73**:167–73.
- 332 16. Harwood AE, Totty JP, Pymer S, Huang C, Hitchman L, Carradice D, et al. Cardiovascular  
333 and musculoskeletal response to supervised exercise in patients with intermittent claudication.  
334 *J Vasc Surg* 2019;**69**:1899–1908.
- 335 17. Jansen SCP, Abaraogu UO, Lauret GJ, Fakhry F, Fokkenrood HJP, Tejjink JAW. Modes of  
336 exercise training for intermittent claudication. *Cochrane Database Syst Rev*

- 337 2020;**8**:CD009638.
- 338 18. Harwood AE, Pymer S, Ingle L, Doherty P, Chetter IC, Parmenter B, et al. Exercise training  
339 for intermittent claudication: a narrative review and summary of guidelines for practitioners.  
340 *BMJ open Sport Exerc Med* 2020;**6**:e000897.
- 341 19. Mockford KA, Gohil RA, Mazari F, Khan JA, Vanicek N, Coughlin PA, et al. Effect of  
342 supervised exercise on physical function and balance in patients with intermittent claudication.  
343 *Br J Surg* 2014;**101**:356–62.
- 344 20. British Association of Sport and Exercise Sciences. The BASES Expert Statement on  
345 Exercise Training for People with Intermittent Claudication due to Peripheral Arterial Disease.  
346 Available at:  
347 [https://www.bases.org.uk/imgs/autumn\\_2018\\_7601\\_bas\\_expert\\_statement\\_\\_v2\\_569.pdf](https://www.bases.org.uk/imgs/autumn_2018_7601_bas_expert_statement__v2_569.pdf)  
348 [Accessed 23 November 2023].
- 349 21. Bianco M, Mottola FF, Cerrato E, Giordana F, Cinconze S, Baralis G, et al. Acute coronary  
350 syndrome in very elderly patients-a real-world experience. *Heart Vessels* 2023;**38**:1019–27
- 351 22. Fashandi AZ, Mehaffey JH, Hawkins RB, Kron IL, Upchurch GR, Robinson WP. Major  
352 adverse limb events and major adverse cardiac events after contemporary lower extremity  
353 bypass and infrainguinal endovascular intervention in patients with claudication. *J Vasc Surg*  
354 2018;**68**:1817.
- 355 23. Idrissi J, Amine M. Multilayer perceptron: architecture optimization and training.
- 356 24. Schoenfeld DA. Sample-size formula for the proportional-hazards regression model.  
357 *Biometrics* 1983;**39**:499.
- 358 25. Harwood AE, Smith GE, Cayton T, Broadbent E, Chetter IC. A systematic review of the  
359 uptake and adherence rates to supervised exercise programs in patients with intermittent

**Commented [ACG3]:** AQ: Please ref. 20: I've updated it according to the new link you sent

- 360 claudication. *Ann Vasc Surg* 2016;**34**:280–9.
- 361 26. Voci D, Fedeli U, Valerio L, Schievano E, Righini M, Kucher N, et al. Mortality rate related to  
362 peripheral arterial disease: a retrospective analysis of epidemiological data (years 2008–2019).  
363 *Nutr Metab Cardiovasc Dis* 2023;**33**:516–22.
- 364 27. Klaphake S, Fakhry F, Rouwet E V., Van Der Laan L, Wever JJ, Teijink JA, et al. Long-term  
365 follow-up of a randomized clinical trial comparing endovascular revascularization plus  
366 supervised exercise with supervised exercise only for intermittent claudication. *Ann Surg.*  
367 2022;**276**:E1035–43.
- 368 28. van den Houten MML, Hageman D, Gommans LNM, Kleijnen J, Scheltinga MRM, Teijink  
369 JAW. The effect of supervised exercise, home based exercise and endovascular  
370 revascularisation on physical activity in patients with intermittent claudication: a network  
371 meta-analysis. *Eur J Vasc Endovasc Surg* 2019;**58**:383–92.
- 372 29. Hammond MM, Tian L, Zhao L, Zhang D, McDermott MM. Attendance at supervised  
373 exercise sessions and walking outcomes in peripheral artery disease: results from 2  
374 randomized clinical trials. *J Am Hear Assoc Cardiovasc Cerebrovasc Dis* 2022;**11**:26136.
- 375 30. McDermott MMG, Criqui MH, Liu K, Guralnik JM, Greenland P, Martin GJ, et al. Lower  
376 ankle/brachial index, as calculated by averaging the dorsalis pedis and posterior tibial arterial  
377 pressures, and association with leg functioning in peripheral arterial disease. *J Vasc Surg*  
378 2000;**32**:1164–71.
- 379 31. Harwood AE, Smith GE, Cayton T, Broadbent E, Chetter IC. A Systematic review of the  
380 uptake and adherence rates to supervised exercise programs in patients with intermittent  
381 claudication. *Ann Vasc Surg* 2016;**34**:280–9.
- 382 32. Harwood AE, Smith GD, Broadbent E, Cayton TE, Carradice D, Chetter I. Access to  
383 supervised exercise services for peripheral vascular disease patients. *Bull R Coll Surg Engl*

- 384 2017;**99**:207–11.
- 385 33. Waddell A, Seed S, Broom DR, McGregor G, Birkett ST, Harwood AE. Safety of home-based  
386 exercise for people with intermittent claudication: a systematic review. *J Vasc Surg*  
387 2021;**75**:1490.
- 388 34. Harwood AE, Pymer S, Ibegazene S, Ingle L, Caldow E, Birkett ST. Provision of exercise  
389 services in patients with peripheral artery disease in the United Kingdom. *Vascular*  
390 2022;**30**:874–81.
- 391 35. Harwood AE, Hitchman LH, Ingle L, Doherty P, Chetter IC. Preferred exercise modalities in  
392 patients with intermittent claudication. *J Vasc Nurs* 2018;**36**:81–4.
- 393 36. Mazari FAK, Gulati S, Rahman MNA, Lee HLD, Mehta TA, McCollum PT, et al. Early  
394 outcomes from a randomized, controlled trial of supervised exercise, angioplasty, and  
395 combined therapy in intermittent claudication. *Ann Vasc Surg* 2010;**24**:69–79.
- 396 37. Mazari FAK, Khan JA, Samuel N, Smith G, Carradice D, McCollum PC, et al. Long-term  
397 outcomes of a randomized clinical trial of supervised exercise, percutaneous transluminal  
398 angioplasty or combined treatment for patients with intermittent claudication due to  
399 femoropopliteal disease. *Br J Surg* 2017;**104**:76–83.
- 400 38. Thanigaimani S, Phie J, Sharma C, Wong S, Ibrahim M, Huynh P, et al. Network meta-  
401 analysis comparing the outcomes of treatments for intermittent claudication tested in  
402 randomized controlled trials. *J Am Heart Assoc* 2021;**10**:19672.
- 403 39. Harwood AE, Broadbent E, Totty JP, Smith GE, Chetter IC. “Intermittent claudication a real  
404 pain in the calf?”—Patient experience of diagnosis and treatment with a supervised exercise  
405 program. *J Vasc Nurs* 2017;**35**:131–5.
- 406 40. Vemulapalli S, Dolor RJ, Hasselblad V, Schmit K, Banks A, Heidenfelder B, et al. Supervised  
407 vs unsupervised exercise for intermittent claudication: s systematic review and meta-analysis.

- 408 *Am Heart J* 2015;**169**:924–37.
- 409 41. Saratzis A, Paraskevopoulos I, Patel S, Donati T, Biasi L, Diamantopoulos A, et al. Supervised  
410 exercise therapy and revascularization for intermittent claudication: network meta-analysis of  
411 randomized controlled trials. *JACC Cardiovasc Interv* 2019;**12**:1125–36.
- 412 42. Murphy TP, Cutlip DE, Regensteiner JG, Mohler ER, Cohen DJ, Reynolds MR, et al.  
413 Supervised exercise versus primary stenting for claudication resulting from aortoiliac  
414 peripheral artery disease: Six-month outcomes from the claudication: Exercise versus  
415 endoluminal revascularization (CLEVER) study. *Circulation* 2012;**125**:130–9.
- 416 43. McDermott MM, Ferrucci L, Tian L, Guralnik JM, Lloyd-Jones D, Kibbe MR, et al. Effect of  
417 granulocyte-macrophage colony-stimulating factor with or without supervised exercise on  
418 walking performance in patients with peripheral artery disease: the PROPEL randomized  
419 clinical trial. *JAMA* 2017;**318**:2089–98.
- 420 44. Sivagangan P, Harwood AE, Stather PW. Patient and healthcare professional priorities for a  
421 mobile phone application for patients with peripheral arterial disease. *Cureus* 2023;**15**:e33993.
- 422 45. Aalami OO, Lin J, Savage D, Ho V, Bertges D, Corriere M. Use of an app-based exercise  
423 therapy program including cognitive-behavioral techniques for the management of intermittent  
424 claudication. *J Vasc Surg* 2022;**76**:1651–6.
- 425 46. Pymer S, Harwood A, Ibeggazene S, McGregor G, Huang C, Twiddy M, et al. High Intensity  
426 Interval Training In pATiEnts with intermittent claudication (INITIATE): protocol for a  
427 multicentre, proof-of-concept, prospective interventional study. *BMJ Open* 2020;**10**:e038825.
- 428 47. Harzand A, Vakili AA, Alrohaibani A, Abdelhamid SM, Gordon NF, Thiel J, et al. Rationale  
429 and design of a smartphone-enabled, home-based exercise program in patients with  
430 symptomatic peripheral arterial disease: The smart step randomized trial. *Clin Cardiol*  
431 2020;**43**:537–45.



- 432 48. Persson AB, Buschmann EE, Lindhorst R, Troidl K, Langhoff R, Schulte KL, et al.  
433 Therapeutic arteriogenesis in peripheral arterial disease: combining intervention and passive  
434 training. *Vasa* 2011;**40**:177–87.
- 435 49. Mays RJ, Hiatt WR, Casserly IP, Rogers RK, Main DS, Kohrt WM, et al. Community-based  
436 walking exercise for peripheral artery disease: an exploratory pilot study. *Vasc Med*  
437 2015;**20**:339–47.
- 438 50. Austin PC. A critical appraisal of propensity-score matching in the medical literature between  
439 1996 and 2003. *Stat Med Stat Med* 2008;**27**:2037–49.
- 440 51. Stuart EA. Matching methods for causal inference: a review and a look forward. *Stat Sci*  
441 2010;**25**:1–21.
- 442 52. Caliendo M, Kopeinig S. Some practical guidance for the implementation of propensity score  
443 matching. *J Econ Surv* 2008;**22**:31–72.
- 444 53. Amusa L, North D, Zewotir T. A tailored use of the mahalanobis distance matching for causal  
445 effects estimation: A simulation study. *Sci African*. 2022;**16**:e01155.

446 **Figure 1.** Supervised exercise therapy protocol. Outline of each session during weeks 1–6, with an  
447 additional station added each week from week 7 until the patient had completed two full circuits. The  
448 figure illustrates the progression of the supervised exercise therapy protocol used in the study.

449 **Figure 2.** Independent variable importance analysis using multilayer perceptron to identify the most  
450 significant predictors of chronic limb threatening ischaemia to guide propensity score matching along  
451 with multivariable and logistic regression analyses. SET = supervised exercise therapy.

452 **Figure 3.** Number of cardiovascular events for patients who did and did not complete supervised  
453 exercise therapy (SET) after median follow up of 2 164 days. CLTI = chronic limb threatening  
454 ischemia; MALE = major adverse limb events; MACE = major adverse cardiovascular events.

455 **Figure 4.** Cumulative Kaplan–Meier estimate of (A) time to chronic limb threatening ischaemia, (B)  
 456 time to first major adverse cardiovascular event, and (C) time to first major adverse limb event.

**Table 1. Baseline characteristics of both cohorts.**

<b>Attribute</b>	<b>Patients who did not start SET (n = 183)</b>	<b>Patients who prematurely discontinued SET (n = 19)</b>	<b>Patients who completed SET (n = 64)</b>	<b>p value</b>
Age – y	67.95 ± 10.4	70.1 ± 7.3	69.5 ± 7.8	.40
Male	119 (65.7)	12 (63.2)	44 (68.8)	.87
Diabetes mellitus	54 (29.5)	4 (21.1)	29 (45.3)	.076
Hypertension	131 (71.6)	10 (52.6)	45 (70.3)	.17
Hyperlipidaemia	82 (44.8)	6 (31.5)	30 (46.8)	.24
Ischaemic heart disease	101 (55.8)	11 (57.9)	28 (43.8)	.23
Cerebrovascular disease	25 (13.7)	4 (21)	8 (12.5)	.12
Atrial fibrillation	38 (20.7)	2 (10.5)	8 (12.5)	.18
Albumin – g/L	36.9 ± 4.28	37.1 ± 3.3	35.2 ± 3.7	.16
Haemoglobin – g/L	132.73 ± 20.6	138.3 ± 19.0	136.5 ± 22.7	.16
Compliance with smoking cessation	45 (24.9)	5 (26.3)	22 (34.0)	.34
<b><i>ABPI at presentation</i></b>				
Right	0.79 ± 0.18	0.74 ± 0.19	0.80 ± 0.15	.41
Left	0.81 ± 0.20	0.82 ± 0.29	0.84 ± 0.15	.58

Self reported claudication distance – m	77.5 ± 6.75	79.1 ± 7.5	79.4 ± 6.0	.11
No iliac disease	37 (20.2)	3 (15.7)	29 (45.3)	
Unilateral iliac disease	63 (34.4)	6 (31.5)	8 (12.5)	.010
Bilateral iliac disease	83 (45.4)	10 (52.6)	26 (40.6)	
No femoral disease	11 (6.0)	1 (5.2)	5 (7.8)	
Unilateral femoral disease	76 (41.5)	9 (47.3)	8 (12.5)	.030
Bilateral femoral disease	96 (52.5)	9 (47.3)	50 (78.1)	
No crural disease	87 (47.5)	10 (52.6)	38 (59.3)	
Unilateral crural disease	56 (30.6)	7 (36.8)	13 (20.3)	

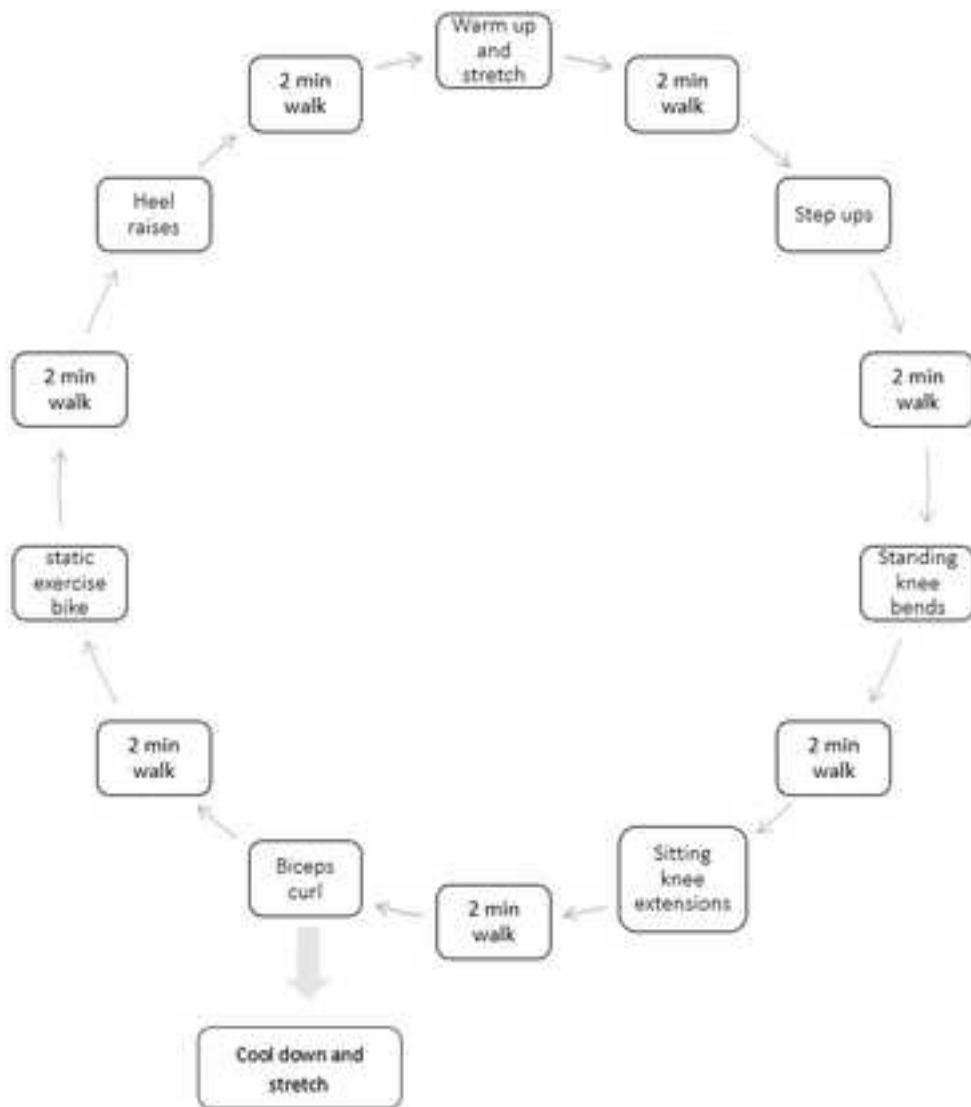
Bilateral crural disease	40 (21.9)	2 (10.5)	13 (12.5)	.47
--------------------------	-----------	----------	-----------	-----

457 Data are presented as mean  $\pm$  SD or *n* (%). SD = standard deviation; IQR = interquartile range; SET =  
458 supervised exercise therapy; ABPI = ankle-brachial pressure index.

<b>Table 2. Impact of propensity score matching on significant confounders.</b>			
<b>Attribute</b>	<b>Non-completion SET (<i>n</i> = 49)</b>	<b>Completion SET (<i>n</i> = 49)</b>	<b><i>p</i> value</b>
Haemoglobin – g/L	130.9 $\pm$ 19.3	138.6 $\pm$ 18.8	.080
Ischaemic heart disease	59.2	63.3	.56
Claudication distance – m	131.1 $\pm$ 19.4	130.2 $\pm$ 18.9	.81
<i>Ankle-brachial pressure index</i>			
Left	0.81 $\pm$ 0.16	0.86 $\pm$ 0.15	
Right	0.71 $\pm$ 0.12	0.64 $\pm$ 0.16	.11

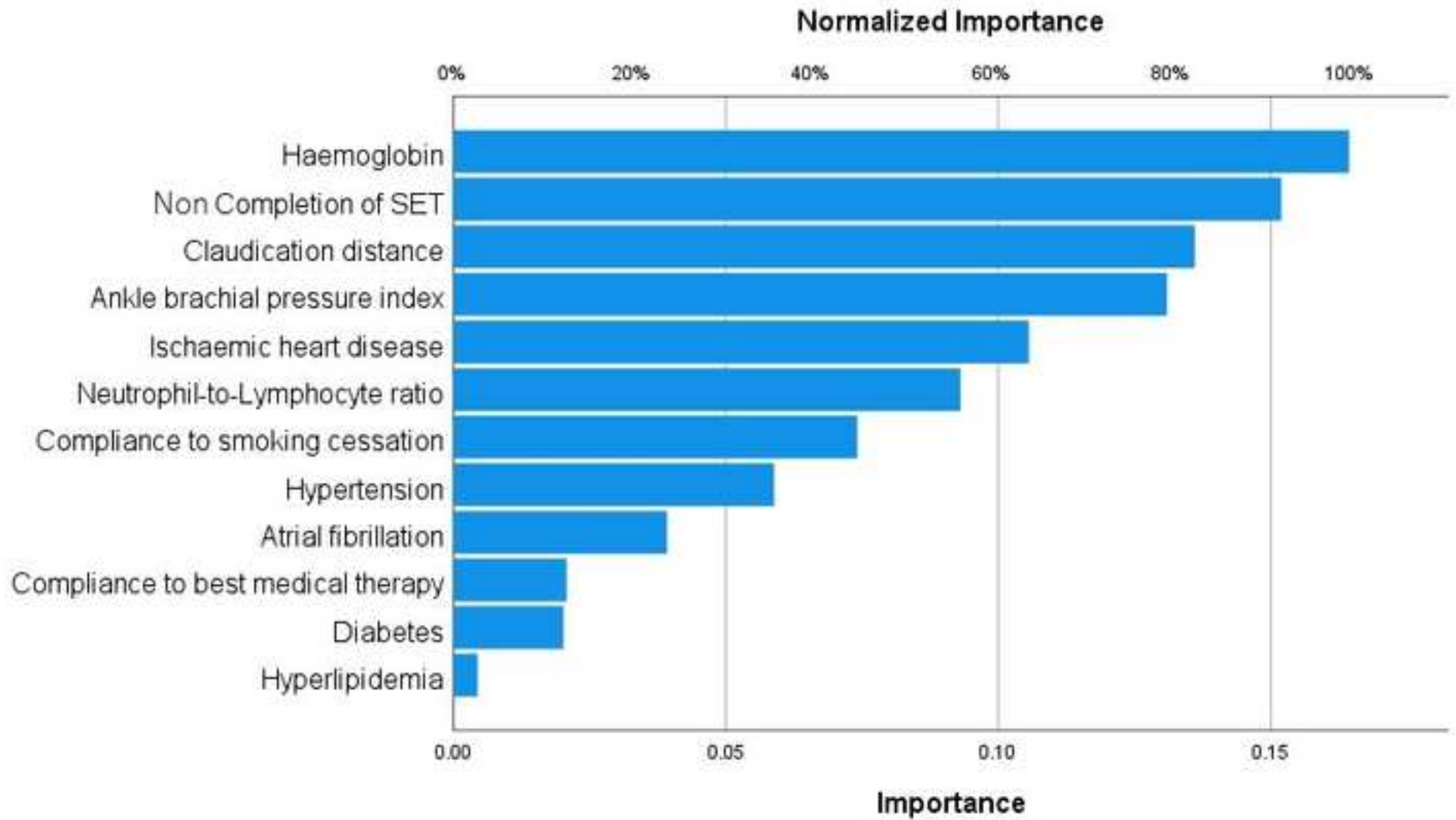
459 Data are presented as mean  $\pm$  SD or *n* (%).

Figure 1: Supervised Exercise Therapy Protocol: Outline of each session during weeks 1-6, with an additional station added each week from week 7 until the patient had



Station	Description
Step ups	Step ups on a 20cm high platform by alternating the lead leg after every 10 repetitions, for a duration of 2 minutes.
Standing knee bends	The patient stands on one leg with support from parallel handrails and flexes and extends the weight-bearing knee for 10 repetitions. This is repeated for 2 minutes before switching to the other leg.
Sitting knee extensions	The patients sit on a high stool with a 2kg weight strapped to their ankle. They fully extend the knee and then flex it for 10 repetitions before switching to the other leg. This is repeated for 2 minutes.
Biceps curl	Patients hold 2kg dumbbells and perform flexion and extension of their elbows continuously for a duration of 2 minutes.
Static exercise bike	The patient cycles on the bike for 2 minutes at a self-selected resistance level, aiming to maintain a target revolution per minute of 60-80.
Heel raises	While holding onto wall bars for stability, the patient stands on a step and rises onto the ball of their foot for 5 seconds before releasing and repeating the movement. This is performed continuously for a duration of 2 minutes.
Warm up and stretch ( Same as cool down and stretch)	1 minute of marching on the spot 1 minute of stepping side to side 1 minute of marching on the spot 2 minutes of walking Stretching – thigh, calf, hamstring, deltoid, hamstring

Figure 2: Independent variable importance analysis using Multilayer perceptron to identify the most significant predictors of chronic limb threatening ischemia to guide



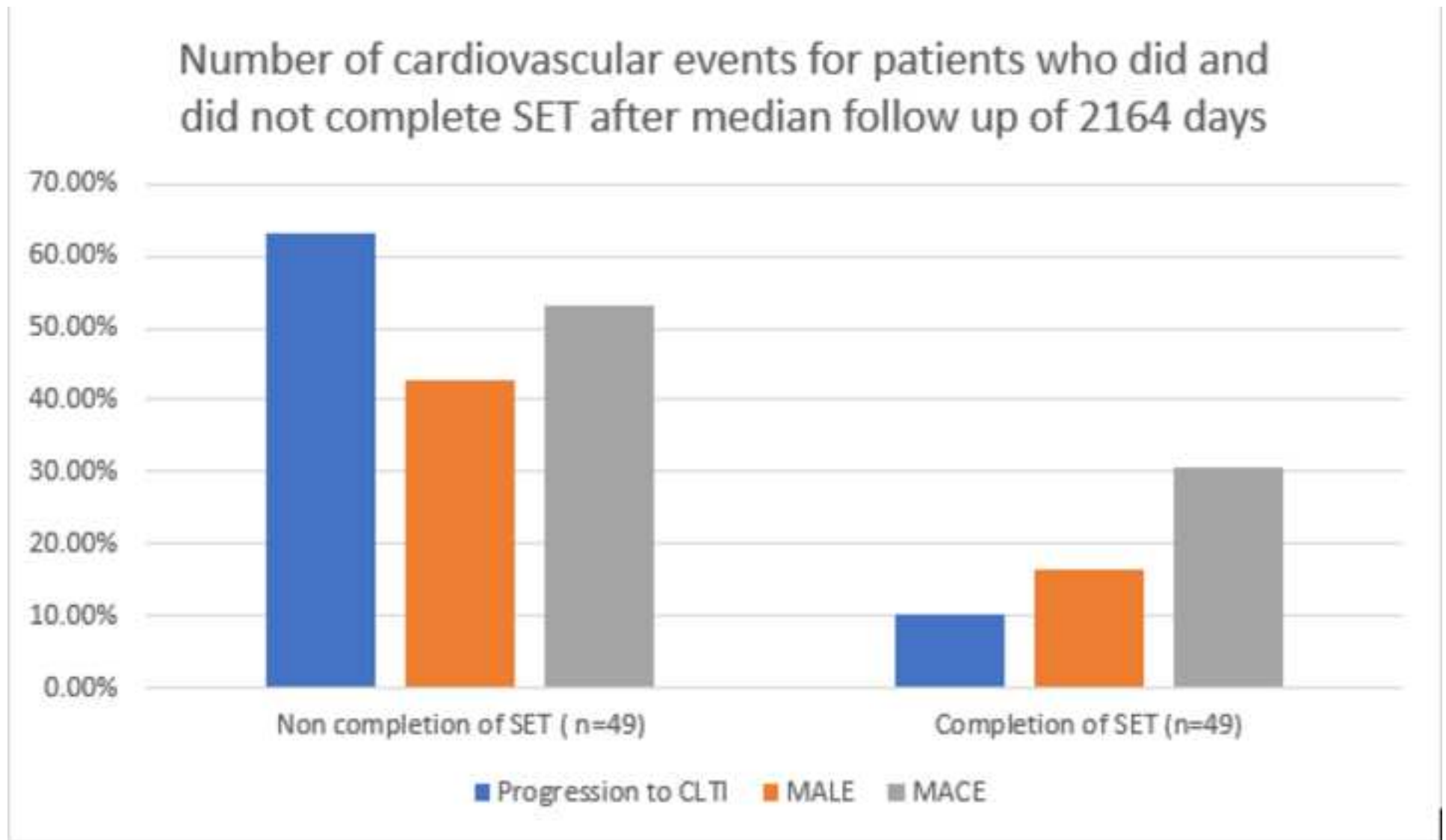
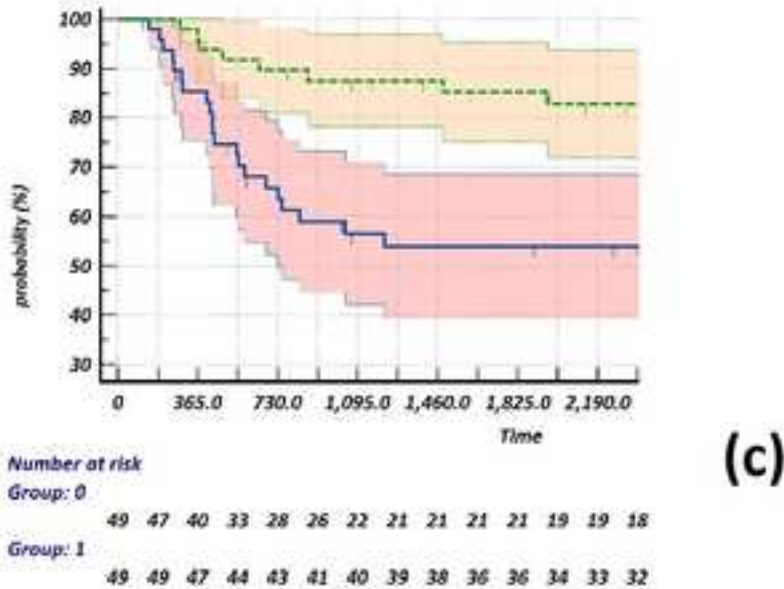
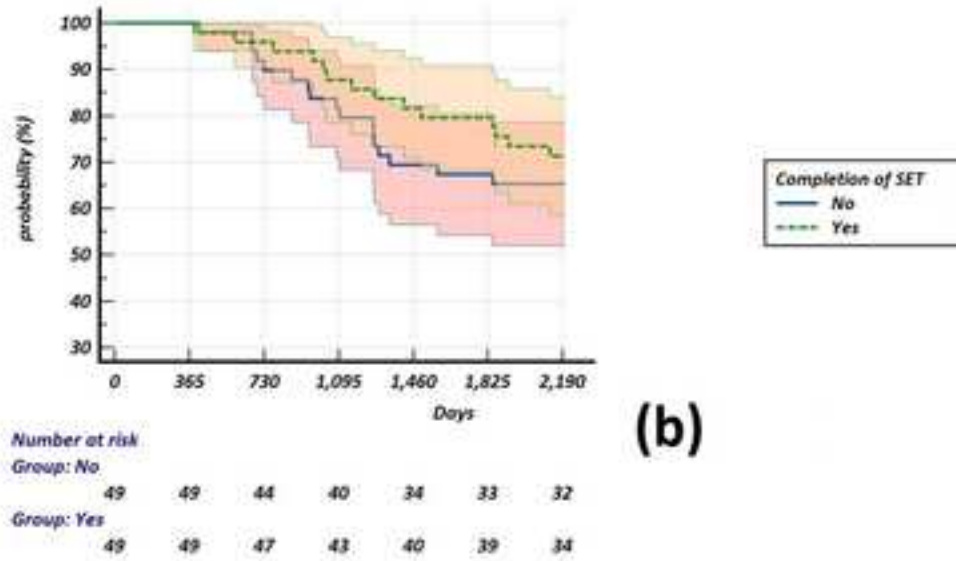
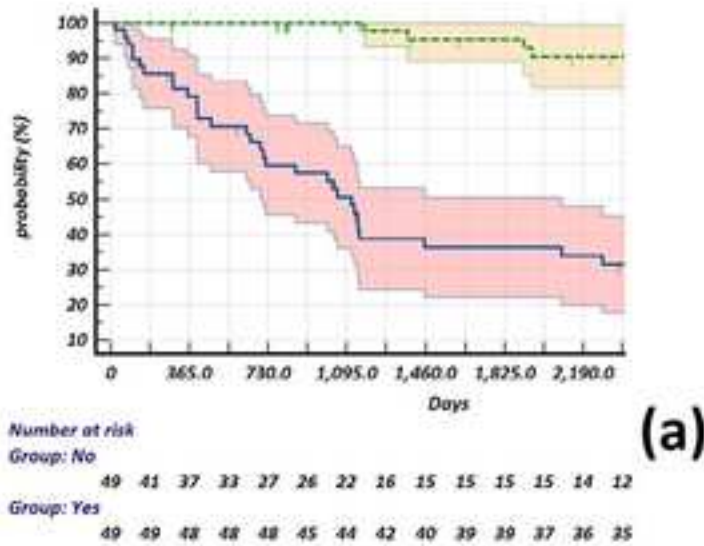


Figure 4: Survival curves obtained by the Kaplan-Meier method demonstrating time to chronic limb threatening ischemia(a), time to

[Click here to access/download;Figure\(s\);Figure 4 \(2\).jpg](#)





Short title: Long Term Outcomes Following Supervised Exercise Therapy in Intermittent Claudication

Use white star with blue outline as the footnote symbol and for the title symbol

**Figure 1:** diagram; insert this space before units cm and kg; use en dash between number ranges

**Figure 2:** Hyperlipidemia to Hyperlipidaemia; delete hyphens and use spaces; Non Completion to Non-completion; Top axis: change to Normalised importance – % and delete % symbols from the axis

**Figure 3:** Follow E1 and E2; delete title

**Figure 4:** Follow H1 and H2; change vertical axes to Probability – %; use thin space not comma in large numbers

The Editorial team

European Journal of Vascular and Endovascular Surgery

Subject: Request for Inclusion of All Original Authors in Manuscript

We are writing to request the inclusion of all the original authors in the manuscript titled "The association between completion of supervised exercise therapy for intermittent claudication and long-term outcomes: A propensity score matched analysis" submitted to the European Journal of Vascular and Endovascular Surgery (EJVES). We firmly believe that these authors have made substantial contributions to the research and meet the criteria for authorship as outlined by the International Committee of Medical Journal Editors

Based on these criteria, we would like to provide a justification for each author's inclusion:

1. Acquisition of data:
  - Bharadhwaj Ravindhran
  - Thomas Kurian
  - Arthur Lim
2. Drafting the manuscript:
  - Bharadhwaj Ravindhran
  - Josie Walshaw
  - Sean Pymer
3. Analysis:
  - Bharadhwaj Ravindhran
  - Daniel Carradice
  - Ian Chetter
  - Sean Pymer
4. Final approval of the version:
  - George Smith
  - Louise Hitchman
  - Ross Lathan
5. Concept and design:
  - Bharadhwaj Ravindhran
  - Daniel Carradice
  - Sean Pymer

We firmly believe that all the listed authors have met the ICMJE criteria for authorship and have made substantial contributions to the manuscript. Their inclusion as authors is essential to acknowledge their significant efforts and ensure the integrity of the research process.

We kindly request the editors to reconsider including all the authors in the publication of this manuscript. We are confident that this decision will be in line with the ICMJE guidelines and will appropriately recognize the contributions of each author.

Thank you for your attention to this matter. We look forward to your favourable response.

Yours Sincerely,

Bharadhwaj Ravindhran

NIHR Academic Clinical Fellow

Specialty trainee in Vascular Surgery

Yorkshire and Humber, United Kingdom

(On behalf of all authors)