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

--Manuscript Draft--

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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.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. Conclusion: 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.

Response to reviewers:

Reviewer 1:

Comment: My main concern cannot be completely adressed due to the nature of the data/design, but the authors did a good job nunancing 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 of 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

2 Multiple Choice Questions and 5 possible answers (highlight correct answer)

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)

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

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

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

Word counts

Abstract: 285

What this paper adds: 37

The text body: 2932

Number of tables and figures: 3 tables and 3 figures

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.

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.

Conclusion: Completion of SET is associated with ~~significant improvements~~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.

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

Introduction:

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[1–5]. 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 ischemia (ALI), or loss of untreated patency[6,7].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.[8]

To achieve this, the National Institute for Health and Care Excellence (NICE) guideline 147[9] and the European society for vascular surgery (ESVS)[10] recommend supervised exercise therapy (SET) for 2-hours per week over a 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 home-based exercise and walking advice[11]. Further evidence also shows that SET is comparable to endovascular revascularisation for improving walking distance and importantly, QoL[11]. Given the positive effect that SET also has on cardiovascular risk factors,[12,13] 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[14,15].

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 IC that did not complete SET

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

Methods:

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.

Patient selection:

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

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

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

Supervised exercise therapy:

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

Outcome measures:

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

Statistical analyses:

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

expressed as numbers and/or percentages. Time to event data is presented using Kaplan-Meier survival curves. Comparative hypothesis testing was performed using Chi-squared tests, t-tests or Mann Whitney U tests as appropriate, and log- rank tests. Statistical significance was set at $p = < .05$. Serial univariable analysis and logistic regression was performed to identify the statistically significant clinical variables that were independent predictors of each outcome measure. This was confirmed by performing an independent variable importance analysis using the multilayer perceptron tool, which is a popular tool in machine learning and deep learning for pattern recognition.[23] 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. The differences between these two matched groups were compared by using the Mann–Whitney U test, and categorical data were analysed using the Pearson's Chi-square test, the Fisher's exact test, or continuity correction where appropriate. Survival curves were obtained by the Kaplan-Meier method and 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. All statistical analyses were performed using Statistical Package for the Social Sciences (IBM Corp. 2020; Windows Version 27.0) and Medcalc (MedCalc Statistical Software version 19.2.6; MedCalc Software bv, Ostend, Belgium;)

Results:

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

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

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

After PSM based on these variables, 49 patients were analysed in each cohort. There was no difference between groups with respect to haemoglobin (g/l) (130.9 ± 19.3~~132 ± 19.3~~ vs 138.6 ± 18.8~~130 ± 18.8~~; *p* = .080), IHD (59.2% vs 63.3% *p* = .56), self-reported claudication distance (metres) (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 proportional hazards analysis revealed a significant association between 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 Kaplan-Meier curves demonstrated a consistent and statistically significant difference in

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

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

Discussion:

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

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

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

Recent evidence has also demonstrated that SET produces a notable improvement in cardiovascular risk factors, such as cholesterol levels and resting and exercising blood pressure[12,13]. Interestingly, the greater the improvement in cardiovascular health, the greater the improvement in walking

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

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

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

Limitations

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

randomisation that can affect the objectivity of our analysis. The limitations associated with the retrospective nature of this study were addressed by enrolling consecutive patients over an eighteen-month period and conducting a meticulous PSM method with a 0.2 calliper. While there are many alternatives to 1:1 PSM such as mahalanobis distance matching, kernel matching and covariate matching, propensity score matching is considered the best approach due to its ability to balance covariates, flexibility in handling different types of covariates, interpretability, and the opportunity for sensitivity analysis.[50–53] Despite using rigorous propensity score matching, it is impossible to fully account for confounding by indication. This is because there might be unmeasured factors that impact both the variable being studied and the outcome of interest. In our study, we 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. The lack of differences observed in Table 1b after implementing PSM could potentially be attributed to a type II error. The use of inverse probability weighting (IPW) is a valid approach that can enhance the robustness of findings by retaining a larger sample size. However, we chose PSM for our study due to specific reasons. PSM allows us to best mimic a randomized controlled trial by matching patients who completed SET with control patients based on observed characteristics, reducing bias from confounding variables. While IPW could retain a larger sample size, it can introduce challenges such as sensitivity to model specification and unstable estimates with extreme weights. We believe PSM is more suitable for our study, considering these factors, although we acknowledge limitations such as potential bias from unobserved confounding and a reduced sample size. Additionally, it is important to acknowledge that although this analysis offers valuable insights and indicates a potential connection, we cannot definitively establish the effectiveness of SET in improving cardiovascular outcomes.

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

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

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Legends for figure:

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 completed two full circuits. The figure illustrates the progression of the supervised exercise therapy protocol used in the study.

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

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

Figure ~~4~~3: Survival curves obtained by the Kaplan-Meier method demonstrating time to chronic limb threatening ischemia(a), time to first major adverse cardiovascular event(MACE)(b) and time to first major adverse limb event(MALE)(c)

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 ± 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 Left (Mean ,SD)	 0.79 ± 0.18 0.81 ± 0.20	 0.74 ± 0.19 0.82 ± 0.29	 0.80 ± 0.15 0.84 ± 0.15	 .41 .58
Self-reported claudication distance(metres) (Mean ,SD)	77.5 ± 6.75	79.1 ± 7.5	79.4 ± 6.0	.11
No iliac disease Unilateral iliac disease Bilateral iliac disease	37(20.2%) 63(34.4%) 83(45.4%)	3(15.7%) 6(31.5%) 10(52.6%)	29(45.3%) 8(12.5%) 26(40.6%)	.010
No femoral disease Unilateral femoral disease Bilateral femoral disease	11(6.0%) 76(41.5%) 96(52.5%)	1(5.2%) 9(47.3%) 9(47.3%)	5(7.8%) 8(12.5%) 50(78.1%)	.030
No crural disease Unilateral crural disease	87(47.5%) 56(30.6%) 40(21.9%)	10(52.6%) 7(36.8%) 2(10.5%)	38(59.3%) 13(20.3%) 13(12.5%)	.47

~~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			

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

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

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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

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

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*

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

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

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

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

~~Word counts~~

~~Abstract: 285~~

~~What this paper adds: 37~~

~~The text body: 2932~~

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

WHAT THIS PAPER ADDS~~:~~

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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 ischaemia based on this retrospective propensity score matched analysis of patients who completed, discontinued, or declined SET.

~~Abstract:~~

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

Methods: ~~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~~ were 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 0.2. ~~A~~ Cox proportional hazards regression was used to estimate the hazard ratio (HR) and 95% confidence interval (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:~~HR 0.46 95% CI 0.25 – 0.84; ~~*p*~~ *p* ~~=~~= .011), completion of SET and progression to CLTI (~~HR:~~HR 0.091, 95% CI 0.04 – 0.24; ~~*p*~~ *p* < ~~=~~.001), completion of SET and MACE (~~HR:~~HR 0.52; 95% CI 0.28 – 0.99; *p* = ~~p =~~.05) and completion of SET and MALE (~~HR:~~HR 0.28, 95% CI 0.13 – 0.65; *p* = ~~p =~~.003). The Harrell's C-index for all of these models were greater than 0.75, indicating good predictive accuracy.

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Conclusion: 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~~ seven years.

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

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INTRODUCTION

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.[1–5] Patients with IC are at risk of disease progression to chronic limb threatening ischaemia (CLTI) and major adverse limb events (MALE) such as major lower limb amputation (MLLA), acute limb ischaemia (ALI), or loss of untreated patency.[6,7] 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.[8]

To achieve this, the National Institute for Health and Care Excellence (NICE) guideline 147[9] and the European Society for Vascular Surgery (ESVS)[10] recommend supervised exercise therapy (SET) for two hours per week over a three month period as the first-line treatment. Evidence shows that SET is significantly superior for improving walking performance, and therefore symptoms, when compared with home-based exercise and walking advice.[11] Further evidence also shows that SET is similar to endovascular revascularisation for improving walking distance and, importantly, QoL.[11] Given the positive effect that SET also has on cardiovascular risk factors,[12,13] 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.[14,15]

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

MATERIALS AND METHODS

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.

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Patient selection~~:~~

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

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

Supervised exercise therapy~~:~~

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

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

Outcome measures~~:~~

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

Statistical analyses~~:~~

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

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

RESULTS~~:~~

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

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

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

After PSM based on these variables, 49 patients were analysed in each cohort. There was no difference between groups with respect to haemoglobin (g/~~l~~L) (130.9 ± 19.3 *vs.* 138.6 ± 18.8; $p = ~~p =~~$ .080), IHD (59.2% ~~*vs*~~*vs.* 63.3% $p = ~~p =~~$ .56), self- reported claudication distance (metres) (131 ± 19.4 ~~*vs*~~*vs.* 130 ± 18.9; $p = ~~p =~~$.81), and ABPI (0.7 ± 0.1 ~~*vs*~~*vs.* 0.7 ± 0.2; $p = ~~p =~~$.29) (Table ~~1b~~2). The Cox proportional hazards analysis revealed a significant association between completion of SET and progression to CLTI (~~HR:~~HR 0.091, 95% CI 0.04 – 0.24; $p < ~~p <~~$.001), completion of SET and MACE (~~HR:~~HR 0.52; 95% CI 0.28 – 0.99; $p = ~~p =~~$.050) and completion of SET and MALE (~~HR:~~HR 0.28, 95% CI 0.13 – 0.65; $p = ~~p =~~$.003). The Kaplan-Meier curves demonstrated a consistent and statistically significant difference in outcomes among~~st~~ those who completed SET, compared ~~to~~ with those who did not complete SET (~~Figure~~ Fig. 3). The Harrell's C- index for all of these models were greater than 0.75 indicating good predictive accuracy.

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

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significance level of .05, 80% power, a 16% incidence of SET completion among referred patients,[25] a relative hazard of 3, a median survival of 12 years, and a planned follow- up of ~~7~~ seven years (Fig. 4).[15,26,27]

DISCUSSION

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

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

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

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

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

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

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

Limitations

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

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

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

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

CONFLICT OF INTEREST

None.

FUNDING

None.

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~~Legends for figure:~~

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 completed two full circuits. The figure illustrates the progression of the supervised exercise therapy protocol used in the study.

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

Figure 3~~:~~ . Number of cardiovascular events for patients who did and did not complete supervised exercise therapy (SET) ~~SET~~ after median follow up of 2 164 days~~;~~ . ~~IC: Intermittent Claudication;~~ CLTI~~:~~ = ~~Chronic~~ chronic limb threatening ischemia; MALE~~:~~ = ~~Major~~ major adverse limb events; MACE~~:~~ = ~~Major~~ major adverse cardiovascular events~~; SET: Supervised exercise therapy~~.

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

~~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~~mellitus	54 (29.5~~%~~)	4 (21.1~~%~~)	29 (45.3~~%~~)	.076

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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/lL; Mean ± SD)	36.9 ± 4.28	37.1 ± 3.3	35.2 ± 3.7	.16
Haemoglobin (– g/lL) 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
ABPI at presentation Right Left (Mean ,SD)	0.79 ± 0.18 0.81 ± 0.20	0.74 ± 0.19 0.82 ± 0.29	0.80 ± 0.15 0.84 ± 0.15	.41 .58
Self- reported claudication distance (metres) – m (Mean ,SD)	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)	
No iliac disease Unilateral iliac disease Bilateral iliac disease	37(20.2%) 63 (34.4%)	3(15.7%) 6 (31.5%)	29(45.3%) 8 (12.5%))	.010

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Bilateral iliac disease	83 (45.4)	10 (52.6)	26 (40.6)	
No femoral disease	11 (6.0)	1 (5.2)	5 (7.8)	
~~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%)~~	
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)	
~~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~~%~~)	

-Data are presented as mean ± SD or *n* (%).

SD~~:~~ = ~~Standard~~ standard deviation; IQR~~:~~ = ~~Interquartile~~ interquartile range; SET~~:~~ = supervised exercise therapy; ABPI~~:~~ = ~~A~~ankle~~-~~–brachial pressure index~~:~~.

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

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Table 2. Impact of propensity score matching on significant confounders.

Attribute	Non-completion SET (n = 49)	Completion SET (n = 49)	p value
Haemoglobin (g/L)	130.9 ± 19.3	138.6 ± 18.8	.080
Ischaemic heart disease	59.2	63.3	.56
Claudication distance (m)	131.1 ± 19.4	130.2 ± 18.9	.81
Ankle–brachial pressure index			
Left	0.81 ± 0.16	0.86 ± 0.15	
Right	0.71 ± 0.12	0.64 ± 0.16	.11

Data are presented as mean ± SD or *n* (%).

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

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

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

Word counts

Abstract: 285

What this paper adds: 37

The text body: 2932

Number of tables and figures: 2 tables and 4 figures

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.

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.

Conclusion: 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.

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

Introduction:

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[1–5]. 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 ischemia (ALI), or loss of untreated patency[6,7].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.[8]

To achieve this, the National Institute for Health and Care Excellence (NICE) guideline 147[9] and the European society for vascular surgery (ESVS)[10] recommend supervised exercise therapy (SET) for 2-hours per week over a 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 home-based exercise and walking advice[11]. Further evidence also shows that SET is comparable to endovascular revascularisation for improving walking distance and importantly, QoL[11]. Given the positive effect that SET also has on cardiovascular risk factors,[12,13] 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[14,15].

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 IC that did not complete SET using propensity score matching(PSM).Methods:

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.

Patient selection:

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

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

Supervised exercise therapy:

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

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

Outcome measures:

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

Statistical analyses:

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

test, the Fisher's exact test, or continuity correction where appropriate. Survival curves were obtained by the Kaplan-Meier method and 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. All statistical analyses were performed using Statistical Package for the Social Sciences (IBM Corp. 2020; Windows Version 27.0) and Medcalc (MedCalc Statistical Software version 19.2.6; MedCalc Software bv, Ostend, Belgium;)

Results:

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

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

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

After PSM based on these variables, 49 patients were analysed in each cohort. There was no difference between groups with respect to haemoglobin (g/l) (130.9 ± 19.3 vs 138.6 ± 18.8; p = .080), IHD (59.2% vs 63.3% p = .56), self-reported claudication distance (metres) (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 proportional hazards analysis revealed a significant association between 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 Kaplan-Meier curves demonstrated a consistent and statistically significant difference in outcomes amongst those who completed SET, compared to those who did not complete SET (Figure 3). The Harrell's C-index for all of these models were greater than .75 indicating good predictive accuracy.

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

Discussion:

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

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

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

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

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

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

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

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

Limitations

Although this study provides useful insights, its retrospective nature encompasses several inherent limitations, including unmeasurable confounding factors, potential biases, and the lack of blinding or randomisation that can affect the objectivity of our analysis. The limitations associated with the retrospective nature of this study were addressed by enrolling consecutive patients over an eighteen-month period and conducting a meticulous PSM method with a 0.2 calliper. While there are many alternatives to 1:1 PSM such as mahalanobis distance matching, kernel matching and covariate matching, propensity score matching is considered the best approach due to its ability to balance covariates, flexibility in handling different types of covariates, interpretability, and the opportunity for sensitivity analysis.[50–53] Despite using rigorous propensity score matching, it is impossible to fully account for confounding by indication. This is because there might be unmeasured factors that impact both the variable being studied and the outcome of interest. In our study, we 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. The lack of differences observed in Table 1b after implementing PSM could potentially be attributed to a type II error. The use of inverse probability weighting (IPW) is a valid approach that can enhance the robustness of findings by retaining a larger sample size. However, we chose PSM for our study due to specific reasons. PSM allows us to best mimic a randomized controlled trial by matching patients who completed SET with control patients based on observed characteristics, reducing bias from confounding variables. While IPW could retain a larger sample size, it can introduce challenges such as sensitivity to model specification and unstable estimates with extreme weights. We believe PSM is more suitable for our study, considering these factors, although we acknowledge limitations such as potential bias from unobserved confounding and a reduced sample size. Additionally, it is important to acknowledge that although this analysis offers valuable insights and indicates a potential connection, we cannot definitively establish the effectiveness of SET in improving cardiovascular outcomes.

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

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Legends for figure:

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 completed two full circuits. The figure illustrates the progression of the supervised exercise therapy protocol used in the study.

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

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

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

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 ± 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 Left (Mean ,SD)	 0.79 ± 0.18 0.81 ± 0.20	 0.74 ± 0.19 0.82 ± 0.29	 0.80 ± 0.15 0.84 ± 0.15	 .41 .58
Self-reported claudication distance(metres) (Mean ,SD)	77.5 ± 6.75	79.1 ± 7.5	79.4 ± 6.0	.11
No iliac disease Unilateral iliac disease Bilateral iliac disease	37(20.2%) 63(34.4%) 83(45.4%)	3(15.7%) 6(31.5%) 10(52.6%)	29(45.3%) 8(12.5%) 26(40.6%)	.010
No femoral disease Unilateral femoral disease Bilateral femoral disease	11(6.0%) 76(41.5%) 96(52.5%)	1(5.2%) 9(47.3%) 9(47.3%)	5(7.8%) 8(12.5%) 50(78.1%)	.030
No crural disease Unilateral crural disease Bilateral crural disease	87(47.5%) 56(30.6%) 40(21.9%)	10(52.6%) 7(36.8%) 2(10.5%)	38(59.3%) 13(20.3%) 13(12.5%)	.47

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

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

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

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

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

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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 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 ischaemia based on this retrospective propensity score matched analysis of patients who completed, discontinued, or declined SET.

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

Methods: 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. Serial univariable analysis and logistic regression were 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 0.2. Cox proportional hazards regression was used to

estimate the hazard ratio (HR) and 95% confidence interval (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 0.75, indicating good predictive accuracy.

Conclusion: 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 seven years.

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

INTRODUCTION

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.[1–5] Patients with IC are at risk of disease progression to chronic limb threatening ischaemia (CLTI) and major adverse limb events (MALE) such as major lower limb amputation (MLLA), acute limb ischaemia (ALI), or loss of untreated patency.[6,7] 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.[8]

To achieve this, the National Institute for Health and Care Excellence (NICE) guideline 147[9] and the European Society for Vascular Surgery (ESVS)[10] recommend supervised exercise therapy

(SET) for two hours per week over a three month period as the first line treatment. Evidence shows that SET is significantly superior for improving walking performance, and therefore symptoms, when compared with home based exercise and walking advice.[11] Further evidence also shows that SET is similar to endovascular revascularisation for improving walking distance and, importantly, QoL.[11] Given the positive effect that SET also has on cardiovascular risk factors,[12,13] 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.[14,15]

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

MATERIALS AND METHODS

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.

Patient selection

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

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

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

Supervised exercise therapy

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

Outcome measures

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

Statistical analyses

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

RESULTS

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

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

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

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

To assess the adequacy of sample size, a *post hoc* power analysis was conducted, revealing that a total of 48 events and a sample size of 36 patients in the SET completion cohort and 186 patients in the non-completion cohort were required to detect a significant association between SET and outcomes. This estimation followed the methodology outlined by Schoenfeld *et al.*,[24] assuming a significance level of .05, 80% power, a 16% incidence of SET completion among referred patients,[25] a relative hazard of 3, a median survival of 12 years, and a planned follow up of seven years (Fig. 4).[15,26,27]

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DISCUSSION

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

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

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

During the last two decades there has been a substantial increase in the number of studies 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.[36–38] 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.[39–41] 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.[12,13]
221 Interestingly, the greater the improvement in cardiovascular health, the greater the improvement in
222 walking performance.[12] 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.[42,43] 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.[34] 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.[44,45] 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.[46] 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.[46]

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

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

Limitations

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

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

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

CONFLICT OF INTEREST

None.

FUNDING

None.

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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 completed two full circuits. The figure illustrates the progression of the supervised exercise therapy protocol used in the study.

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

Figure 3. Number of cardiovascular events for patients who did and did not complete supervised exercise therapy (SET) after median follow up of 2 164 days. CLTI = chronic limb threatening 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.

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 – 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
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

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

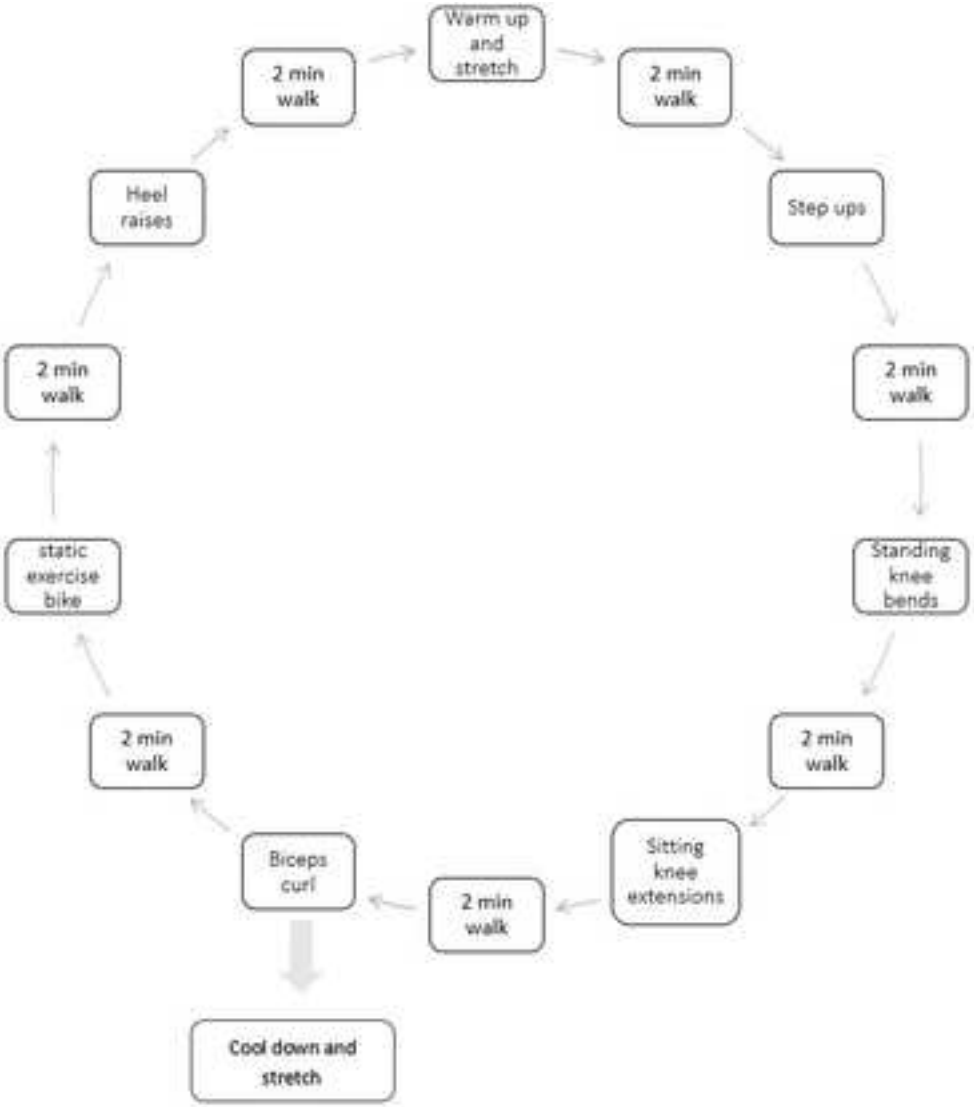
457 Data are presented as mean ± SD or *n* (%). SD = standard deviation; IQR = interquartile range; SET =
458 supervised exercise therapy; ABPI = ankle–brachial pressure index.

Table 2. Impact of propensity score matching on significant confounders.

Attribute	**Non-completion SET (*n* = 49)**	**Completion SET (*n* = 49)**	***p* value**
Haemoglobin – g/L	130.9 ± 19.3	138.6 ± 18.8	.080
Ischaemic heart disease	59.2	63.3	.56
Claudication distance – m	131.1 ± 19.4	130.2 ± 18.9	.81
Ankle–brachial pressure index			
Left	0.81 ± 0.16	0.86 ± 0.15	
Right	0.71 ± 0.12	0.64 ± 0.16	.11

459 Data are presented as mean ± 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

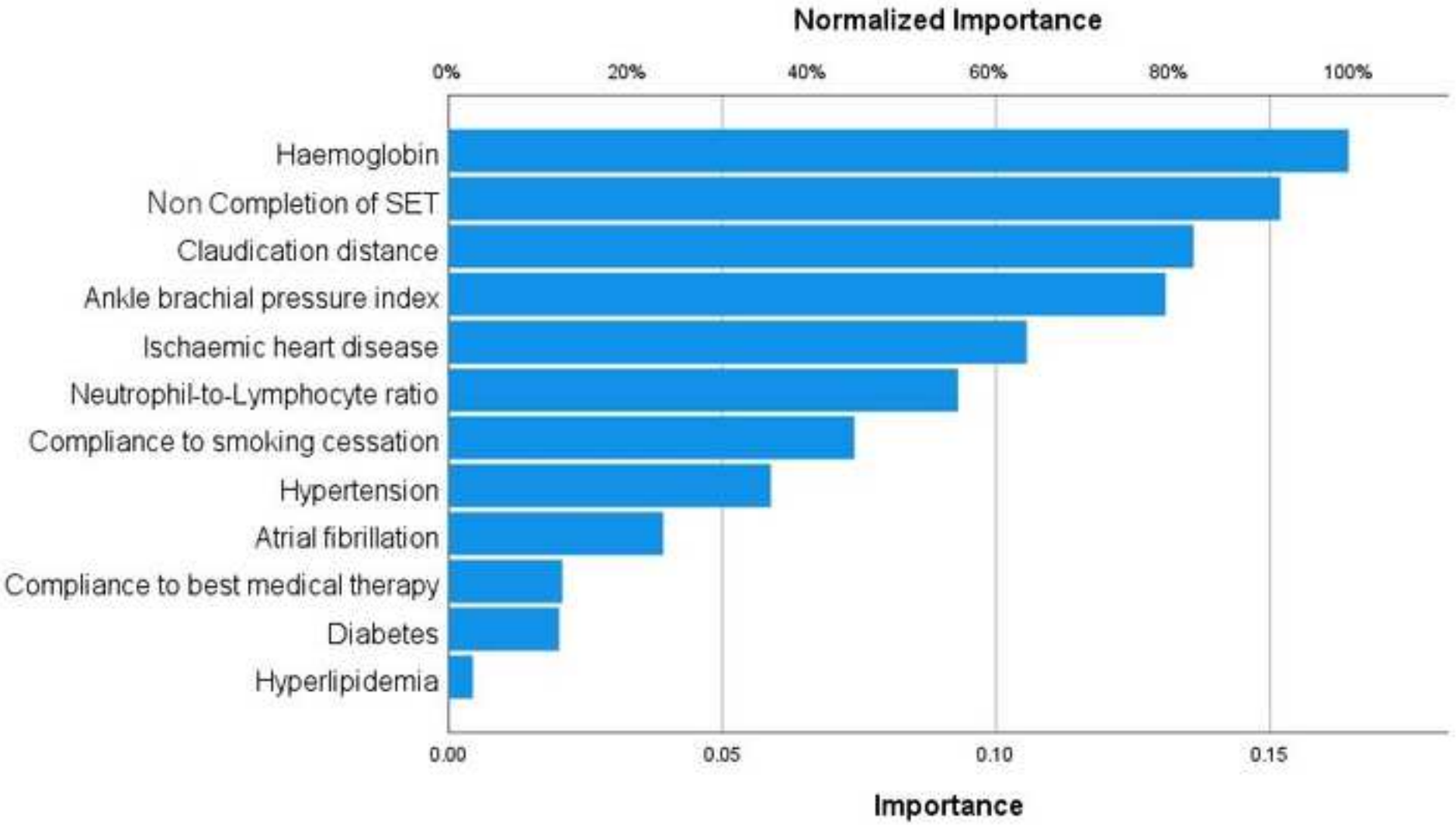


Figure 3: Number of cardiovascular events for patients who did and did not complete SET after median follow up of 2164 days

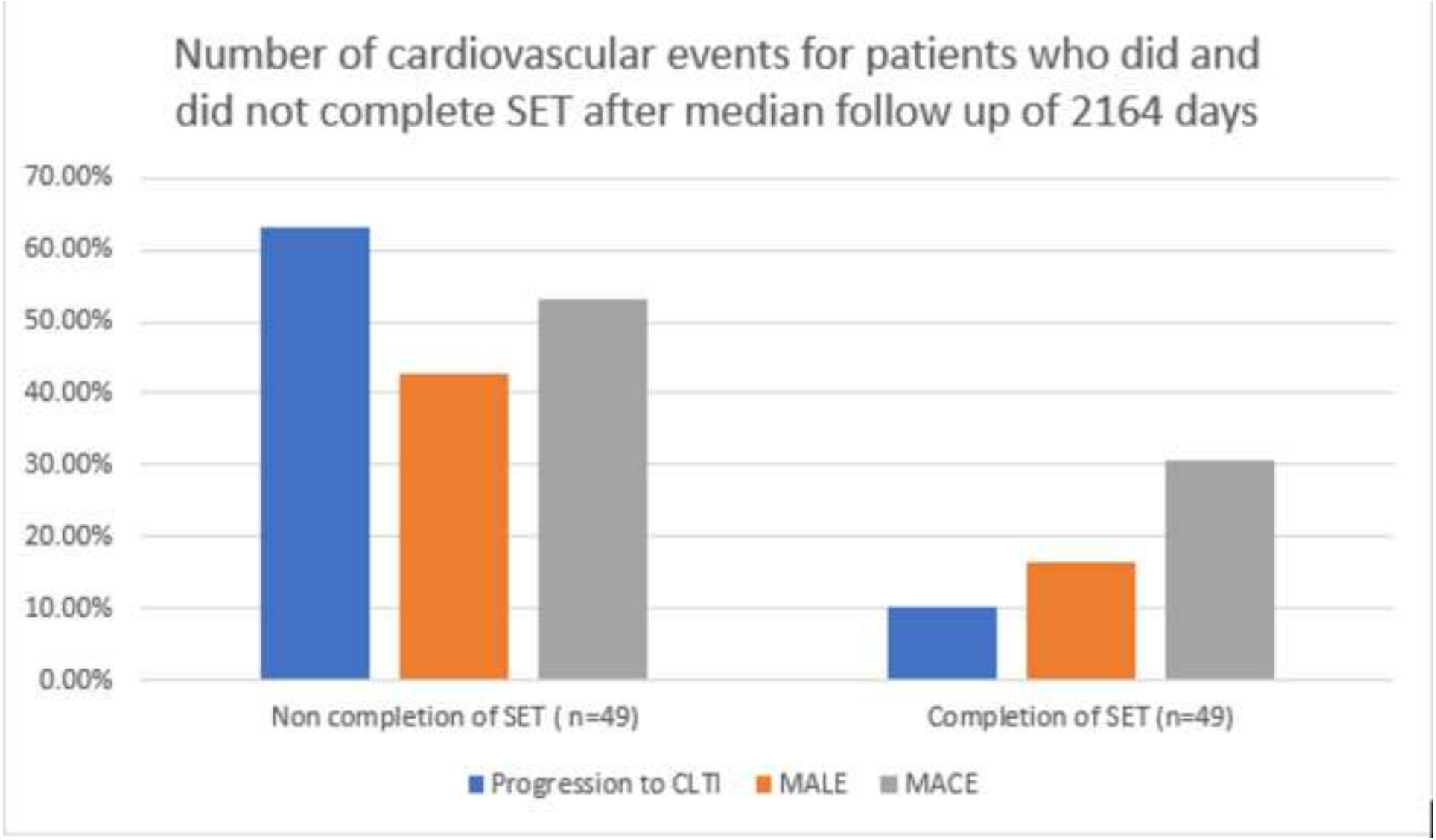
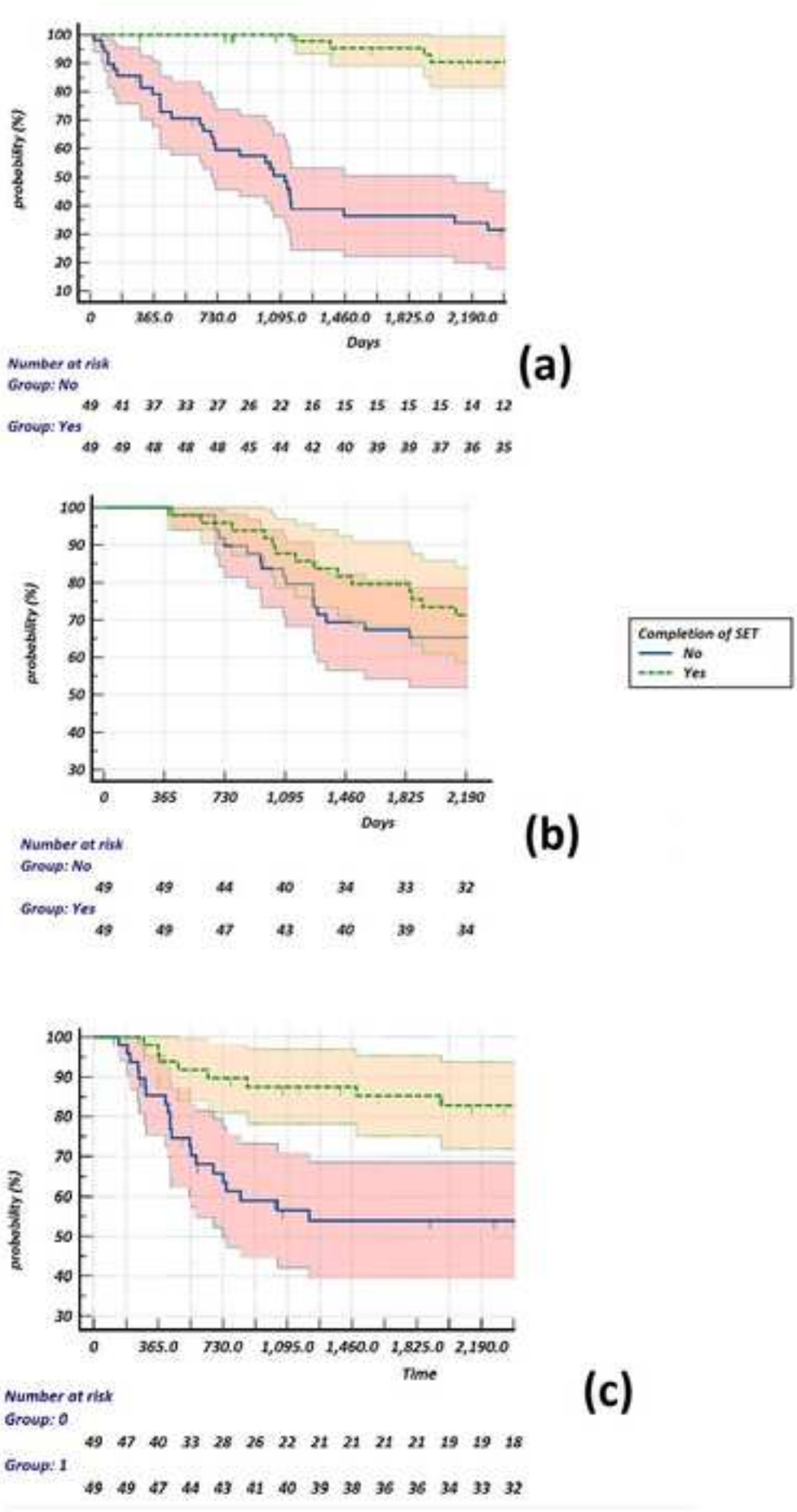


Figure 4: Survival curves obtained by the Kaplan-Meier method demonstrating time to chronic limb threatening ischemia(a), time to



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

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(On behalf of all authors)