SYSTEMATIC REVIEW

The Effect of Supervised Exercise, Home Based Exercise and Endovascular Revascularisation on Physical Activity in Patients With Intermittent Claudication: A Network Meta-analysis

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WHAT THIS PAPER ADDS
Despite extensive research regarding the favourable effect of supervised exercise therapy (SET), home based exercise therapy (HBET), and endovascular revascularisation (ER) on intermittent claudication symptoms, it remains unclear whether they have a meaningful impact on physical activity. The sparse previous research indicates treatment seemingly fails to improve sedentary behaviour. This network meta-analysis allowed for aggregation of all available randomised controlled trials in a single analytical framework. This revealed that SET results in a moderate increase in daily physical activity compared with control. ER and HBET may have similar effects, but low quality evidence and statistical insignificance impeded definite conclusions.

Background: It is unclear whether supervised exercise therapy (SET), home based exercise therapy (HBET), and endovascular revascularisation (ER) for intermittent claudication (IC) have a meaningful impact on physical activity, despite extensive research on their effect on walking performance.
Methods: Multiple databases were searched systematically up to May 2018 for randomised controlled trials with objective measurements of physical activity in patients with IC. A Bayesian network meta-analysis was performed comparing the change in physical activity between baseline and follow up between treatments (SET, HBET, ER) and control (usual care). The standardised mean difference (SMD) with 95% credible interval (CI) was calculated as a summary statistic and converted into steps per day to aid interpretation.
Results: Eight trials involving 656 patients with IC investigating the short-term effect of treatment on daily physical activity were included. Both SET (SMD 0.41, 95% CI 0.10—0.72: this corresponds to a difference of + 803 steps/day on a pedometer) and HBET (SMD 0.50, 95% CI 0.18—0.88: + 980 steps/day) displayed a benefit over control, based on evidence of moderate and low quality, respectively. The benefit of ER compared with control was SMD 0.36 (95% CI −0.22 to 0.99: + 705 steps/day), but only one trial supplied direct evidence, resulting in a low rating of the quality of evidence. Comparisons between treatments yielded no statistically significant differences. The results were robust to several sensitivity analyses.
Conclusion: SET improves daily physical activity levels in patients with IC over control. HBET may have a similar benefit, while invasive treatment failed to lead to a statistically significant improvement of physical activity compared with control. However, the underlying quality of evidence for comparisons with ER and HBET is low, impeding definite conclusions.

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INTRODUCTION

Lower extremity peripheral arterial disease (PAD) is a manifestation of systemic atherosclerosis and thus

associated with high rates of cardiovascular morbidity and mortality.[1,2] Among patients with PAD, greater physical activity levels are associated with reduced functional decline,[3] mortality, and cardiovascular events.[4] Owing to these potential benefits, there is a growing clinical interest in battling inactivity in this population.[5] Unfortunately, intermittent claudication (IC), the most common symptom of PAD, renders patients sedentary, evidenced by diminished daily physical activity levels compared with healthy individuals.[6,7]

Current guidelines recommend supervised exercise therapy (SET) as the preferred initial treatment for patients with IC, reserving endovascular revascularisation (ER) for patients unresponsive to SET.[1] Home based exercise therapy (HBET) is a feasible alternative to SET when the latter is unavailable, as remains the case in most countries.[8] SET, HBET, and ER all aim primarily to increase the distance patients are able to walk at the maximum of their capacity, thereby improving functional status and quality of life.[1] However, walking capacity and daily physical activity are different concepts, evidenced by their minimal correlation in patients with IC.[9] Consequently, successful treatment of claudication symptoms (i.e., improvement of walking capacity) may fail to influence inactive behaviour. Notwithstanding extensive research on their respective clinical effectiveness regarding walking ability, it remains unclear whether SET, HBET, and ER have a meaningful impact on physical activity. Observational studies revealed no statistically significant improvement in daily activity after invasive treatment[10] and SET[11] in patients with IC, despite substantial increases in walking capacity measures. Likewise, improvements after HBET failed to reach statistical significance in recent trials, despite the inherent focus of HBET on increasing ambulatory activity in the home environment.[12,13]

Objectively measured physical activity is only sparsely used as outcome in clinical trials,[5] and, to the authors' knowledge, HBET, SET, and ER have never been compared in one trial. Thus, a standard meta-analysis does not suffice for simultaneous comparison of all three treatment modalities. A network meta-analysis combines direct evidence from head to head trials with "indirect" evidence derived from multiple trials with a common reference treatment. As a consequence, the precision of the inferred treatment effects is increased and inferences regarding the relative effectiveness of several interventions can be made despite the absence of trials comparing all of them directly.[14] The aim of this study was to compare the effects of SET, HBET and ER on physical activity in patients with IC.

MATERIALS AND METHODS

Study design

A systematic review with network meta-analysis of randomised controlled trials (RCTs) was conducted to evaluate the comparative effects of different treatment modalities on daily ambulatory physical activity in patients with IC. The study was performed according to standards described in the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA).[15] The study protocol has been registered at PROSPERO (https://www.crd.york.ac.uk/prospero/) with the registration number CRD42017056355 prior to data synthesis.

Eligibility criteria

A study was eligible for inclusion if it was a parallel group RCT with patients with IC (PAD Fontaine Stage II, Rutherford 1-3) and if it reported both baseline, as well as follow up assessments of an objective measure of free living physical activity (i.e., using an accelerometer or pedometer). Furthermore, a comparison of at least two of the following treatment regimens had to be considered: SET, HBET, ER, or control as common reference treatment.

A study reporting on treatment modalities was considered eligible for inclusion if the following conditions were met: (i) SET, treadmill walking performed under the supervision of trained medical personnel (e.g., physical therapists), either hospital or community based, with a minimum of two supervised sessions per week for at least six weeks; (ii) HBET, the advice to increase walking in the home setting, quantified by keeping a walking diary or using a physical activity tracker (pedometer or accelerometer), prompted by follow up telephone calls or visits by a healthcare professional (at least one follow up contact, with a maximum of twice a week); (iii) invasive treatment, comprised of either endovascular or open revascularisation. Reference treatment was considered "control" in this meta-analysis if no known effective or (oral) placebo treatment was given. No limitations for inclusion on the (non-)use of additional cardiovascular risk modification methods, including the use or non-use of an explicit walking advice, were formulated.

Search strategy, study selection, and data extraction

Multiple databases were searched (Embase, MEDLINE, and Cochrane Central Register of Controlled Trials) from inception to 23 May 2018. Additionally, clinical trial registries (http://www.clinicaltrials.gov and http://www.clinicaltrialsregister.eu) and reference lists of published reviews and meta-analyses were checked for potentially eligible studies. The search terms included variations on PAD and IC, the treatment modalities of interest, and physical activity outcomes (see Appendix S1 for the detailed search strategy). Two investigators (M.v.d.H., D.H.) independently screened titles and abstracts and subsequently retrieved and reviewed the full texts of RCTs evaluating the treatments of interest. Conflicts were solved by consensus. Studies meeting the eligibility criteria were selected, in consultation with a third investigator (L.G.). All relevant data on study, patient, and treatment characteristics, co-interventions, and outcome assessment were extracted and independently checked by the two investigators (M.v.d.H., D.H.).

Outcomes

The primary outcome of interest was the comparative change in objectively measured physical activity between

baseline and follow up. Ambulatory physical activity is a complex health behaviour that is difficult to measure accurately.[16] Self report methods, being subject to recall bias, have been proven to be of limited use for the assessment of physical activity in PAD populations.[6] Therefore, only objective measurements (i.e., pedometers or accelerometers) were included into the primary analysis. The inclusion of trials in which physical activity was assessed through self report was evaluated in a sensitivity analysis.

Quality assessment

Two investigators (M.v.d.H., D.H.) independently assessed the included studies' risks of bias using the Cochrane Collaboration's tool.[17] The characteristics of the included trials were evaluated to assess whether sufficient similarity existed regarding potential effect modifiers to allow network meta-analysis. It was postulated that this so called transitivity would be violated by differences across comparisons regarding the content and duration of the exercise programme, median age of the study population, proportion of male participants, baseline ankle brachial index, comorbidities, duration of follow up, and method of outcome measurement.

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group approach was used to rate the quality of the evidence underlying the estimates from the network meta-analysis. The GRADE tool considers the quality of evidence underlying direct or indirect treatment comparisons factoring; study limitations (risk of bias); the existence of important differences between populations, treatments, outcomes and other potential effect modifiers among studies (indirectness); if trials show similar estimates of treatment effect (consistency, low heterogeneity); and precision of effect estimates (narrow confidence intervals).[18,19]

Statistical analysis

A traditional pairwise meta-analysis was performed for treatment comparisons where direct RCT evidence was available. A random effects models according to DerSimonian and Laird was used for pooling of the continuous outcomes to account for between study variance.[20] Indirect comparisons were calculated using the method described by Bucher et al.[21] Network meta-analysis was performed to incorporate direct and indirect treatment comparisons in a single analytical framework. A range of measurement tools for physical activity were used among trials, with various units (kcal, steps, metabolic equivalents) and time denominators (per day, per hours) reported. Therefore, the standardised mean difference (SMD, Hedges g) was calculated as a summary statistic. The SMD expresses the size of the intervention effect in each study relative to the variability observed. Generally, an SMD of $< .4$ is considered small, $.4–.7$ moderate, and $>.7$ large.[22] SMDs were calculated by dividing reported change from baseline scores by their SDs. Considerable differences between baseline values

existed. Change scores from baseline to follow up take such baseline variability into account, as opposed to the sole use of follow up scores. Furthermore, some studies only reported change scores. To re-express the SMDs as steps per day the outcomes of network meta-analysis were multiplied by the pooled SD of the baseline daily steps in the control groups of included trials where this was reported, as recommended by the Cochrane Handbook.[22]

A Bayesian Markov Chain Monte Carlo (MCMC) model was computed using the gemtc package in R.[23] The gemtc package implements the models recommended by the National Institute for Health and Care Excellence in their technical support document 2,[24] using JAGS (Just Another Gibbs Sampler) to provide the underlying MCMC simulations. JAGS is a software program for analysis of Bayesian hierarchical models. A burn in of 40,000 simulations was used, followed by a further run of 40,000 simulations, which were used for obtaining parameter estimates. Model convergence was assessed using graphical assessment of the MCMC trace, autocorrelation plots, and posterior distributions of the model parameters. If there were any doubts about convergence of the estimates then more simulations were conducted. The analysis used the SMD with corresponding standard error (SE) for each treatment comparison within each trial in a random effects model. In trials with more than two arms, the variance of the control arm was assumed to be the same as the SE for the first treatment comparison. The uncertainty around the effect estimate is expressed with 95% credible intervals (CIs), the Bayesian statistics equivalent of confidence intervals.
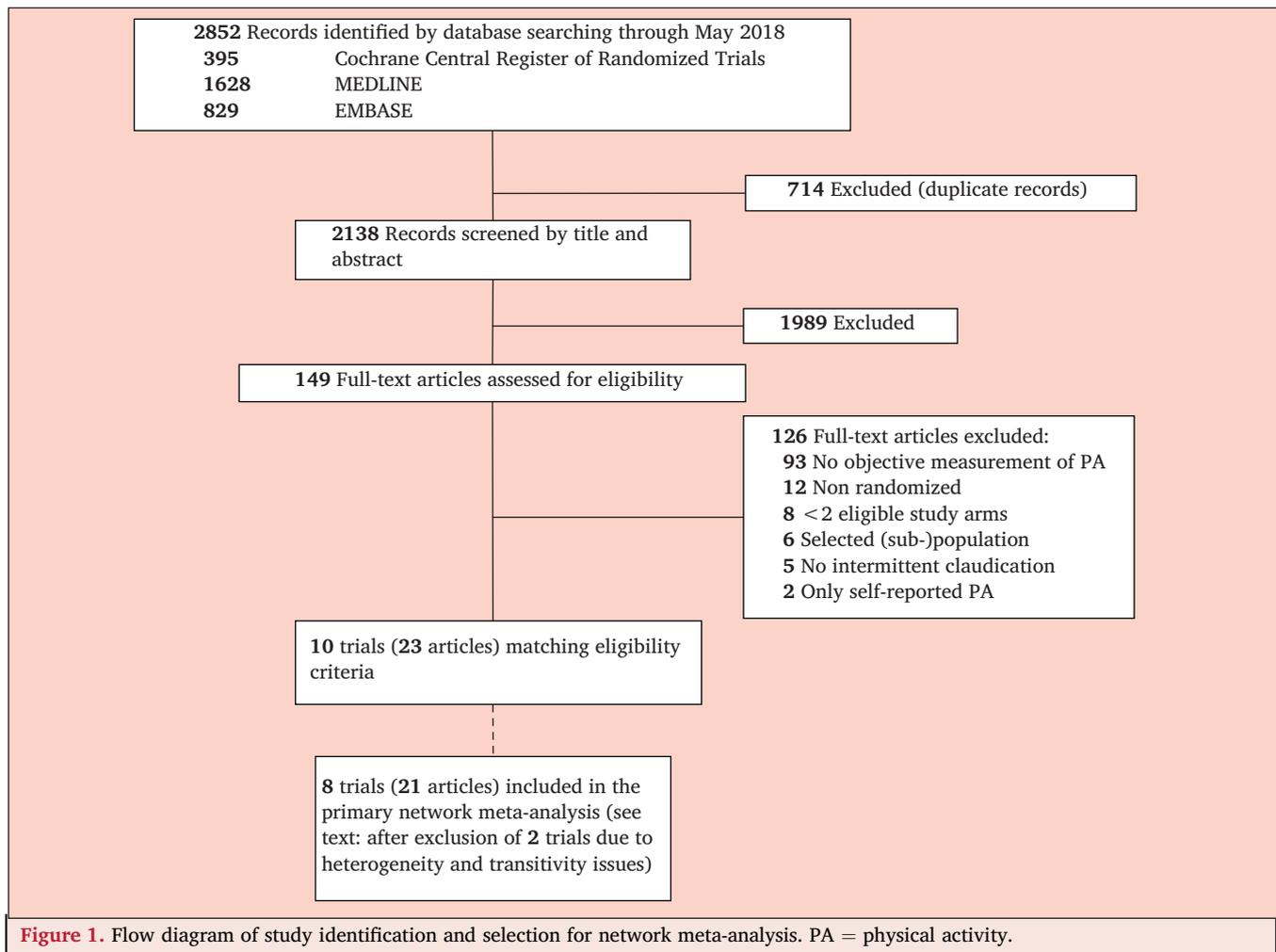
All analyses were performed using intention to treat data. Statistical heterogeneity was assessed with the I^2 statistic. A formal assessment of potential publication bias was omitted owing to the limited number of studies included. To validate the assumption of consistency in the network, the disagreement between direct and indirect evidence was assessed. To this end, the inconsistency factor was calculated between the direct and indirect estimates for closed evidence loops, and expressed as the Z-statistic with its p value. Paucity of data decreases the power to detect inconsistency in network meta-analysis.

Sensitivity analysis

Several sensitivity analyses were performed to assess whether the results of the primary analysis were robust to changes regarding important assumptions. Several parameters were adjusted to determine whether this induced a meaningful change in the results. Including applying a fixed effect model and the inclusion of a trial that assessed physical activity using a self report tool.

RESULTS

Electronic search up to 23 May 2018 retrieved 2,852 citations, 2,138 after removal of duplicates (Fig. 1). A total of 23 citations on 10 trials fulfilled the eligibility criteria. However, significant statistical heterogeneity for the treatment outcome of trials investigating SET vs. control was found

Figure 1. Flow diagram of study identification and selection for network meta-analysis. PA = physical activity.

(I^2 = 93%, p < .00001, Table S1). This reduced to 0% (p = .82) on exclusion of a single study,[25] without obvious reasons for these extreme outlying results. Thus, primary analysis was presented after omission of this study. Indeed, sensitivity analysis revealed that inclusion of this trial led to grossly imprecise outcomes across all comparisons (Appendix S2). Furthermore, a trial by Crowther *et al.*[26] presented the outcomes of a SET programme at the 12 month follow up. Other > 12 month results were sparse, precluding meta-analysis. For the transitivity assumption to hold, these longer-term results were not included in the primary meta-analysis but were described qualitatively.

Thus, a total of eight trials involving 656 patients with IC were included in the primary meta-analysis. Three trials evaluated SET vs. control, two trials compared HBET with control, two trials evaluated HBET vs. SET vs. control, and one trial compared ER with SET and control. Table 1 summarises the key characteristics of studies included in the primary analysis. The risk of bias assessment is presented in Table 2. Blinding of participants is not possible for exercise interventions and was therefore not considered in the overall risk of bias assessment. The clinical trials were deemed sufficiently similar regarding study level intervention characteristics, population characteristics (Table S2),

and trial methodology (follow up duration), ensuring that a network meta-analysis was appropriate. Control treatment was defined differently among trials, consisting of non-exercise usual care (either including advice to walk more[27–30] or excluding such walking advice[25,31]), attention control with light resistance training,[13] and health education sessions.[32,33]

Direct meta-analysis

Conventional pairwise meta-analyses using direct evidence (Table S3) indicated that HBET and SET were both more efficacious than control, with SMDs of 0.53 (95% CI 0.09–0.97) and 0.29 (95% CI 0.09–0.49), respectively. Significant heterogeneity was found for the HBET vs. control estimate (I^2 = 69%). ER showed no statistically significant benefit over control (SMD 0.51, 95% CI −0.04 to 1.05), based on the results of a single trial. There was no significant difference found between SET and HBET (SMD 0.01 95% CI −0.28 to 0.30), or SET and ER (SMD −0.19, 95% CI −0.63 to 0.25).

Network meta-analysis

Table 3 shows the results of the network meta-analyses for the effect of SET, HBET, and ER on daily physical

Table 1. Characteristics of trials included for the primary analysis								
Trial	Patients per treatment arm				Follow up (mo)[b]	Physical activity outcome	Number of monitoring days	Risk of bias
	SET	HBET	ER	Control		Measure (device)[b]		
Regensteiner (1996)[31,a]	10	—	—	10	3	% time active (accelerometer)	1	Moderate
McDermott (2009)[33,a]	12	—	—	6	6	Units/7d (accelerometer)	7	Moderate
Gardner (2011)[28]	33	29	—	30	3	Steps/d (pedometer)	7	Moderate
Gardner (2012)[29]	106	—	—	36	4	Kcal/d (accelerometer)	2	Moderate
Murphy (2012)[30]	38	—	41	20	6	Steps/h (pedometer)	7	Moderate
Cunningham (2012)[27]	—	28	—	30	4	Steps/d (pedometer)	6	High
McDermott (2013)[32]	—	26	—	21	6	Units/7d (accelerometer)	7	Low
Gardner (2014)[13]	60	60	—	60	3	Steps/d (pedometer)	7	Moderate

SET = supervised exercise therapy; HBET = home based exercise therapy; ER = endovascular revascularisation; mo = months; d = day; h = hour.
[a] Three arm trial, third arm not relevant to current meta-analysis.
[b] Used for the primary meta-analysis.

activity in patients with IC considering a follow up of 3—6 months. Compared with control, both SET (SMD 0.41, 95% CI 0.10—0.72) and HBET (SMD 0.50, 95% CI 0.18—0.88) displayed a statistically significant benefit, based on moderate and low quality of evidence, respectively. The benefit of ER on daily physical activity over control was not statistically significant (SMD 0.36, 95% CI −0.22 to 0.99), but only one trial supplied the evidence, resulting in a low rating of the quality of evidence. Network meta-analysis revealed no important differences among the various treatments (SET vs. HBET, SET vs. ER, and HBET vs. ER; see Table 3).

The pooled SD of the baseline mean steps per day of the control groups of Gardner et al.,[13] Cunningham et al.,[27] and Murphy et al.[30] amounted to 1,959 steps/day. Thus, re-expressing the SMDs resulted in a benefit of SET over control of 803 steps/day (95% CI 196—1,410), of HBET over control of 980 steps/day (95% CI 352—1,724), and ER over control of 705 steps/day (95% CI −429 to 1939).

Network consistency

A graphical representation of the networks of direct comparisons is shown in Fig. 2. No inconsistencies between direct and indirect evidence were detected by visual inspection of the forest plots (Table 3). The inconsistency factor was calculated for the closed loops of control vs. SET vs. HBET ($Z = .293$; $p = .77$) and control vs. SET vs. ER ($Z = .198$; $p = .84$), and revealed no evidence of statistical inconsistency between direct and indirect estimates.

Sensitivity analyses

The results of the primary analysis were robust to variations in several parameters assessed through sensitivity analysis. The details of these analyses and the forest plots are presented in the supplementary material (Appendix S2). Notably, the results of ER vs. control were more precise when applying a fixed effect network meta-analysis compared with the primary analysis. Thereby, ER showed

a statistical significant benefit of SMD 0.35 (95% CI 0.08—0.61) over control treatment.

Review of longer term treatment results

The late effects of a HBET programme, from the trial by Cunningham et al.[34] showed an adjusted difference in daily steps of 1,374 (95% CI 528—2,220) at 12 months, and 1,630 (95% CI 495—2,765) at 24 months, compared with control. Similarly, Gardner et al.[35] reported a maintained benefit for SET over control at 18 months follow up (560 ± 87 vs. 408 ± 58 kcal/d; $p < .05$). In contrast, Crowther et al.[26] found no statistically significant effect for SET vs. usual care after 12 months on daily steps.

DISCUSSION

This network meta-analysis represents a comprehensive synthesis of the effect of various treatment modalities on objectively measured daily physical activity in patients with IC. SET showed a moderate effect over usual care control treatments. Potential benefits of HBET appeared similar, but quality of evidence was graded "low" owing to heterogeneity and risk of bias in the underlying trials. No significant differences between the efficacy of ER, SET, and HBET were found. The effect size of ER compared with control based on this study is similar to that of SET and HBET, but not statistically significant. However, only one trial reported objectively measured daily physical activity after ER, which was detrimental for the reliability. In general, the paucity of randomised trials investigating the effect of IC treatment on physical activity undermined the quality of evidence across comparisons. Therefore, cautious interpretation of the results is warranted and facilitated by the reported GRADE scores.

Daily physical activity is increasingly recognised as an important treatment goal and outcome measure in IC management.[5] Nonetheless it has been sparsely investigated in randomised trials where treatment effects generally failed to reach statistical significance owing to inadequate sample size. Aggregation of all available

Table 2. Risk of bias assessment

Study	Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias
	Sequence generation	Allocation concealment	Participants and personnel[a]	Outcome assessment	Incomplete outcome data	Selective reporting
Regensteiner (1996)[31]	?	?	–	?	+	+
McDermott (2009)[33]	?	?	–	+	–	+
Gardner (2011)[28]	+	+	–	?	+	+
Murphy (2012)[30]	+	?	–	?	+	+
Cunningham (2012)[27]	+	+	–	–	+	+
Gardner (2012)[29]	+	+	–	?	+	+
McDermott (2013)[32]	+	+	–	+	+	+
Gardner (2014)[13]	?	?	–	?	+	+

(+) = low risk of bias; (–) = high risk of bias; (?) = unclear risk of bias.
[a] Participants and direct personnel cannot be blinded to exercise interventions, thus this was not factored in the overall assessment of risk of bias.

evidence in this network meta-analysis revealed a statistically significant benefit of SET and HBET compared with control treatments. The current study thus provides novel evidence to indicate that SET and HBET lead to substantial increases equating to some 800 and 1,000 steps per day over control treatment, respectively. This may already be a clinically meaningful improvement, as the baseline mean daily steps among the included studies' populations was approximately 3,000. Few studies investigated the dose response effect of increases in daily steps on (cardiovascular) mortality and morbidity, but the available evidence supports a graded inverse relationship.[36,37] To further increase the benefits confirmed by this meta-analysis, the aims of IC treatment need to extend beyond merely improving walking distance limitations. Interestingly, HBET has an inherent larger focus on increasing physical activity in the home environment than SET, but failed to show more benefit in this meta-analysis. Home based programmes stimulate patients to quantify home exercise using techniques such as walking diaries and pedometers.[12,13,28] Modern ambulatory devices, such as wearable accelerometers and smartphone apps, make monitoring of daily life

behaviour increasingly accessible. These devices can function as potentiators of health behaviour change, but probably only when incorporated into larger engagement strategies.[38,39] Indeed, such technology adjunctive to SET has recently shown promising results,[40] but failed to improve physical activity in a HBET programme with limited in person guidance.[41] The benefits of exercise therapy on daily activity found in the current study may be potentiated by incorporating the supervised use of new wearable devices.

The effects of percutaneous revascularisation on daily physical activity in claudication patients are poorly studied. Despite a thorough systematic search with a wide scope, only one randomised trial was identified by the current study.[30] Subsequent network meta-analysis revealed no statistically significant difference between ER compared with SET, HBET, or control treatment. Even so, the lack of direct evidence was detrimental for the reliability of the inferred summary effect. This is indicative of the general tendency in research on invasive treatment in vascular disease to focus on anatomical and haemodynamic end points rather than functional measures. Indeed, clinical

Table 3. Standardised mean differences produced by random effects network meta-analysis of physical activity using direct and indirect comparisons

| Comparison	Estimate		SMD (95% CI)	Quality of evidence
SET vs. control	Network meta-analysis		0.41 (0.10−0.72)	⊕⊕⊕⊖[a]
	Direct evidence		0.29 (0.09−0.49)	⊕⊕⊕⊖[a]
	Indirect evidence		0.54 (0.01−1.07)	⊕⊕⊕⊖
		−1.50 Favours control 0.00 Favours SET 1.50		
HBET vs. control	Network meta-analysis		0.50 (0.18−0.88)	⊕⊕⊖⊖
	Direct evidence		0.53 (0.09−0.97)	⊕⊕⊖⊖[a,c]
	Indirect evidence		0.28 (−0.07 to 0.63)	⊕⊕⊖⊖[a,d]
		−1.50 Favours control 0.00 Favours HBET 1.50		
ER vs. control	Network meta-analysis		0.36 (−0.22 to 0.99)	⊕⊕⊖⊖
	Direct evidence		0.51 (−0.04 to 1.05)	⊕⊕⊖⊖[a,d]
	Indirect evidence		0.48 (−0.20 to 1.16)	⊕⊕⊖⊖[a,d]
		−1.50 Favours control 0.00 Favours ER 1.50		
SET vs. HBET	Network meta-analysis		−0.06 (−0.52 to 0.38)	⊕⊕⊖⊖
	Direct evidence		0.01 (−0.28 to 0.30)	⊕⊕⊖⊖[a,d]
	Indirect evidence		−0.16 (−0.47 to 0.15)	⊕⊕⊖⊖[a,d]
		−1.50 Favours HBET 0.00 Favours SET 1.50		
SET vs. ER	Network meta-analysis		0.05 (−0.56 to 0.60)	⊕⊕⊖⊖
	Direct evidence		−0.19 (−0.63 to 0.25)	⊕⊕⊖⊖[a,d]
	Indirect evidence		−0.22 (−0.80 to 0.36)	⊕⊕⊖⊖[a,d]
		−1.50 Favours ER 0.00 Favours SET 1.50		
HBET vs. ER	Network meta-analysis		0.13 (−0.50 to 0.81)	⊕⊖⊖⊖
	Direct evidence		NA	NA
	Indirect evidence		−0.06 (−0.66 to 0.54)	⊕⊖⊖⊖[a,b,d]
		−1.50 Favours ER 0.00 Favours HBET 1.50		

SMD = standardised mean difference; CI = credible interval; SET = supervised exercise therapy; HBET = home based exercise therapy; ER = endovascular revascularisation; NA = not applicable; ⊕⊕⊕⊕ = high quality; ⊕⊕⊕⊖ = moderate quality; ⊕⊕⊖⊖ = low quality; ⊕⊖⊖⊖ = very low quality.
Forest plots showing the relative effect of each treatment strategy on objective measurements of free living physical activity among patients with intermittent claudication. Direct estimates and indirect estimates are shown and combined in the results of the network meta-analyses. Quality of evidence was established using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool for network meta-analysis.[18] Quality can be downgraded by one point for each of: [a] Study limitations (contributing evidence of moderate quality); [b] indirectness; [c] inconsistency and/or heterogeneity; [d] imprecision.

trials investigating new percutaneous therapies mainly report on arterial patency and the consequent need for repeat revascularisation, all important indicators of technical success. Unfortunately, the degree of lumen narrowing (i.e., patency) is poorly related to function and symptomatology, thus repeat revascularisation is often not truly 'clinically driven'.[42] Even the ankle brachial index, a parameter that integrates the haemodynamic impact of all stenoses in the limb into a single measure, shows poor correlation with walking function.[42,43] Arguably, the most

used functional outcomes, exercise capacity on standardised treadmill tests or during corridor walking, are a poor reflection of patients' actual daily disability as well.[9,44] Future studies should incorporate an assessment of physical activity as it is an important modifiable risk factor and treatment goal in IC and objective measurements are readily available.

Based on this network meta-analysis, SET and HBET are probably preferred treatments when attempting to increase ambulatory physical activity in patients with IC. ER failed to
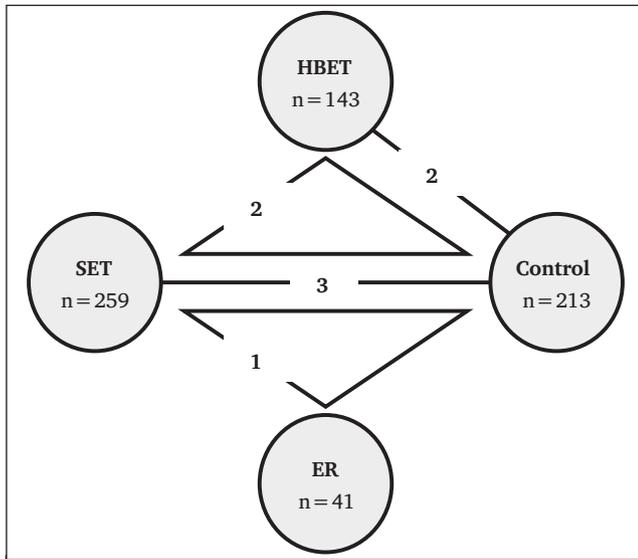
Figure 2. Graphical representation of the distribution of the primary network meta-analysis. Nodes represent treatment modalities. Connecting lines between nodes represent head to head comparisons in randomised trials (RCTs), triangles represent three arm RCTs. The number of trials are presented within the lines, the number of included patients are presented within the nodes. ER = endovascular revascularisation; HBET = home based exercise therapy; SET = supervised exercise therapy.

show a statistically significant benefit over control treatment, as opposed to SET and HBET, although with similar effect size. While no differences between ER and SET or HBET were found, the underlying quality of evidence for these comparisons was low to very low, indicating that the true effects may be substantially different from the estimates.[18] One can argue that the impact of ER on lifestyle factors such as physical activity is minimal as there is little time for in person guidance, apart from the short clinical consultations with the interventionalist. In contrast, exercise programmes permit a trained healthcare professional to influence patients through multiple face to face contacts over an extended period, using several behavioural change techniques.[45] The current study cannot definitively add weight to this argument owing to the lack of quality of evidence for comparisons among treatments. Moreover, the actual impact of supervised or home based exercise programmes on cardiovascular mortality and morbidity remains unknown. Exercise programmes provide the opportunity to induce meaningful changes in a patient's cardiovascular health, arguably more so than a vascular intervention, but these benefits need to be substantiated beyond the current study.

Several limitations need to be considered. Firstly, many treatment comparisons were assessed as low or very low quality of evidence in the GRADE framework. This is mainly caused by the moderate to high risk of bias of the included trials and the fact that physical activity is not commonly measured in RCTs. To ameliorate this drawback, authors were contacted for additional data and network meta-analysis was used to allow the inclusion of indirect comparisons thereby improving the preciseness of the estimates. Nonetheless, this is a limitation and the reported GRADE scores are added for transparency, aiding the reader with interpretation of the results. Secondly, follow up durations differed from three to six months, which may be a cause of bias. However, improvements in walking function with SET are mostly obtained in the first months.[29] However six months is a short timeframe: longer term adherence to the gained activity level is probably a greater challenge. While some longer term results were reported, such data are largely unavailable, warranting more research. Thirdly, the common reference "control" group of this meta-analysis consisted of various usual care variants. Notably, the current meta-analysis combined study arms where explicit verbal walking advice was given, with usual care treatments where this was not the case. This may be deemed controversial,[46] but advice for mere walking (without quantification as in HBET) has a marginal effect and cannot really be seen as an active intervention distinct from best medical treatment or usual care. Furthermore, whether clinicians refrained from such advice in trials where it was not explicitly mentioned in the article text cannot be established.

In conclusion, this study shows that SET leads to a moderate short-term improvement of physical activity in patients with IC vs. control therapies. HBET demonstrated similar effects, but the confidence in this evidence was graded low. The effects of ER on physical activity are not well studied and statistical insignificance and low quality evidence barred definite conclusions for this treatment modality.

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