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SYSTEMATIC REVIEW AND META-ANALYSIS

Network Meta-Analysis Comparing the Outcomes of Treatments for Intermittent Claudication Tested in Randomized Controlled Trials

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BACKGROUND: No network meta-analysis has considered the relative efficacy of cilostazol, home exercise therapy, supervised exercise therapy (SET), endovascular revascularization (ER), and ER plus SET (ER+SET) in improving maximum walking distance (MWD) over short- (<1 year), moderate- (1 to <2 years), and long-term (≥2 years) follow-up in people with intermittent claudication.

METHODS AND RESULTS: A systematic literature search was performed to identify randomized controlled trials testing 1 or more of these 5 treatments according to Preferred Reporting Items for Systematic Review and Meta-Analysis guidelines. The primary outcome was improvement in MWD assessed by a standardized treadmill test. Secondary outcomes were adverse events and health-related quality of life. Network meta-analysis was performed using the gemtc R statistical package. The Cochrane collaborative tool was used to assess risk of bias. Forty-six trials involving 4256 patients were included. At short-term follow-up, home exercise therapy (mean difference [MD], 89.4 m; 95% credible interval [CrI], 20.9–157.7), SET (MD, 186.8 m; 95% CrI, 136.4–237.6), and ER+SET (MD, 326.3 m; 95% CrI, 222.6–430.6), but not ER (MD, 82.5 m; 95% CrI, –2.4 to 168.2) and cilostazol (MD, 71.1 m; 95% CrI, –24.6 to 167.9), significantly improved MWD (in meters) compared with controls. At moderate-term follow-up, SET (MD, 201.1; 95% CrI, 89.8–318.3) and ER+SET (MD, 368.5; 95% CrI, 195.3–546.9), but not home exercise therapy (MD, 99.4; 95% CrI, –174.0 to 374.9) or ER (MD, 84.2; 95% CrI, –35.3 to 206.4), significantly improved MWD (in meters) compared to controls. At long-term follow-up, none of the tested treatments significantly improved MWD compared to controls. Adverse events and quality of life were reported inconsistently and could not be meta-analyzed. Risk of bias was low, moderate, and high in 4, 24, and 18 trials respectively.

CONCLUSIONS: This network meta-analysis suggested that SET and ER+SET are effective at improving MWD over the moderate term (<2 year) but not beyond this. Durable treatments for intermittent claudication are needed.

Key Words: cilostazol ■ endovascular revascularization ■ exercise therapy ■ intermittent claudication ■ maximum walking distance ■ network meta-analysis ■ peripheral artery disease

Intermittent claudication is a common cause of walking impairment, reduced health-related quality of life (QOL) and low physical activity.[1] The main treatment options for intermittent claudication are the medication cilostazol, supervised exercise therapy (SET), home exercise therapy (HET), and endovascular revascularization (ER).[2] Despite a number of randomized controlled trials, systematic reviews, and traditional and network meta-analyses (NMA), there remains controversy regarding the most

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CLINICAL PERSPECTIVE

What Is New?

- This network meta-analysis of randomized controlled trials suggested that home exercise therapy, supervised exercise therapy, and a combination of supervised exercise therapy with peripheral revascularization significantly improved walking distance in patients with intermittent claudication over the short term compared with controls.
- None of the tested treatments improved walking distance significantly compared with controls in the longer term.

What Are the Clinical Implications?

- Larger and better designed clinical trials testing treatments for intermittent claudication are needed.

Nonstandard Abbreviations and Acronyms

CrI	credible interval
ER	endovascular revascularization
HET	home exercise therapy
MCMC	Markov Chain Monte Carlo
MD	mean difference
MWD	maximum walking distance
NMA	network meta-analysis
SET	supervised exercise therapy
SF-36	36-Item Short Form Health Survey
WIQ	Walking Impairment Questionnaire

appropriate therapy.[3–6] Assessment of the available evidence regarding the most effective treatment for intermittent claudication is difficult because of the absence of head-to-head comparison of all available therapies in 1 trial or in previous meta-analyses.[3–5] Most randomized clinical trials have included a small number of participants or involved a limited number of the available therapies, meaning standard meta-analyses are not ideally suited to testing the most effective treatment. NMA have been designed to combine all available evidence for randomized trials, including treatments not compared head to head. A number of prior NMA have compared treatments for intermittent claudication but these have been subject to a number of limitations.[4,7–9] These include not incorporating all available treatments options, not examining outcomes at different follow-up times, and including therapies, such as older endovascular approaches, which are not contemporary.[4,7–9] Assessing long-term, as well as short-term outcomes is important because recent evidence suggests that both exercise therapy and endovascular revascularization are not durable.[6,10] Furthermore, long-term results from 1 clinical trial have been reported since the publication of the most recent NMA and need to be incorporated into the available evidence.[11] In order to address these limitations this NMA examined data from randomized controlled trials published in the past 2 decades that tested cilostazol, exercise therapy, and ER for treating intermittent claudication.

METHODS

All data used in this study are available in the article and supplementary files.

Search Strategy

The systematic review was performed according to the Preferred Reporting Items for Systematic Review and Meta-Analysis with an extension for NMA statement (PRISMA-NMA) and the study protocol was registered in the PROSPERO (International Prospective Register of Systematic Reviews) database (Registration Number: CRD42020197141). The literature search was conducted by 1 author (S.T.). The databases PubMed (Medline), Cochrane Central Register for Controlled Trials, and Web of Science were searched on April 21, 2020. The full search strategy included terms related to intermittent claudication, treatment, and walking capacity (Data S1).

Study Selection

Randomized controlled trials testing cilostazol, SET, HET, ER and combination of any of these strategies for treating intermittent claudication were eligible for inclusion. Control patients were defined as those under attention control, best or optimal medical treatment alone, or receiving placebo. HET was defined as either written exercise advice or a structured program consisting of exercise sessions that were mainly performed without supervision at home. SET was defined as an exercise program performed under direct supervision of a trained health professional. ER was defined to include angioplasty, stenting, or related endovascular procedures. All included trials had to report maximum walking distance (MWD) measured in meters during a standardized treadmill test. Trials that were published as full texts or abstracts were eligible for inclusion if the minimum data requirement (MWD at entry and at least 1 follow-up time) was published or available from the corresponding author. When multiple publications arising from the same clinical trial were identified, data for all applicable time points were included. Trials published

in languages other than English, nonrandomized or crossover trials, and observational studies and trials where baseline and at least 1 follow-up time point MWD were not available were excluded. In order to compare contemporary treatments, because of the substantial evolution in the techniques used for endovascular revascularization over time, trials published before 2000 were excluded. Unpublished studies and abstracts where minimum data were not available were also excluded. Eligibility was determined by 2 authors (S.T. and J.P.), with discrepancies resolved by discussion with the senior author (J.G.).

Data Extraction

Primary outcome data were extracted on a customized spreadsheet by 2 authors (S.T. and S.W.) and findings were validated by 2 authors (J.P. and M.I.). Secondary outcomes were extracted by 2 authors (S.T. and P.H.) and the data were validated by 1 author (J.P.). Study characteristics were extracted by 3 authors (S.T., J.P., and C.S.). Any inconsistencies were resolved through discussion and confirmed with the senior researcher (J.G.). The primary outcome was MWD (in meters) measured in a standardized treadmill test. In trials that did not report MWD, other data including peak walking time, absolute claudication distance, or maximum walking time were used to derive MWD considering the type of treadmill test used. Secondary outcomes included QOL and serious adverse events (SAE). Because multiple different QOL questionnaires were used in the included trials, it was not possible to perform a pooled analysis. QOL data were tabulated and findings reported qualitatively. SAEs were reported as the numbers of patients who had a myocardial infarction, stroke, events requiring hospital admission, lower limb revascularization, any other vascular procedure, any amputation, or death. In patients who were randomized to ER, only secondary lower limb revascularization procedures were considered as SAEs. The following additional data were extracted from the included trials: age, sex, body mass index, smoking, hypertension, diabetes mellitus, ankle brachial pressure index, medications, sample size, type of treadmill test, design of HET or SET program, type of ER, and duration of follow-up. Primary outcome data were categorized depending on the follow-up time as <1 year (short-term follow-up), ≥1 to <2 year (moderate-term follow-up), and ≥2 year (long-term follow-up). Mean difference (MD) was calculated as the difference in mean values between the specified follow-up and baseline. SD of change scores was imputed using the formula[12]: $sd_{change} = \sqrt{\left[sd^2_{baseline} + sd^2_{Final} - (2 \times Corr \times sd_{baseline} \times sd_{Final})\right]}$. Pearson correlation coefficient (Corr in the formula) was calculated using individual participant data from 1 trial[13] as used previously.[14] The relative effect was expressed as MD±95% credible interval (CrI). CrI denotes the predictive distribution or interval within which a potential unobserved fixed effects parameter value could fall with a particular probability. CrI is the Bayesian statistics equivalent of CI. The statistical analyses were overseen by a senior researcher (J.M.) and the network model was validated by another senior researcher with extensive statistical expertise (R.J.).

Statistical Analysis

The Bayesian random effects NMA was performed using the R statistical package gemtc, which uses the arm-based model and provides effect size estimates for multiple comparisons.[15] The package was available through R studio version 3.4.4 from the Comprehensive R Archive Network (CRAN) at https://cran.r-project.org/web/packages/gemtc/index.html. The package contains functions that use Just Another Gibbs Sampler, a program for analyzing Bayesian hierarchical models using Markov Chain Monte Carlo (MCMC) simulation.[16] The gemtc package uses Just Another Gibbs Sampler software to develop a random effects model assuming consistency with variance scaling factor of 2.5 and noninformative normal prior distribution. Between-trial SDs were assumed to follow a noninformative uniform distribution and a weakly informative prior distribution. MCMC simulations were run using 3 chains with different initial values for 100 000 iterations. Convergence of the resulting model was assessed using trace plots. Data were presented according to short-term, moderate-term, and long-term follow-up periods. Network diagrams of all available treatments from the included trials were plotted to compare and illustrate multiple treatment arms at different follow-up times. MCMC simulations were performed to estimate the posterior distributions of MWD data between different arms by running the simulations long enough to reach accurate estimates for the model. Convergence of the network models derived from MCMC simulations were assessed using trace and density plots. The stability of the MCMC simulation output was tested with Gelman-Rubin-Brooks plots and diagnostics were performed to determine Potential Scale Reduction Factor score. A Potential Scale Reduction Factor score of <1.05 is suggestive of good convergence in the network model. Inconsistencies within the network model were assessed using a more sophisticated node split method; which estimates the random effects of different comparison arms when using direct alone, indirect alone, and all available network evidence separately.[17] Any significant differences in estimates between direct and indirect evidence were considered as potential presence of large inconsistencies. In addition, ranking

probability was calculated for all available treatment strategies for each follow-up time.[18] A *P* value of ≤0.05 was considered as statistically significant.

Risk of Bias Assessment

Two authors (S.T. and J.P.) independently assessed the risk of bias of all included trials using the Cochrane Collaboration's tool, which assessed key aspects of the reports including random sequence generation, statistical sample size estimate, the number of patients who completed the study, the primary outcome, blinding of outcome assessors, intent-to-treat principle, and other biases.[19] Quality parameters were marked as (+), (–), and (?) for positive, negative, and unclear risk of bias respectively. Any study having 3 or more negative quality assessments were considered to have high risk of bias. Trials with 1 to 2 negative quality assessments were considered to have moderate risk of bias and those with no negative quality assessments were considered to have low risk of bias. Any inconsistencies were resolved through discussion between the authors until a consensus was reached.

RESULTS

Included Trials and Participants

After screening 46 clinical trials involving a total of 4256 patients were included (Figure 1). Forty-two trials involving 3515 patients reported MWD (in meters) at short-term follow-up.[6,13,20–59] Fourteen trials involving 1327 patients reported MWD (in meters) at moderate-term follow-up[6,43,50–54,56–62] and 6 trials involving 601 patients reported MWD (in meters) at long-term follow-up.[6,54,55,57,62,63] Details such as the specific treatment strategy and outcome assessments are shown in Table S1. The baseline characteristics of the participants are shown in Table 1.

Quality Assessment

A total of 4 clinical trials including 2 trials comparing SET versus ER,[52,59] and 1 trial comparing cilostazol versus control,[46] and 1 trial comparing HET and SET[51] were deemed to have low risk of bias, 24 trials had moderate risk of bias,* and 18 trials were considered to have high risk of bias.† All included trials reported the method of randomization and the number of participants who completed the study. Twenty-four trials used power calculations to estimate the sample size‡ and 25 trials used intention-to-treat principles to analyze the results.§ Twenty-three trials had incomplete outcome data because of losing more than 10% of the study population.‖ Absence of participant and/or investigator blinding was noted in 30 trials.¶ Individual study-level assessments are provided in Table 2.

Network Model

The graphical representation of all treatment arms from all included trials is shown in Figure 2. The model convergence was achieved with 100 000 iterations at all follow-up time points. Node split analysis showed that the estimates of direct, indirect, and network assumptions were not significantly different, suggesting the absence of large inconsistencies within the network models at all follow-up time points (Figure 2A through 2C). The network diagnostics using trace and density plots (Figures S1 through S3) and node split analysis (Figure 3A through 3C) showed that the models converged and were valid to use at all follow-up time points. The Gelman diagnostics showed a Potential Scale Reduction Factor score of 1.000374, 1.000296, and 1.000166 at short-term, moderate-term, and long-term follow-up, respectively, suggesting the reliability of the network model.

Short-Term Follow-Up

Data were available for the comparison of the following treatment combinations at short-term follow-up: cilostazol (n=451, 5 arms), HET (n=392, 15 arms), SET (n=997, 30 arms), ER (n=333, 9 arms), and SET plus ER (n=280, 6 arms) compared with controls (n=1062, 28 arms). The forest plot suggested that the largest improvement in MWD was achieved by SET plus ER (MD, 326.3 m; 95% CrI, 222.6–430.6). SET (MD, 186.8 m; 95% CrI, 136.4–237.6), and HET (MD, 89.4 m; 95% CrI: 20.9–157.7) also significantly increased MWD. Cilostazol (MD, 71.1 m; 95% CrI, –24.6 to 167.9) and ER (MD, 82.5 m; 95% CrI, –2.4 to 168.2) had no significant effect on MWD (Figure 4A).

Moderate-Term Follow-Up

Data were available for the comparison of the following treatment combinations at moderate-term follow-up: HET (n=36, 2 arms), SET (n=499, 12 arms), ER (n=367, 7 arms), and SET plus ER (n=197, 4 arms) compared with controls (n=228, 7 arms). The forest plot suggested that the largest improvement in MWD was observed for SET plus ER (MD, 368.5 m; 95% CrI, 195.3–546.9) and SET alone (MD, 201.1 m; 95% CrI, 89.8–318.3). ER (MD, 84.2 m; 95% CrI, –35.3 to 206.4)

*References 13, 23–25, 30, 33, 35, 38, 40, 42–44, 48-50, 53–58, 61-63..

†References 6, 20–22, 26–29, 31, 32, 34, 36, 37, 39, 41, 45, 47, 60.

‡References 6, 23–25, 30, 33, 35, 38, 40, 43–48, 51, 52, 54–57, 59, 61, 63.

§References 13, 25, 26, 28, 30, 33–35, 38, 40, 42–44, 46, 48, 49, 52–56, 59, 61–63.

‖References 6, 21, 24–26, 28, 31, 32, 34, 35, 37–40, 43–45, 47, 48, 54–56, 61.

¶References 6, 20–22, 25–30, 33, 34, 36, 37, 39–45, 47, 49, 53–55, 57, 61–63.

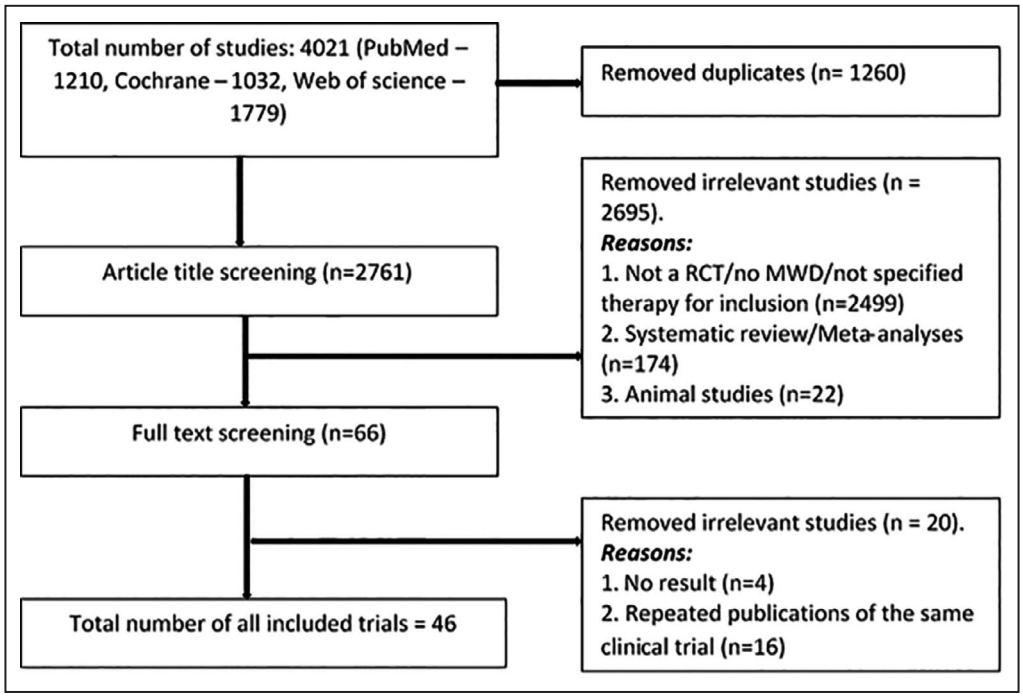

Figure 1. Preferred Reporting Items of Systematic Review and Meta-Analyses (PRISMA) flow diagram.
A total of 4021 studies were screened and 46 randomized controlled trials (RCT) were ultimately included. MWD indicates maximum walking distance.

and HET (MD, 99.4 m; 95% CrI, –174.0 to 374.9) had no significant effect on MWD (Figure 4B).

Long-Term Follow-Up

Data were available for the comparison of the following treatment combinations at long-term follow-up: SET (n=124, 4 arms), ER (n=223, 5 arms), and SET plus ER (n=104, 3 arms) compared with controls (n=150, 3 arms). The forest plots suggested that none of the treatments significantly improved MWD as compared with controls: SET plus ER (MD, 140.9 m; 95% CrI, –195.4 to 507.7), ER (MD, 122.7 m; 95% CrI, –64.8 to 347.6), and SET (MD, 29.0 m; 95% CrI, –297.1 to 384.6) (Figure 4C).

Ranking Probability

Ranking probability suggested that the SET plus ER combination was the best treatment strategy followed by SET alone during short-term and moderate-term follow-up (Table S2). Initial benefits were abolished at long-term follow-up for all treatment strategies with available data (Figure 4).

Secondary Outcomes

QOL

A total of 29 trials reported QOL outcomes using different generic and disease-specific questionnaires as detailed in Table S3. Generic QOL outcomes were reported in 26 trials using the 36-Item Short Form Health Survey (SF–36), 12-Item SF,[#] or the EuroQOL-5.[13,44,63] Disease-specific QOL outcomes were reported in 25 trials using the Walking Impairment Questionnaire (WIQ),[**] the Vascular QOL Questionnaire (VascuQOL),[6,46,52,55,59,62] the claudication score,[50,57] or the Baltimore Activity Scale for Intermittent Claudication Questionnaire,[29] the Intermittent Claudication Questionnaire,[51] and peripheral artery questionnaire[56] respectively. The QOL outcomes are reported in Table S3.

Short-Term Follow-Up

Four of 6 arms reported that cilostazol significantly improved QOL as assessed with the SF-36, VascuQOL, or WIQ by comparison with controls.[38,46,48] Five of 11 arms reported that HET significantly improved QOL as assessed with the SF-36 or WIQ compared with controls.[25,26,28,29] Eleven of 18 arms reported that SET significantly improved QOL as assessed with the Baltimore Activity Scale for Intermittent Claudication Questionnaire, SF-36, VascuQOL, or WIQ compared with controls.[25,26,29,34,40,45,52] Seven of 9 arms reported that ER significantly improved QOL as assessed with the SF-36, claudication score, VascuQOL, or EuroQOL

[#]References 6, 25, 26, 28, 30, 34, 36, 38, 39, 43–46, 48, 50–52, 54, 55, 57, 59, 62, 63.

[**]References 13, 25, 26, 30, 34, 36, 38–40, 43, 48, 53, 56, 63.

Table 1. Baseline Characteristics of All Patients Included in All Treatment Arms of the Included Trials

Reference	Intervention	No. of Patients	Age (y) in Mean±SD/ Median (IQR)	Male Sex (%)	Body Mass Index Mean±SD/ Median (IQR)	Ankle-Brachial Pressure Index in Mean±SD/ Median (IQR)	Currently Smoking (%)	Diabetes Mellitus (%)	Coronary Heart Disease (%)	Hypertension (%)	Dylipidemia (%)	Cilostazol (%)	Statins (%)	Angiotensin-Converting Enzyme Inhibitors (%)	Angiotensin Receptor Blockers (%)	Aspirin (%)	Anti-Platelet Drugs (%)
57	Control	28	69 (61, 75)	69.0	25 (36, 50)	0.6 (0.5, 0.7)	67.9	21.4	17.8	15.0	92.8	NR	NR	NR	NR	NR	46.4
	ER	28	68 (56, 72)	68.0	26 (23, 28)	0.6 (0.5, 0.7)	71.4	14.3	7.1	8.0	85.7	NR	NR	NR	NR	NR	17.9
55	ER	60	74.5 (67.8, 79.0)	NR	NR	0.7 (0.6, 0.7)	6.7	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	SET	60	75.0 (67.0, 80.0)	NR	NR	0.7 (0.6, 0.8)	15.0	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	SET+ER	58	75.0 (70, 81)	NR	NR	0.6 (0.6, 0.7)	12.1	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
62	SET	75	NR	NR	NR	0.6 (0.6, 0.7)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	ER	76	NR	NR	NR	0.6 (0.6, 0.7)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
6	ER	79	68±7.0	51.9	26±5.0	0.7±0.2	30.4	14.0	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Control	79	68±6.0	53.2	26±4.0	0.7±0.1	27.8	16.0	NR	NR	NR	NR	NR	NR	NR	NR	NR
63	ER	48	71.3±5.3	45.1	NR	0.6±0.1	7.0	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Control	52	69.8±5.8	52.3	NR	0.6±0.2	11.0	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
56	Control	22	62.3±8.5	60.0	29.0±5.9	0.7±0.2	53.3	21.4	NR	93.3	73.2	13.3	73.3	NR	NR	NR	86.7
	SET	43	65.9±8.8	56.3	27.5±5.0	0.7±0.2	53.1	18.8	NR	90.6	78.1	18.7	78.1	NR	NR	NR	78.1
	ER	46	65.2±10.5	68.8	28.9±6.4	0.6±0.2	53.1	32.3	NR	81.3	78.1	21.9	71.9	NR	NR	NR	81.3
54a	ER+SET	48	63.9±9.0	68.7	27.0±5.1	0.7±0.1	79.2	NR	43.7	72.9	NR	NR	83.3	NR	NR	NR	91.7
	SET	45	68.5±9.4	57.8	26.9±4.5	0.7±0.1	84.4	NR	22.2	75.6	NR	NR	66.7	NR	NR	NR	88.9
54b	ER+SET	19	63.9±8.6	63.2	27.2±3.6	0.7±0.2	89.5	NR	26.3	57.9	NR	NR	57.9	NR	NR	NR	84.2
	SET	15	62.5±9.8	66.7	25.2±3.8	0.7±0.1	100.0	NR	40.0	53.3	NR	NR	80.0	NR	NR	NR	73.3
61	Control	89	67 (47–81)	67.0	NR	0.5±NR*	49.0	16.0	NR	NR	NR	NR	NR	NR	NR	NR	NR
	SET	88	67 (45–81)	66.0	NR	0.5±NR*	53.0	14.0	NR	NR	NR	NR	NR	NR	NR	NR	NR
	ER	87	66 (38–80)	64.0	NR	0.5±NR*	52.0	19.0	NR	NR	NR	NR	NR	NR	NR	NR	NR
50	ER	21	66±8.3	47.6	27.4±4.0	NR	42.8	19.0	NR	61.9	NR	NR	90.5	NR	NR	NR	95.2
	SET+ER	29	66.9±7.1	48.3	27.2±5.0	NR	37.9	10.3	NR	51.7	NR	NR	96.6	NR	NR	NR	86.2
59	ER	76	65±11.4	59.0	26±4.3	0.6±0.2	16.0	15.0	19.0	43.0	53.0	NR	NR	NR	NR	NR	NR
	SET	75	66±9.1	52.0	25±4.9	0.6±0.2	23.0	20.0	28.0	37.0	51.0	NR	NR	NR	NR	NR	NR
60	Control	11	68.1±6.8	45.0	25.2±3.2	1.2±0.1	0	0	0	9.0	NR	NR	NR	NR	NR	NR	NR
	SET	10	72.3±8.5	50.0	29.2±29.5	0.7±0.2	10.0	10.0	20.0	30.0	NR	NR	NR	NR	NR	NR	NR
51	HET	30	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	SET	29	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
53	Control	14	71±3.7	NR	NR	0.7±0.1	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	SET	17	72±4.1	NR	NR	0.7±0.2	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

(*Continued*)

Table 1. Continued

Reference	Intervention	No. of Patients	Age (y) in Mean±SD/ Median (IQR)	Male Sex (%)	Body Mass Index Mean±SD/ Median (IQR)	Ankle-Brachial Pressure Index in Mean±SD/ Median (IQR)	Currently Smoking (%)	Diabetes Mellitus (%)	Coronary Heart Disease (%)	Hypertension (%)	Dylipidemia (%)	Cilostazol (%)	Statins (%)	Angiotensin-Converting Enzyme Inhibitors (%)	Angiotensin Receptor Blockers (%)	Aspirin (%)	Anti-Platelet Drugs (%)
20	SET	29	66 (58, 69)	83.0	28.7 (26, 30.4)	0.6 (0.5, 0.8)	17.0	45.0	NR	93.0	NR	31.0	69.0	NR	NR	NR	NR
	Control	35	67 (60, 76)	49.0	28.6 (24.5, 30.9)	0.6 (0.5, 0.8)	37.0	29.0	NR	74.0	NR	17.0	77.0	NR	NR	NR	NR
35	Cilostazol	89	64.5 (50–84)	94.6	NR	0.6±0.1	51.4	14.9	NR	NR	NR	NR	47.3	NR	NR	NR	87.8
	Control	87	62.9 (44–82)	89.7	NR	0.6±1	61.5	15.4	NR	NR	NR	NR	44.9	NR	NR	NR	74.4
36	Control	73	66.8±10.1	80.0	33.7±7.0	0.9±0.4	13.0	NR	NR	57.0	54.0	NR	NR	NR	NR	NR	NR
	HET	72	66.2±10.2	75.0	35.0±9.3	1.0±0.4	7.0	NR	NR	62.0	54.0	NR	NR	NR	NR	NR	NR
37	SET	11	71.3±8.5	50.0	29.2±4.1	0.7±0.1	10.0	10.0	20.0	10.0	NR	NR	NR	NR	NR	NR	NR
	Control	11	67.1±6.8	50.0	25.7±4.9	0.5±0.1	30.0	17.0	33.0	50.0	NR	NR	NR	NR	NR	NR	NR
38	Cilostazol	227	66±9.0	75.8	NR	0.7±0.2	41.4	31.7	NR	73.1	65.2	NR	NR	NR	NR	NR	NR
	Control	239	66±9.0	73.6	NR	0.7±0.4	37.7	31.4	NR	72.0	66.9	NR	NR	NR	NR	NR	NR
52	SET+ER	106	64±9.0	60.0	27.0±4.1	0.7±0.2	65.0	16.0	33.0	58.0	44.0	NR	NR	NR	NR	NR	NR
	SET	106	66±10.0	72.0	26.2±4.4	0.7±0.2	55.0	26.0	40.0	62.0	42.0	NR	NR	NR	NR	NR	NR
39	SET	31	71±1.0	89.0	NR	0.7±0.04	NR	46.0	50.0	82.0	64.0	NR	NR	NR	NR	NR	NR
	Control	30	70±1.0	92.0	NR	0.7±0.04	NR	38.0	46.0	79.0	88.0	NR	NR	NR	NR	NR	NR
25	SET	60	65±11.0	48.0	29.3±6.7	0.7±0.2	37.0	48.0	30.0	90.0	88.0	NR	NR	NR	NR	NR	NR
	HET	60	67±10.0	52.0	29.0±5.7	0.7±0.2	35.0	40.0	35.0	88.0	93.0	NR	NR	NR	NR	NR	NR
	Control	60	65±9.0	60.0	29.0±6.1	0.7±0.2	42.0	37.0	28.0	83.0	87.0	NR	NR	NR	NR	NR	NR
40	SET	106	68±8.0	86.0	27.9±4.7	0.6±0.2	46.0	26.0	NR	64.0	58.0	NR	NR	NR	NR	NR	NR
	Control	36	68±8.0	83.0	29.5±4.6	0.7±0.2	39.0	20.0	NR	64.0	60.0	NR	NR	NR	NR	NR	NR
26	HET	40	65±11.0	45.0	29.9±5.6	0.7±0.2	10.0	43.0	NR	88.0	90.0	NR	NR	NR	NR	NR	NR
	SET	40	66±12.0	45.0	29.2±7.1	0.7±0.2	10.0	43.0	NR	88.0	88.0	NR	NR	NR	NR	NR	NR
	Control	39	65±10.0	54.0	29.7±6.9	0.8±0.2	10.0	31.0	NR	79.0	85.0	NR	NR	NR	NR	NR	NR
41	Control	7	77 (56–78)	57.1	NR	NR	14.3	57.1	NR	NR	NR	NR	100.0	57.1	NR	NR	100.0
	ER	9	67 (57–76)	66.7	NR	NR	22.2	22.2	NR	NR	NR	NR	100.0	22.2	NR	NR	100.0
	SET	7	67 (58–71)	85.7	NR	NR	42.9	57.1	NR	NR	NR	NR	100.0	71.4	NR	NR	100.0
42	SET	9	66 (63–71)	77.8	NR	NR	44.4	11.1	NR	NR	NR	NR	100.0	55.6	NR	NR	100.0
	Cilostazol	9	58 (52–71)	88.9	NR	NR	33.3	33.3	NR	NR	NR	NR	100.0	33.3	NR	NR	100.0
	SET+cilostazol	7	72 (63–74)	71.4	NR	NR	28.6	14.3	NR	NR	NR	NR	100.0	57.1	NR	NR	100.0
	Control	9	67 (63.5–74)	77.8	NR	NR	33.3	22.2	NR	NR	NR	NR	88.9	55.6	NR	NR	100.0

(*Continued*)

Table 1. Continued

Reference	Intervention	No. of Patients	Age (y) in Mean±SD/ Median (IQR)	Male Sex (%)	Body Mass Index Mean±SD/ Median (IQR)	Ankle-Brachial Pressure Index in Mean±SD/ Median (IQR)	Currently Smoking (%)	Diabetes Mellitus (%)	Coronary Heart Disease (%)	Hypertension (%)	Dylipidemia (%)	Cilostazol (%)	Statins (%)	Angiotensin-Converting Enzyme Inhibitors (%)	Angiotensin Receptor Blockers (%)	Aspirin (%)	Anti-Platelet Drugs (%)
27	SET	28 total	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Control		NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
43	HET	9	66±10.5	89.0	24.7±10.9	NR	33.0	11.0	11.0	22.0	56.0	NR	NR	NR	NR	NR	NR
	SET	12	69±11.8	92.0	24.9±5.3	NR	17.0	25.0	17.0	33.0	42.0	NR	NR	NR	NR	NR	NR
44	ER	35	60.2±10.0	60.0	27.5±4.9	0.7±0.2	60.0	14.3	20.0	68.6	88.6	NR	NR	NR	NR	NR	NR
	SET+ER	35	64.5±9.3	62.9	26.6±3.4	0.7±0.2	51.4	25.7	37.1	71.4	85.7	NR	NR	NR	NR	NR	NR
28	HET	18	68±7.0	67.0	25±4.0	NR	89.0	39.0	33.0	83.0	61.0	0	61.0	NR	NR	NR	94.0
	ER	9	69±7.0	100.0	27±3.0	NR	100.0	33.0	56.0	100.0	67.0	0	67.0	NR	NR	NR	100.0
45	SET	12	65.6±11.0	81.8	27.3±3.3	0.5±0.1	9.0	36.0	NR	NR	NR	NR	100.0	82.0	82.0	82.0	9.0
	Control	8	62.0±8.3	75.0	28.5±2.3	0.5±0.1	50.0	25.0	NR	NR	NR	NR	75.0	63.0	63.0	50.0	38.0
29	SET	16	69 (58–72)	50.0	31 (26–37)	0.5 (0.4–0.6)	38.0	44.0	50.0	94.0	86.0	NR	75.0	NR	NR	69.0	44.0
	HET	7	65 (55–71)	43.0	26 (20–33)	0.7 (0.6–0.8)	57.0	29.0	14.0	71.0	86.0	NR	57.0	NR	NR	57.0	29.0
30	Control	10	63.1±11.8	80.0	30.6±5.9	0.8±0.2	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	HET	9	68.0±12.5	77.8	126.6±19.6	0.8±0.3	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
31	SET	49	61.4±6.5	85.4	NR	0.7±0.1	87.8	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	HET	49	60.9±5.4	79.5	NR	0.7±0.1	82.0	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
32	SET	34	63.5±7.2	90.0	27.6±3.5	0.8±0.1	83.3	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Control	34	62.1±6.9	83.9	27.7±2.9	0.8±0.1	77.4	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
46	Cilostazol	39	M—65 (46–86)/ F—63 (49–78)	66.7	NR	0.9 (0.8v1.0)	46.1	NR	NR	56.4	74.4	NR	NR	NR	NR	NR	NR
	Control	41	M—66 (39–78)/ F—68 (46–80)	65.8	NR	0.8 (0.6–0.9)	51.2	NR	NR	61.0	73.2	NR	NR	NR	NR	NR	NR
33	SET	13	66±8	76.9	26.3±4.5	0.6±0.01	38.5	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	HET	15	62±14	80.0	27.1±4.2	0.6±0.01	40.0	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Control	15	67±6	66.7	27.7±6.7	0.6±0.1	46.7	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
58	SET	20	69±8	65.0	NR	0.6±0.1	100.0	35.0	40.0	100.0	100.0	NR	100.0	65.0	20.0	90.0	55.0
	Control	20	70±11	55.0	NR	0.5±0.2	100.0	45.0	35.0	100.0	95.0	NR	95.0	65.0	25.0	85.0	35.0
47	SET	30	68±7.7	66.7	25.5±4.3	0.6±0.03	23.3	26.7	NR	63.3	40.0	NR	NR	NR	NR	NR	NR
	HET	30	68±8.9	73.3	26.5±4.5	0.6±0.04	30.0	16.7	NR	53.3	46.7	NR	NR	NR	NR	NR	NR

(*Continued*)

Table 1. Continued

Reference	Intervention	No. of Patients	Age (y) in Mean±SD/ Median (IQR)	Male Sex (%)	Body Mass Index Mean±SD/ Median (IQR)	Ankle-Brachial Pressure Index in Mean±SD/ Median (IQR)	Currently Smoking (%)	Diabetes Mellitus (%)	Coronary Heart Disease (%)	Hypertension (%)	Dylipidemia (%)	Cilostazol (%)	Statins (%)	Angiotensin-Converting Enzyme Inhibitors (%)	Angiotensin Receptor Blockers (%)	Aspirin (%)	Anti-Platelet Drugs (%)
48	Cilostazol	133	63.1±117.6	76.7	NR	NR	50.4	23.3	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Control	129	64.4±115.8	77.5	NR	NR	48.1	17.1	NR	NR	NR	NR	NR	NR	NR	NR	NR
13	Control	9	67.8±14.1	66.7	29.6±7.4	0.6±0.2	0	22.0	33.0	78.0	NR	NR	78.0	NR	NR	NR	78.0
	HET	14	69.1±7.6	71.4	27.9±3.5	0.7±0.2	0	7.0	14.0	64.0	NR	NR	100.0	NR	NR	NR	100.0
34	SET	32	76.3±3.8	81.0	NR	0.7±0.1	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Control	32	76.1±3.7	85.0	NR	0.7±0.1	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
49	SET	37	69 (50–85)	81.0	26.6±0.6	0.6±0.03	38.0	8.0	NR	NR	NR	NR	NR	NR	NR	NR	NR
	SET	34	66 (54–84)	79.0	28.6±0.6	0.6±0.03	24.0	18.0	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Control	33	72 (56–84)	73.0	27.8±1.0	0.7±0.03	33.0	27.0	NR	NR	NR	NR	NR	NR	NR	NR	NR
22	HET	10	66.1±9.8	80.0	26.6±4.5	0.6±0.2	100.0	10.0	60.0	60.0	100	20.0	90.0	60.0	NR	NR	100.0
	Control	9	73.1±4.7	88.9	31.2±7.6	0.6±0.1	100.0	33.3	66.7	77.8	88.9	22.2	88.9	55.5	NR	NR	100.0
21	SET	31	67.0±9.3	57.1	NR	0.7±0.2	NR	38.1	47.6	57.1	42.9	NR	NR	NR	NR	NR	NR
	HET	21	67.0±7.4	80.7	NR	0.7±0.2	NR	38.7	32.3	87.1	61.3	NR	NR	NR	NR	NR	NR
23	SET	21	58.2±10.4	88.9	27.4±4.5	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	HET	21	60.9±11.3	87.5	26.5±4.5	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
24	SET	28	65.0±10.6	67.9	29±1.0	0.6±0.2	14.3	25.0	21.4	53.6	92.9	NR	88.0	NR	NR	NR	83.0
	HET	24	65.0±9.8	66.7	28±1.0	0.6±0.2	20.8	37.5	20.8	66.7	87.5	NR	93.0	NR	NR	NR	82.0

% indicates percentage; ER, endovascular revascularization; F, female; HET, home exercise therapy; IQR, inter quartile range; M, male; NR, not reported; and SET, supervised exercise therapy.
*Mean data only, SD not reported. References showing a & b are different comparisons.

Table 2. Quality Assessment of All Included Trials

Study Reference	Sample Size Estimate	Intention-to-Treat Analysis	Mentioned the Number of Patients Who Completed the Study	Random Sequence Generation	Incomplete Outcome Data (>10% loss)	Performance Bias (Participants and Personnel Blinding)	Total Risk of Bias
20	(–)	(–)	(+)	(+)	(+)	(–)	High
50	(–)	(–)	(+)	(+)	(+)	(+)	Moderate
35	(+)	(+)	(+)	(+)	(–)	(+)	Moderate
21	(–)	(–)	(+)	(+)	(–)	(–)	High
51	(+)	(–)	(+)	(+)	(+)	(+)	Low
36	(–)	(–)	(+)	(+)	(+)	(–)	High
60	(–)	(–)	(+)	(+)	(+)	(?)	High
37	(–)	(–)	(+)	(+)	(–)	(–)	High
38	(+)	(+)	(+)	(+)	(–)	(+)	Moderate
6	(+)	(–)	(+)	(+)	(–)	(–)	High
22	(–)	(–)	(+)	(+)	(+)	(–)	High
52	(+)	(+)	(+)	(+)	(+)	(+)	Low
62	(–)	(+)	(+)	(+)	(+)	(–)	Moderate
39	(–)	(–)	(+)	(+)	(–)	(–)	High
53	(–)	(+)	(+)	(+)	(+)	(–)	Moderate
26	(–)	(+)	(+)	(+)	(–)	(–)	High
40	(+)	(+)	(+)	(+)	(–)	(–)	Moderate
25	(+)	(+)	(+)	(+)	(–)	(–)	Moderate
61	(+)	(+)	(+)	(+)	(–)	(–)	Moderate
23	(+)	(–)	(+)	(+)	(+)	(+)	Moderate
54	(+)	(+)	(+)	(+)	(–)	(–)	Moderate
41	(–)	(–)	(+)	(+)	(+)	(–)	High
42	(–)	(+)	(+)	(+)	(+)	(–)	Moderate
27	(–)	(–)	(+)	(+)	(+)	(–)	High
43	(+)	(+)	(+)	(+)	(–)	(–)	Moderate
44	(+)	(+)	(+)	(+)	(–)	(–)	Moderate
28	(–)	(+)	(+)	(+)	(–)	(–)	High
63	(+)	(+)	(+)	(+)	(+)	(–)	Moderate
29	(–)	(–)	(+)	(+)	(+)	(–)	High
30	(+)	(+)	(+)	(+)	(+)	(–)	Moderate
55	(+)	(+)	(+)	(+)	(–)	(–)	Moderate
32	(–)	(–)	(+)	(+)	(–)	(+)	High
31	(–)	(–)	(+)	(+)	(–)	(+)	High
56	(+)	(+)	(+)	(+)	(–)	(+)	Moderate
45	(+)	(–)	(+)	(+)	(–)	(–)	High
57	(+)	(–)	(+)	(+)	(+)	(–)	Moderate
46	(+)	(+)	(+)	(+)	(+)	(+)	Low
33	(+)	(+)	(+)	(+)	(+)	(–)	Moderate
58	(–)	(–)	(+)	(+)	(+)	(+)	Moderate
24	(+)	(–)	(+)	(+)	(–)	(+)	Moderate
59	(+)	(+)	(+)	(+)	(+)	(+)	Low
47	(+)	(–)	(+)	(+)	(–)	(–)	High
48	(+)	(+)	(+)	(+)	(–)	(+)	Moderate
13	(–)	(+)	(+)	(+)	(+)	(+)	Moderate
34	(–)	(+)	(+)	(+)	(–)	(–)	High
49	(–)	(+)	(+)	(+)	(+)	(–)	Moderate

Trials with 3 or more negative assessment outcomes were considered to have HIGH risk of bias. Trials with 1 to 2 negative assessment outcomes were considered to have MODERATE risk of bias and those with no negative assessment outcomes were considered to have LOW risk of bias.

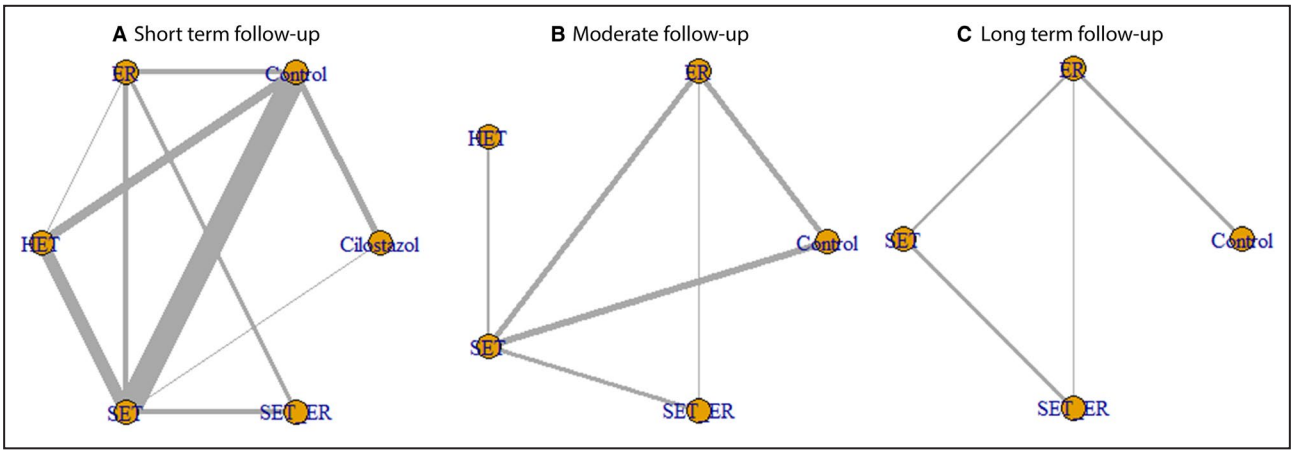

Figure 2. Network plots summarizing all intervention arms in the included trials.
(A) Short-term follow-up, (**B**) Moderate-term follow-up, (**C**) Long-term follow-up. The size of the grey lines represent the number of trials and the size of the orange circles represent the number of participants in that specific arm. ER indicates endovascular revascularization; HET, home exercise therapy; and SET, supervised exercise therapy.

by comparison with control.[6,28,44,57,59] Four of 4 arms reported that the combination of SET and ER significantly improved QOL as assessed with the SF-36, VascuQOL, or EuroQOL compared with controls.[44,52]

Moderate-Term Follow-Up

Seven of 13 arms reported that ER significantly improved QOL as assessed with the SF-36, VascuQOL, claudication score, or peripheral artery questionnaire compared with control.[6,56,57,62]

Two of 4 arms reported that HET significantly improved QOL as assessed with the SF-36, WIQ, or Intermittent Claudication Questionnaire compared with control.[43,51] Ten of 16 arms reported that SET significantly improved QOL assessed by the SF-36, SF-12, WIQ, peripheral artery questionnaire, Intermittent Claudication Questionnaire, or VascuQOL compared with controls.[43,51,52,56,62] Two of 4 arms reported that the combination of SET and ER significantly improved QOL assessed with the SF-36 or VascuQOL compared with controls.[52]

Long-Term Follow-Up

Six out of 11 arms reported significant improvement in certain domains of QOL in the ER group using the SF-36, claudication score, VascuQOL, and WIQ questionnaires.[57,62,63] One arm reported that HET did not significantly improve QOL as assessed with the WIQ questionnaire.[43] Two of 7 arms reported that SET significantly improved QOL as assessed with the SF-36 and VascuQOL questionnaires.[54] None of the 4 arms testing SET and ER combined reported any significant improvement of QOL as assessed with the SF-36 and VascuQOL questionnaires.[54,55]

Adverse Events

A total of 28 clinical trials reported adverse events as defined within the methods section[††] (Table S4). None of the trials reported any significant differences in SAEs between groups. Twenty-one patients had an myocardial infarction as reported in 9 trials.[2,4–26,40,55,56,58,59,63] Thirty patients were reported to have had a stroke in 10 trials.[‡‡] Events requiring hospital admissions were not reported in any of the included trials. Twelve trials reported lower limb revascularization procedures performed in 158 patients during the study follow-up period.[§§] Three trials reported other vascular procedures performed in 6 patients.[40,54,59] Fifteen patients were reported to have required an amputation in 8 trials.[6,40,52,53,55,61–63] Twenty-one trials reported 149 deaths during the follow-up period.[‖‖]

DISCUSSION

The results of this NMA, suggested that during short-term follow-up ER plus SET, SET alone, and HET alone all significantly improved MWD in people with intermittent claudication. During moderate-term follow-up only ER plus SET and SET alone significantly improved MWD. During follow-up of 2 years or more, none of these treatments significantly improved MWD. These analyses were limited by the small number of participants included within the available trials meaning the

[††]References 6, 13, 24–26, 33, 35, 38–40, 43, 44, 47–59, 61–63.

[‡‡]References 6, 13, 25, 26, 35, 40, 47, 54, 55, 63.

[§§]References 6, 25, 26, 33, 44, 47, 50, 55, 56, 59, 62, 63.

[‖‖]References 6, 24, 35, 38, 43, 47–59, 61–63.

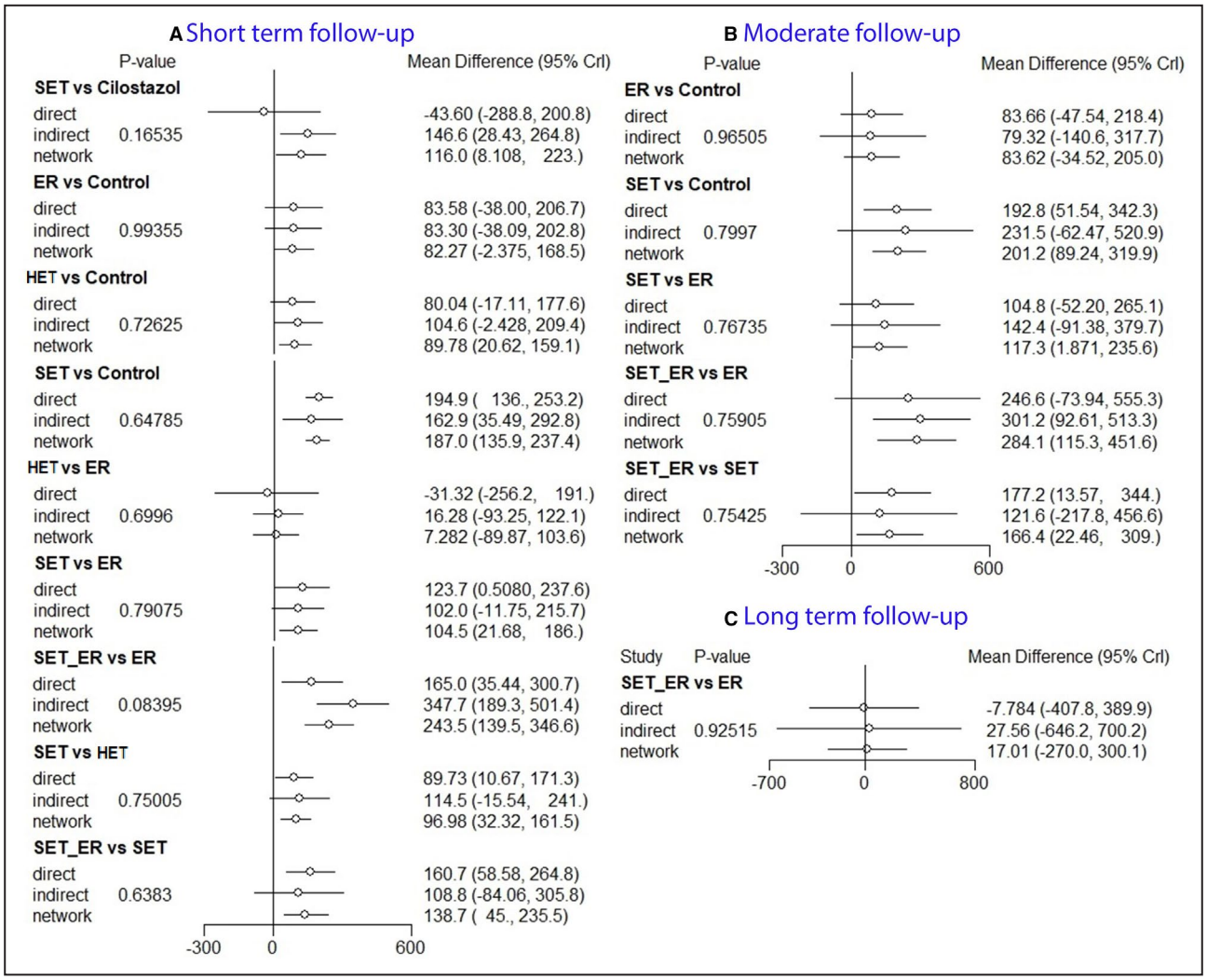

Figure 3. There were no significant differences in mean difference obtained from direct and indirect evidence.
(A) Short-term follow-up, (**B**) Moderate-term follow-up, (**C**) Long-term follow-up. This suggests that very large inconsistencies were not present within the network model. ER indicates endovascular revascularization; HET, home exercise therapy; and SET, supervised exercise therapy.

analyses were not adequately powered to identify moderate treatment effects.

Cilostazol did not significantly improve MWD during short-term follow-up and no trials testing longer-term use were identified. The largest benefit was achieved for ER plus SET. The findings agree with a prior NMA which reported ER plus SET was the most effective intervention, although this study did not consider the length of follow-up.[64] Unlike the prior NMA the current report found that ER alone did not significantly improve MWD at any time point. This difference is likely reflective of the separation of outcome data by time of follow-up in the current study. The prior NMA reported all outcome data together irrespective of follow-up time. The effect of ER alone on MWD during short-term follow-up in the current study (MD, 82.5 m; 95% CrI, –2.4 to 168.2) was very similar to that reported in the prior NMA (MD, 85 m; 95% CrI, 4–170]). The additional findings of the current NMA are important because lack of benefit as early as 2 years after treatment may lead to many participants feeling that having the treatment is not worthwhile. The findings differ from a prior Cochrane review that included a conventional MA and reported cilostazol was effective in improving MWD.[65] This disparity may be because of the much smaller number of comparator groups included in the Cochrane review, which reported traditional meta-analyses. The Cochrane review also included unpublished data and trials reported before 2000, which were not included within this meta-analysis. This difference in included data likely contributed to the disparate findings of the meta-analyses. NMA includes analyses of all included trials including those not compared head to head or directly. NMA assumes that it is reliable to

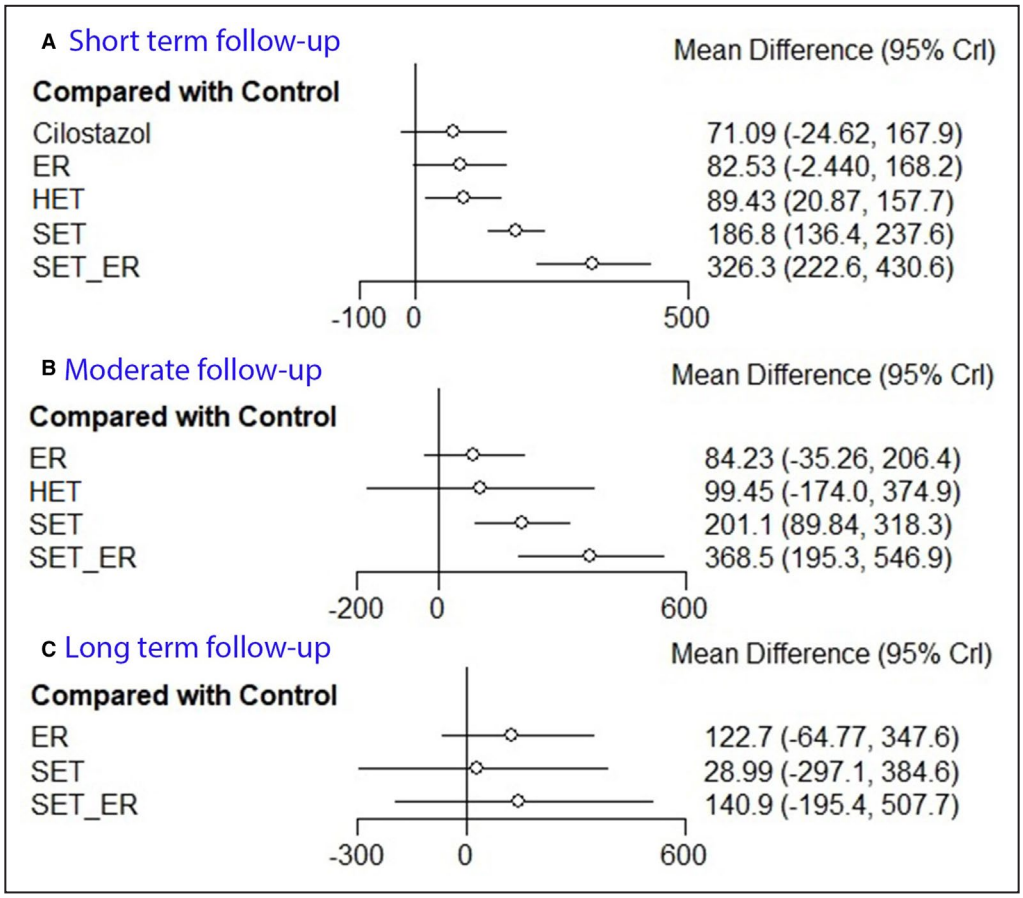

Figure 4. Forest plots of multiple treatment strategies at different follow-up periods.
(**A**) Short-term follow-up, (**B**) Moderate-term follow-up, (**C**) Long-term follow-up. Results are expressed as mean difference (95% CrI) in meters. There was significant improvement in maximum walking distance at short- and moderate-term follow-up with a combination of SET and ER and SET alone. HET only significantly improved maximum walking distance compared with controls at short-term follow-up. No treatment was significantly better than controls at long-term follow-up. CrI indicates credible intervals; ER, endovascular revascularization; HET, home exercise therapy; and SET, supervised exercise therapy.

compare between participant group included in different trials and the consistency analysis and other model diagnostics performed in this NMA suggested that the indirect comparisons did not introduce any important biases or large inconsistencies.

After 2 years follow-up, none of the treatments was found to be effective at improving MWD, in line with findings from a recent randomized trial.[6] These findings emphasize the poor durability of the available treatments for intermittent claudication, highlighting the need for new therapies. It should be noted, however, that the number of patients for whom data were available at long-term follow-up was limited and the findings may in part reflect the need for further trials testing long-term outcomes. Intensive medical management is important in people with intermittent claudication in order to reduce the risk of major cardiovascular events, such as myocardial infarction and stroke. There is now good evidence that intensive medical management can also reduce the risk of major adverse limb events. The recent COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategies) trial found that low-dose rivaroxaban (2.5 mg twice daily) plus aspirin significantly lowered the incidence of major adverse limb events as compared with aspirin alone.[66,67] Intensive low-density lipoprotein lowering has also been reported to have similar benefits in patients with peripheral artery disease.[68] Observational studies also report a significant reduction in limb loss and mortality in high-intensity statin users compared with low-intensity statin users.[69] Greater focus on optimizing medical management in people with intermittent claudication may improve QOL and reduce major adverse limb events.

Important considerations in selecting treatments for intermittent claudication include QOL and adverse events. Because of the inconsistent and limited reporting of these outcomes, however, it was not possible

to meta-analyze these outcomes. Among the included trials there was evidence in some trials that all 5 treatment combination were able to improve QOL at short-term follow-up, although findings were inconsistent. Findings were similar at moderate-term follow-up, except that no trials testing cilostazol were identified and where available most trials suggested that QOL was not improved at long-term follow-up.

Adverse events were infrequently reported in the included trials and may not be representative of outcomes in clinical practice. Little information was reported on perioperative complications following ER, drug-related adverse events, and requirement for amputation. In addition, because of the inconsistent and poor reporting of adverse events, the minimum data requirement for meta-analyses focused on serious adverse events and mortality was not met. Large trials are needed to examine the effect of exercise on mortality and cardiovascular events in people with peripheral artery disease. These are important considerations when selecting the very different treatment strategies available and need more consistent and complete reporting in future trials.

A number of limitations of this NMA should be acknowledged, including the limited number of trials, particularly testing outcome over the long term and examining the effects of cilostazol and HET. Further trials examining long-term outcomes, in particular, are required to draw reliable conclusions. Limited and inconsistent information about the medical management of participants was reported from the included trials. Most authors did not report even the frequency of statin or antiplatelet medication prescription. Importantly, NMA assumes overall similarity between studies, and interstudy differences of the included population could not be addressed. Variation in medical management between the included trials may have contributed to the heterogeneous outcomes reported. Furthermore, NMA has a number of inherent limitations as it models evidence from both direct and indirect comparisons and therefore should be interpreted cautiously.[70] The ranking probability approach shows only the relative ranks but not the absolute differences between the different treatment strategies.[71] One limitation of the current NMA was that trials published before 2000 were excluded. This was felt to be required in order for the comparison to be contemporary owing to the marked evolution of management approaches, particularly ER, and trial methods over time. Furthermore, there was substantial variation in the HET programs tested.[14] Most SET programs tested involved regular treadmill walking. Because the primary outcome was MWD in a treadmill test, it is likely this NMA has overestimated the benefit of SET owing to an established training to the outcome measure phenomenon.[72] Furthermore, detailed SAEs were not reported in most trials. These data are required to appropriately interpret the value of each treatment strategy.

CONCLUSIONS

In conclusion, this NMA suggests that ER plus SET and SET alone are effective at improving MWD in the short and moderate term (ie, under 2 years). None of the treatments, however, was effective at improving MWD during long-term follow-up. More durable therapies are needed for intermittent claudication.

ARTICLE INFORMATION

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Disclosures

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Supplementary Material

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Tables S1–S4
Figures S1–S3

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Supplemental Material

Data S1.

Search Strategy:

PubMed

((Intermittent claudication[Title/Abstract] OR Peripheral arterial disease[Title/Abstract] OR Peripheral arterial disease[Title/Abstract] OR peripheral vascular disease[Title/Abstract] OR lower extremity arterial disease[Title/Abstract]) AND (SET[Title/Abstract] OR Exercise[Title/Abstract] OR Best medical therapy[Title/Abstract] OR BMT[Title/Abstract] OR Percutaneous angioplasty[Title/Abstract] OR PCA[Title/Abstract] OR Surgical intervention[Title/Abstract] OR Revascularization[Title/Abstract] OR Cilostazol[Title/Abstract])) AND (Maximum walking distance OR MWD OR treadmill OR walking distance OR quality of life OR walking capacity OR claudication distance OR claudication onset distance)

Table S1. Characteristics of the included trials and treatments tested.

Study reference	Intervention	MWD measurement method	QoL assessment	Type of exercise	Support/method
Nylande 2007	Control	Graded treadmill test	Short Form (SF-36) and Claudication Scale (CLAU-S)	-	Smoking advice, exercise training, nutritional advice, prescribed statins and acetylsalicylic acid
	ER			-	Percutaneous transluminal angioplasty
Mazari 2017	ER	Fixed load treadmill test	Short Form 36 (SF-36) and VascuQoL	-	Percutaneous transluminal angioplasty
	SET			Gym exercise included step-ups, bicycle exercise, knee extensions with weights, heel raises, knee bends and rest station to recover.	Conducted 3 times per week for 12 weeks. The session was supervised by a physiotherapist and conducted in the cardiac gym. For the first 6 weeks, patients complete one full circuit, followed by on extra station/week, thus by 12 weeks patients will complete 2 full circuits. Finally patients perform a series of gentle stretching and cooling down exercises.
	SET+ER				Combination of both the SET and ER strategies.
Fakhry, 2013	SET	Standard treadmill test	Short Form 36 (SF-36) and VascuQoL	Treadmill walking	24 weeks supervised treadmill exercise, 2x30 minute sessions/week. Patients were encouraged to walk at least 30 minutes 3 times/week + walk 1 hour per day
	ER			-	Iliac revascularisation - self expanding nitinol stent (if initial balloon angioplasty not technically successful). Femoral revascularisation - self expanding nitinol stent if lumen diameter <50% after initial balloon angioplasty. All patients given general recommendations for lifestyle changes and strongly advised to walk regularly.
Djerf 2019	ER	Graded treadmill test	Short Form 36 (SF-36) and VascuQoL	-	TASC II A-C treated with endovascular intervention, TASC II D treated with surgical revascularisation. Procedures listed: Aortoiliac endovascular procedure, Percutaneous transluminal angioplasty/subintimal angioplasty with stent, Aortoiliac open procedure, Aortobifemoral bypass, Femoro-femoral bypass.

	Control			-	All patients given smoking cessation program + secondary preventative pharmacotherapy (single anti-platelet therapy + normal intensity statin therapy). All patients also offered Cilostazol treatment. Patients received advice including structured exercise therapy (submaximal walking sessions for at least 30 minutes, minimum 3 times per week).
Lindgren 2018	ER	Standard treadmill test	Short Form 36 (SF-36) and EuroQoL 5-dimensions (EQ5D)	-	Modern nitinol bare metal stents (BMS) were used. Calibrated angiogram compared pre- and post-implant minimum lumen diameters. IV heparin bolus of 5000 units was administered.
	Control			-	Both groups received daily antiplatelet therapy (75mg aspirin or 75mg clopidogrel), lipid lowering and antihypertensive drugs). Patients received a pedometer and were encouraged to exercise when readouts were recorded
Murphy 2015	Control	Graded treadmill test	SF-12 (23), the Walking Impairment Questionnaire (WIQ) (10), and the Peripheral Artery Questionnaire (PAQ)	-	Control group received OMC according to current guidelines - use of atherosclerosis risk factor management, cilostazol, home exercise counselling
	SET			Treadmill walking	SET patients received OMC + SET. Consisted of treadmill walking for up to 78 scheduled exercise sessions that were 1 hour long, 3 days a week for 6 months. Patients received quarterly contact by research coordinators during supervised phase - then participated in a telephone-based maintenance program (7-12 months) to promote exercise adherence.
	ER			-	EVR patients received OMC + stent revascularisation of hemodynamically significant stenoses in the aorta and iliac arteries in the symptomatic leg(s)
Greenhalgh 2008	ER+SET	Graded treadmill test	SF36 short-form	Stair climbing, heel raises and treadmill walking	Percutaneous transluminal angioplasty
	SET			Stair climbing, heel raises and treadmill walking	SET consisted of 30 minutes of continuous exercise to a maximum pain threshold using walking circuit interspersed with 7 lower limb training stations (eg. stair climbing, heel raises, treadmill walking) supervised by physiotherapists or nursing staff. All participants underwent OMC which involved: assessment of BP measure, dyslipidaemia, serum glucose and anti-platelet treatments and drug therapy was commenced when necessary.

Gelin 2001	Control	Graded treadmill test	Quality of life evaluation reported in different publication	-	All patients were advised to give up smoking. Control patients received no other specific advice or treatment apart from the general advice given to the two treatment groups
	SET			Treadmill walking	SET patients were referred to trained physiotherapists - 30 minute sessions of specific walking training per week during the initial 6 months with 10-12 patients participating in each training class as described. After 6 months 2 sessions per week were offered
	ER			-	EVR patients were referred for standard angiography. Based on these findings, endovascular or open surgical procedures were chosen.
Bo 2015	ER	Graded treadmill test	Short Form 36 (SF-36) [26], as well as a disease-specific instrument, the Claudication Scale (CLAU-S)	-	Percutaneous transluminal angioplasty
	SET+ER			Treadmill walking and high intensity exercises	SET two days per week for 12 weeks + one home based exercise session per week. After hospital based SET, participants conducted home based exercise sessions every week for an additional 12 weeks. Each session lasted 60 minutes (consisted of warm-up exercises, 3 high intensity intervals, two moderate intensity intervals and cool down exercises)
Spronk 2009	ER	Standard treadmill test	Short Form 36 (SF-36) and VascuQoL	-	Endovascular revascularisation was performed by an interventional radiologist. For iliac revascularisation: initial balloon angioplasty, if that failed then self-expanding nitinol stent was used. For femoral revascularisation: self-expanding nitinol stent was chosen based on angiography.
	SET			Treadmill walking without a graded incline and variations in speed	SET performed over 24 weeks on a walking treadmill - 30 minutes per session, twice weekly supervised by a vascular technologist. Treadmill exercise was initiated at a workload of 3.5km/h without a graded incline and decreased to 1km/h when perceived maximum claudication pain occurred, and increased after a few minutes after the pain subsided.
Crowther 2008	Control		NA	-	Control

	SET	Graded treadmill test		Treadmill walking with progressive increase in intensity and duration	Exercise program initial consisted of treadmill walking 3 days per week for 25 minutes at 3.2 km/hr. Participants were required to walk until pain level was perceived as 3 or 4 on the CPS. Exercise intensity (treadmill grade and walking speed) and duration (25 to 40 minutes) was progressively increased. This was performed over a 12 month period
Cheetham 2004	HET	Graded treadmill test	the Short-Form-36, the Charing Cross Symptom Specific Claudication Questionnaire (CCCQ)	-	All patients were given best medical treatment (antiplatelet therapy, antihypertensive therapy, cholesterol lowering agents and diabetic control. Each patient received verbal and written exercise advice - recommended a program of walking at least 3 times a week to near maximal pain for at least half an hour per session. Additional leg exercises were to be performed at home (stair climbing and tiptoe walking)
	SET			Gym exercise included stair climbing, low step climbing, high step climbing, tip toe walking, standing on tip toe from flat, standing on tip toe from ankle dorsi-flexion and power-jogger walking	A 45 minute class was conducted under physiotherapy and medical supervision in a standard hospital gym. Commenced with a 5-10 minute talk on benefits of walking. Followed by half an hour of exercise consisting of a walking circuit and performing seven 2 minute exercise stations for lower limb strengthening. Stair climbing, low step climbing, high step climbing, tip toe walking, standing on tip toe from flat, standing on tip toe from ankle dorsi-flexion and power-jogger walking. Each 2 minute station was interspersed with a 2 minute walking circuit
Gardner 2002	Control		Self-reported Walking	-	Control

	SET	Graded treadmill test	Impairment Questionnaire	Treadmill walking and bicycle ergometer exercise	Supervised 6 months progressive exercise program followed by supervised, 12-month maintenance exercise program. The progressive program consisted of intermittent treadmill walking to near maximal claudication pain 3 days per week at a walking speed of approximately 2 mph. Walking duration began at 15 minutes for the first month of the program, and progressively increased by 5 minutes per month until a total of 40 minutes of walking was accomplished by the sixth month of rehabilitation. Walking intensity began at 50% of the maximal work load achieved during a maximal effort treadmill test, and progressively increased on an individual basis throughout the program to 80% by the sixth month of rehabilitation. Five minutes of cycling on a stationary bicycle ergometer served as both warm-up and cool-down exercise during each session. The final 12 months of the exercise program was considered the maintenance phase in which the frequency of exercise sessions was reduced to 2 days per week. Walking duration and intensity were maintained at 40 minutes and 80% of the maximal work load respectively.
Baker 2017	SET	Graded treadmill test	NA	Treadmill exercise	Subjects performed three 60-minutes supervised exercise training sessions each week for a period of 3 months. Subjects walk on a treadmill at an initial speed of 2.0 mph to a mild to moderate pain level, stop and rest until the claudication pain has completely abated, and then resume walking. This pattern was repeated for a total of 60 minutes. If subjects can walk longer than 8 minutes without rest, the treadmill walking becomes more challenging via grade and speed increases in subsequent training sessions.
	Control			-	Control
Brass 2012	Cilostazol	Graded treadmill test	NA	-	Patients were randomized to one of five study arms: placebo, K-134 at a dose of 25, 50, or 100 mg, or cilostazol at 100 mg, each twice daily.
	Control			-	Placebo

Collins 2011	Control	Graded treadmill test	San Diego Claudication Questionnaire and Physical Activity Readiness Questionnaire (PAR-Q)	-	All participants viewed a 7-minutes educational video about PAD and its clinical leg symptoms, life-threatening consequences of PAD (heart attack and stroke), other adverse outcomes (walking disability), and strategies for disease and risk factor management (smoking cessation, weight control, aerobic activity). After the video, each participant met face-to-face with the research coordinator. Participants were encouraged to ask questions about the video material. The coordinator queried participants regarding self-management behaviors (i.e., glucose monitoring, blood pressure monitoring) and gave them a calendar in which to document their daily glucose results, weekly blood pressures, and any routine lipid results provided by their primary care physician.
	HET			-	Intervention group subjects participated in a home-based walking program with three components: 1) A one-on-one interaction with the research coordinator at baseline; 2) Walking training and weekly group walking classes with an instructor; 3) Bi-weekly telephone calls for 6 months. Participants were then encouraged to walk 1 day per week with the study exercise instructor and other participants, as available, and to continue walking on their own at least 3 days per week for a minimum of 4 days of walking each week. Participants were advised to walk 50 minutes total for each session, and use their pedometers to increase the number of steps by 50 each session.
Crowther 2012	SET	Graded treadmill test	Borg's Rating of Perceived Exertion (RPE) instrument and Claudication Pain Scale (CPS)	Treadmill exercise with progressive increase in intensity and duration	The exercise program initially consisted of intermittent supervised treadmill walking 3 days per week for a total time of 25 minutes at 3.2 km/hr (0.88 m/s). Participants were required to walk until the pain level was perceived as being 3 or 4 on the CPS. Exercise intensity (via treadmill grade and walking speed) and duration (25 minutes up to a maximum of 40 minutes) were progressively increased once the participant could walk continuously for 25 minutes at a level below 3 on the CPS pain scale. This exercise progression strategy was continued over the 6-month period.
	Control			-	Standard medical treatment as outlined in the Trans-Atlantic Inter-Society Consensus (TASC II) guidelines.
Dawson 2000	Cilostazol		NA	-	Cilostazol taken 100 mg twice daily.

	Control	Graded treadmill test		-	Placebo taken daily
Fakhry 2015 (ERASE trial)	SET+ER	Graded treadmill test	VascuQol and Short Form 36 Health Survey (SF-36)	Treadmill walking	ER performed by experienced interventional radiologist or vascular surgeon. For iliac and femoral revascularizations, a stent was used only if the initial balloon angioplasty was not successful (selective stenting). In addition, within 2 to 4 weeks after the procedure, patients were enrolled in the supervised exercise program described above.
	SET			Treadmill walking	Exercise program consisted of treadmill walking to near maximum claudication pain. Physiotherapists were advised to start with a frequency of 2 to 3 sessions every week and approximately 30 to 45 minutes per session during the first 3 months. After this phase, the frequency was reduced to at least 1 session per week between months 3 and 6 and then to a frequency of 1 session every 4 weeks at 12 months depending on patients' progress and preference.
Gardner 2001	SET	Graded treadmill test	Medical Outcomes Study Short-Form 36 (MOS SF-36)	Treadmill walking	The exercise rehabilitation program consisted of 6 months of supervised, intermittent treadmill walking to near maximal claudication pain 3 days per week as previously described.
	Control			-	The control group did not receive any recommendations regarding exercise and both groups received usual medical care from their healthcare providers.
Gardner 2014	SET	Graded treadmill test	Medical Outcomes Study Short-Form 36 (MOS SF-36)	Treadmill walking with progressive increase in duration	Exercise sessions in our supervised exercise program were performed while wearing a step activity monitor as previously described. Briefly, the supervised program consisted of 3 months of intermittent treadmill walking to mild-to-moderate claudication pain 3 days per week at a speed of 2 mph and at a grade equal to 40% of the highest work load achieved during the baseline maximal treadmill test. Sessions progressively increased during the program from 15 to 40 minutes.

	HET			-	This program consisted of 3 months of intermittent walking to mild-to-moderate claudication pain 3 days per week at a self-selected pace, in which exercise duration was progressively increased from 20 to 45 minutes per session. Patients wore the step activity monitor during each exercise session and returned the monitor and a logbook to the research staff at the end of week 1, 4, 8, and 12. During these brief 15-minute meetings, monitor data were downloaded, results were reviewed, and feedback was provided for the upcoming month of training.
	Control			-	Attention-Control, light resistance program. Light resistance training was performed 3 times per week, without any walking exercise, using a Pro-Form Fusion 6.0 LX weight system. On entry, the resistance that caused fatigue in various muscle groups after 15 repetitions (15-rep maximum) was established, and was reassessed each month. The resistance training phase consisted of performing upper extremity exercises that included the bench press, military press, butterfly, biceps curl, triceps press-down, and lat pulldown. Lower extremity exercises included the leg press, leg curl, and leg extension. One set of 15 repetitions was performed for each exercise. If the resistance from the exercise machine could not be lifted, resistance bands were used instead.
Gardner 2012	SET	Graded treadmill test	Walking Impairment Questionnaire	Treadmill walking with progressive increase in intensity and duration	This program consisted of 6 months of supervised intermittent treadmill walking to near-maximal claudication pain 3 days per week. Walking duration and intensity of the sessions were progressively increased during the program. Walking duration began at 15 minutes for the first month of the program and increased by 5 minutes per month until 40 minutes of walking was accomplished by the sixth month of rehabilitation. Walking intensity began at an initial grade of 50% of the final workload attained during the baseline graded treadmill test and was increased by 10% every 6 weeks up to 80% during the final 6 weeks of the exercise program. During each exercise session, patients walked at approximately 2mph until their claudication pain reached a level of 3 on a 0 to 4 pain scale.
	Control			-	This group were encouraged to walk more on their own but did not receive specific recommendations regarding an exercise program during the study.

Gardner 2011	HET	Graded treadmill test	Medical Outcomes Study Short-Form 36 (MOS SF-36) and Walking Impairment Questionnaire (WIQ)	-	Home-based exercise program was designed to be as similar to the supervised exercise program as possible, and consisted of 12 weeks of intermittent walking to near maximal claudication pain three days per week at a self-selected pace. Walking duration began at 20 minutes for the first two weeks, and progressively increased five minutes bi-weekly until a total of 45 minutes of walking was accomplished during the final two weeks of the program. These exercise durations were five minutes longer throughout the program than in the supervised program in an attempt to better match the programs on total volume of exercise determined by multiplying the intensity and the duration of walking.
	SET			Treadmill walking with progressive increase in intensity and duration	This standardized program consisted of three months of supervised intermittent treadmill walking, three days per week at a speed of approximately two mph. Walking duration began at 15 minutes for the first two weeks of the program, and progressively increased by 5 minutes biweekly until a total of 40 minutes of walking was accomplished during the final two weeks of the program. Because we have previously shown that changes in COT and MWT are similar for patients who train at a relatively high exercise intensity (80% of peak work load) and patients who train at a lower intensity (40% of peak work load) for longer duration.
	Control			-	This group were encouraged to walk more on their own but they did not receive specific recommendations regarding an exercise program during the study.
Hobbs 2006	Control	Standard treadmill test	NA	-	Control
	ER			-	Percutaneous transluminal angioplasty

	SET			Gym exercise and treadmill walking with varied intensity	This sequence involved a shuttle walk at moderate to hard pace; paired toe raising to heel raising, with chair support for balance; continuous sitting and standing from chair; spot marching with high knees, swinging arms; arm exercises from the upright sitting position (side arm raising, alternate arm vertical pushing, and side bent-arm lift); shuttle walk at moderate to hard pace; knee bends with chair support for balance; alternate heel raising (left/right) with chair support for balance; step-ups on bench or stairs; and arm exercises from the upright sitting position (straight side arm small backward circling, double arm vertical pushing, and side bent-arm lift, alternating arms. Twice weekly 1 hour exercise sessions - subjects underwent 3 minutes of activity at multiple stations followed by 2 minutes of rest. On days when not attending the supervised sessions, subjects were asked to perform the exercise program unsupervised at home. Training logs were kept to detail the number of repetitions performed and the maximal heart rate at each station to ensure an adequate training effect.
Hobbs 2007	SET	Standard treadmill test	NA	Treadmill exercise	The supervised exercise comprised a 3-month, twice weekly, 1-hour physiotherapist-led exercise program. In addition to the supervised sessions, subjects were provided with a videotape of the exercise program and encouraged to undertake the exercises at home and complete an exercise log on the days that they did not attend the classes.
	Cilostazol			-	Cilostazol was prescribed at a dose of 100 mg twice daily. If side effects were encountered (most commonly headache and diarrhoea), the dosing regimen was halved for 1 week.
	SET + cilostazol			Treadmill exercise	Programs were as followed in both SET and Cilostazol groups
	Control			-	Control
Hodges 2008	SET	Graded treadmill test	Self-reported rating of perceived exertion	Treadmill exercise	Patients in the supervised group visited the hospital twice weekly for a period of 12 weeks. During the session patients were encouraged to walk on a treadmill (3.2 km/h) and 75% of the initial grade achieved during the exercise test) until they reached stage three or four on the PAD pain scale. Repeated until each patient had accrued 30 minutes of exercise per session.

	Control			-	The patients in the control group were given normal treatment. These patients were told to walk as often as possible, but given no exercise regime to follow
Kakkos 2005	HET	Standard treadmill test	Short Form 36 (SF-36), Walking Impairment Questionnaire (WIQ), and Intermittent Claudication Questionnaire (ICQ)	-	All patients received the following: Current smokers were advised to stop smoking, antiplatelet therapy, preferably 75mg aspirin once daily, was commenced if the patient was not already on it and lipid-lowering agents (statins) were prescribed and titrated to reduce LDL serum levels below 2.5–3 mmol/L, if necessary. Patients allocated to unsupervised exercise (control group) were advised to exercise daily by walking as much as possible to near maximal pain, for a period of at least 45 minutes.
	SET			Treadmill walking with progressive increase in intensity and duration	Patients attended the physiotherapy department for exercise therapy three times per week for the first 6 months. Compliance was assessed with logbooks. Supervision was provided on an individual or group basis and each session lasted for about 60 minutes. A session consisted of 5 minutes warm up activities, 50 minutes of intermittent exercise and ended with 5 minutes of cool-down activities. Walking treadmill exercise was started at a low treadmill workload of 2 mph, 0% grade. Patients walked until claudication pain become moderately severe, at which time they step off the treadmill and rest until claudication pain subsides. After the patient had walked 8–10 minutes at the initial workload, either the grade was increased by 1–2%, or the speed was increased by 0.5 mph as tolerated.

Kruidenier 2011	ER	Graded treadmill test	Medical Outcomes Study Short-Form 36 (MOS SF-36) and Euroqol-5D questionnaire	-	All patients received cardiovascular risk factor modification, including therapy with a platelet inhibitor and a statin and treatment of hypertension or diabetes or both as required. All patients who smoked were repeatedly advised to quit smoking and were offered a smoking cessation program. All patients were advised concerning lifestyle changes (eg, physical activity, weight, diet) according to the Dutch standard for cardiovascular risk management. The choice for a primary PVI for the individual patient was based on the results of imaging with duplex ultrasound or magnetic resonance angiography or both as discussed in a multidisciplinary meeting of interventional radiologists and vascular surgeons. Mainly iliac lesions generally were treated with a PVI, and depending on lesion classification, femoropopliteal lesions also were treated. Not all lesions were necessarily treated. All PVIs were performed by an experienced interventional radiologist and consisted of iliac angioplasty with selective stent placement for iliac stenoses, angioplasty with primary stent placement for superficial femoral artery stenoses, or recanalization with primary stent placement for iliac and femoral occlusions.
	SET+ER			Treadmill walking, , Cycle ergometer, Indoor walking space, Small group exercise room	Patients in the PVI SET group, the SET program was scheduled to start within 3 weeks after the PVI. The SET program was performed in a community-based setting, meaning that patients followed exercise therapy by a trained physiotherapist in proximity to their homes. Organization and results of community-based SET have been described previously. SET was administered according to the guidelines of the Royal Dutch Society for Physiotherapy. The main goal of SET is to increase a patient's walking distance by interval training with short (3–5 minutes) walking intervals up to submaximal pain (distraction not possible). Secondary goals are increasing endurance and strength and improving walking patterns. Patients generally started with a frequency of two to three sessions of 30 minutes a week. Frequency of the sessions was phased down according to the patient's progress. Patients were encouraged to walk on a daily basis

Lamberti 2016	HET	Standard treadmill test	Medical Outcomes Study Short-Form 36 (MOS SF-36)	-	The program included two 10-minute sessions/day (6 days/week) of intermittent walking (1-minute work and 1-minute rest while seated) at a prescribed speed converted into a walking cadence and followed at home using a metronome. A semipersonalized training program was proposed according to the patient's baseline exercise capacity (ICD less than or greater than 50 metres). The walking sessions were preferably performed indoors at home (eg., in a hallway or a heated garage) to avoid the influence of weather or on a treadmill.
	ER			-	Open surgery or endovascular revascularization or both were planned. The team included highly experienced vascular surgeons and interventional radiologists. For each patient, the team performed the option that was most likely to yield the best hemodynamic improvement. After intervention, the patients received general recommendations regarding lifestyle changes and standardized advice to be physically active at home.
Novakovic 2018	SET	Standard treadmill test	36-Item Short Form Survey (SF-36)	Treadmill walking followed by recovered on an exercise bike with no resistance	Interventions consisted of 36 training sessions, two or three times per week, according to the patient's preferences. If patients could not attend prescheduled sessions, they were offered a new rescheduled session in the same week. A single training session lasted around 60 minutes and consisted of walking on a treadmill, followed by active recovery on an exercise bike with no resistance.
	Control			-	The control group was advised to continue with secondary preventive activities including regular walking as recommended by the treating vascular specialist.
Mauer 2015	SET	Graded treadmill test	Baltimore Activity Scale for Intermittent Claudication (BASIC) questionnaire	Treadmill walking with progressive increase in duration	Supervised exercise rehabilitation program that was designed to elicit increases in COT and PWT as previously described. This standardized program consisted of 3 months of supervised treadmill walking sessions 3 days per week. Walking duration began at 15 minutes for the first 2 weeks of the program and progressively increased by 5 minutes bi-weekly until a total of 40 minutes of walking was accomplished during the final 2 weeks of the program. Patients walked at a grade equal to 40% of the final workload from the baseline maximal treadmill test to the point of near-maximal claudication pain at which point they stopped to relieve their leg pain.

	Control			-	Patients randomized to this group (n = 7) participated in supervised light resistance training over the 3-month study period. Light resistance training was performed three times per week, without any walking exercise, using a Pro-Form Fusion 6.0 LX weight system. On entry, the resistance that caused fatigue in various muscle groups after 15 repetitions (15-rep maximum) was established and was reassessed each month. The resistance training phase consisted of performing upper extremity exercises that included the bench press, military press, butterfly, biceps curl, triceps press down, and lat pull-down. Lower extremity exercises included the leg press, leg curl, and leg extension. One set of 15 repetitions was performed for each exercise. If the resistance from the exercise machine could not be lifted, resistance bands were used instead.
	HET			-	Home-based exercise rehabilitation program that was designed to be as similar to the supervised Exercise program as possible and consisted of 12 weeks of intermittent walking to near-maximal claudication pain 3 days per week at a self-selected pace. Walking duration began at 20 minutes for the first 2 weeks and progressively increased 5 minutes bi-weekly until a total of 45 minutes of walking was accomplished during the final 2 weeks of the program.
Mays 2015	Control	Graded treadmill test	Walking Impairment Questionnaire and SF-36	-	Patients assigned to the control group received verbal advice to exercise but no other formal training.
	HET			-	Patients in the intervention group received in-hospital exercise training on a treadmill for an initial 2 weeks (3 days/week). Patients then completed 12 weeks of community-based walking exercise training. Patients instructed to walk/rest on treadmill for 35 minutes progressing to 50 minutes as tolerated. Intensity enough to induce moderate leg pain in 3-5 minutes for patients with IC. Attempts were made to increase exercise intensity weekly.
Mika 2005	SET	Standard treadmill test	NA	Treadmill walking	Patients in the treatment group participated in 12 weeks of supervised treadmill training. The exercise training sessions were conducted three times a week on a treadmill during the morning hours. Treadmill speed was set at 3.2 km/hr and at an inclination on 12 degrees. The session consisted of intermittent walking to 85% of the previously individually determined pain-

					free walking distance. The goal of such a workload was not to produce a claudication pain.
	HET			-	Control patients were instructed to maintain their usual level of activity.
Miika 2011	SET	Graded treadmill test	NA	Treadmill walking with progressive increase in inclination, cycling exercise	Patients in the training group participated in a 12-week supervised treadmill training programme. The sessions were conducted in the morning, three times per week and consisted of repetitive walking exercise with 3-minutes resting intervals. During each session, after 5 minutes of warm-up activities (free cycling on a stationary cycle ergometer), subjects walked on the treadmill at a speed of 3.2 km/h and a grade that induced claudication pain within approximately 3 to 5 min. Walking was continued until onset of claudication pain (level 2 on pain scale). The main goal of this protocol was to approach but not continue walking beyond the claudication pain. Patients stopped exercise when the pain level 2 was reached. Both the duration and intensity of sessions were progressively increased during the programme.
	Control			-	Control group were advised not to change their usual level of activity. All study participants were encouraged to stop smoking. Their diet was neither controlled nor modified throughout the study period.
O'Donnell 2009	Cilostazol	Standard treadmill test	Short form 36 (SF-36), Disease-Specific Walking Impairment Questionnaire (WIQ), and Vascular Quality of Life (VascuQoL)	-	Cilostazol 100 mg twice daily
	Control			-	Placebo twice daily
Sandercock 2007	SET	Graded treadmill test	NA	Walking instructions with diary to complete	The SET group were given an exercise diary to complete and instructed to undertake one additional weekly 30 minutes walking session.

	HET			-	HET group were given an exercise diary to complete and instructed to undertake three 30 minutes walking sessions per week at a RPE of 12 - 14. This group was also contacted weekly by telephone and given support and encouragement in adhering to the protocol.
	Control			-	The control group were given verbal information regarding the safety and efficacy of walking exercise but no specific instructions were given regarding exercise duration, intensity or frequency.
Schlager 2011	SET	Standard treadmill test	NA	Incremental exercise training	Patients underwent a standardized training program twice a week for six months. SET was based upon the current guidelines for patients with intermittent claudication and was guided by physiotherapists. After a warm up period of 5–10 min, the initial duration included 35 minutes of intermittent walking which was increased by 5 minutes each session until 50 minutes of intermittent walking was accomplished. The workload of exercise training was set to a walking speed that elicited claudication symptoms within 3–5min. Patients were trained at this workload until they achieved moderate claudication followed by a brief resting period to allow symptoms to resolve
	Control			-	Control
Stewart 2008	SET	Standard treadmill test	NA	Circuit format with no treadmill walking	Supervised exercise program comprised 5 different exercises in a circuit format. Patients were advised to rest when symptoms of claudication became intolerable and to recommence exercise when the pain subsided. After 8 minutes, the patients moved on to the next exercise. Two 1 hour classes were run each week, each with a maximum exercise time of 40 minutes with 10 minutes warm-up and cool down periods. The exercises were mainly based on calf muscle and could be continued at home without the need for specialized equipment. Treadmill exercises were not included to avoid the potential bias between the groups.
	HET			-	Control group that received exercise advice alone.
Strandness 2002	Cilostazol		Medical Outcomes	-	Cilostazol 100 mg twice daily

	Control	Standard treadmill test	Scale Short Form (SF-36), Walking Impairment Questionnaire (WIQ), and Claudication Outcome Measures	-	Placebo twice daily
Tew 2015	Control	Graded treadmill test	EuroQoL	-	Control
	HET			-	The intervention was modelled on the structured education self-management programmes used in diabetes care
Tsai 2002	SET	Graded treadmill test	Medical Outcomes Study Short-Form 36 (MOS SF-36) Chinese version, Walking Impairment Questionnaire	Treadmill walking with progressive increase in inclination	Patients in the exercise group performed the treadmill exercise three times each week until 12 weeks. Exercise training began with 5 minutes of warm up and ended with 5 minutes of cool down. During exercise, patients' heart rate and 12-lead electrocardiogram were continuously monitored to detect any exercise-induced dysrhythmias. Arm blood pressure values and claudication pain scores were collected every 5 minutes Exercise intensity started from 2 mph, 0% grade, with 1% grade increase every 10 minutes if patients reported a claudication pain score below 2. Patients were encouraged to exercise up to 30 minutes with their claudication pain scores between 2 and 3 (pain levels between mild and moderate).
	Control			-	Control - usual care
Zwierska 2005	SET	Incremental shuttle walk	NA	Cycling exercise	SET twice a week for 24 weeks. For each of the supervised training sessions, patients exercised in cycles of 2 minutes exercise at a crank rate of 50 rev/min, followed by 2 minutes rest, for a total exercise time of 20 minutes in a 40-minute session. For the upper limb aerobic exercise training, the arm-crank ergometer was placed on a table in front of the seated patient with the mid-point of the sprocket set at shoulder height.

	SET			Cycling exercise	For lower limb aerobic exercise training, the seat height was adjusted to allow slight knee flexion at bottom dead centre. Up to eight patients exercised together in the same session.
	Control			-	Patients in the control group were given lifestyle advice, including encouragement to undertake regular exercise.
Duscha 2018	HET	PAD-specific maximal treadmill cardiopulmonary exercise	NA	-	Patients wore the Fitbit device for 2 weeks, and were told to continue normal activities without purposely increasing or decreasing exercise.
	Control			-	Control
Bulinska 2016	SET (treadmill)	Graded treadmill test	NA	Treadmill walking with progressive increase in inclination	The program of supervised walk training was carried out for three months (36 training sessions), three times a week from 30 (first week) up to 50 min. Each training began with a short warm-up (5–10 min) which consisted of flexibility exercises for upper and lower extremities and spine. Training was ended with stretching and breathing exercises (3–5 min). Treadmill training was conducted on a treadmill HX-100 with the constant workload protocol based on TASC II guidelines. Speed and slope were constant, amounted to 3.2 km/h (2.0 mph) and 12% grade. Patients walked up to the reach of submaximal level of pain (ACSM – level 4) and next rested in standing position when the level of pain decreased to 1 (no pain) but no longer than 2 min.
	SET (Nordic Pole Walking)			Nordic pole walking	NPW was performed by a qualified physiotherapist using the NW technique according to the guidelines of the International Nordic Walking Federation (INWA) with the KV+ poles. The pole length was adopted for each subject based on body height (0.7 × height). Patients trained under the same conditions as in TT. During the rest period, patients monitored HR individually. NPW was conducted in a group (max 12 participants) generally in outdoor.

Girold 2017	SET (Nordic Pole Walking)	Graded treadmill test	NA	Nordic pole walking	Before Nordic walking sessions, all NWG patients received individual training for 30 minutes on the handling of poles and the technique of Nordic walking, to discover the activity and become familiar with the most effective movements.
	SET (Walking group)			Walking on flat surface	Walking sessions for both groups started after a 10-minutes warm-up to stimulate and effectively prepare the cardiorespiratory and muscular system for the effort. Then, each patient performed a 45-minutes session of walking at a pace dictated by the training heart rate.
Spafford 2014	HET	Modified shuttle walking test	NA	-	The HEP group was given written instructions to walk at their normal pace for at least 30minutes three times per week.
	HET (NPW)			-	Patients in the NPW group were given a pair of LEKI Nordic walking poles adjusted for height (height × 0.7) and asked to walk using the poles for at least 30 minutes three times per week.

ACSM – The American College of Sports Medicine; BMS – Bare metal stent; BP – Blood pressure; COT – Claudication onset time; CPS – Composite pain scale; d – Day; ER – Endovascular revascularization; HET – Home exercise therapy; HR – Heart rate; ICD – Intermittent claudication distance; IC – Intermittent claudication; INWA – International Nordic walking federation; km/h – Kilometer/hour; mg – Milligram; m/s – meters/second; mph – Miles per hour; MWD – Maximum walking distance; MWT – Maximum walking time; NR – Not reported; NPW – Nordic pole walking; OMC – Optimal Medical Care; PAD – Peripheral artery disease; PTA – Percutaneous transluminal angioplasty; PVI – Percutaneous vascular intervention; PWT – Peak walking time; RPE – Ratings of perceived exertion; SET – Supervised exercise therapy; TASC – Transatlantic Inter-Society Consensus; TT – Treadmill testing; Wk – Week; % - Percentage.

Table S2. Ranking probability percentage of each treatment arms.

Ranking probability (%) - Short term follow-up						
	Rank1	**Rank2**	**Rank3**	**Rank4**	**Rank5**	**Rank6**
Control	0	0	0	0.09	6.62	93.28
HET	0	0.28	13.93	47.83	37.23	0.73
ER	0.02	13.79	54.79	22.43	8.75	0.2
Cilostazol	0.03	3.18	14.83	28.79	47.37	5.78
SET	0.25	82.45	16.42	0.85	0.01	0
SET_ER	99.68	0.29	0.02	0	0	0

Ranking probability (%) - Moderate term follow-up					
	Rank1	**Rank2**	**Rank3**	**Rank4**	**Rank5**
Control	0	0.03	1.86	18.48	79.63
ER	0.03	1.62	43.96	50.54	3.83
HET	1.1	10.07	41.6	30.68	16.53
SET	0.95	86.53	12.24	0.26	0
SET_ER	97.9	1.73	0.33	0.03	0

Ranking probability (%) - Long term follow-up				
	Rank1	**Rank2**	**Rank3**	**Rank4**
Control	2.97	9.65	22.6	64.72
ER	41.56	41.93	15.51	1
SET	3.01	16.59	49.59	30.49
SET_ER	52.46	31.82	12.28	3.43

Table S3. Quality of life outcomes as reported at different follow-up periods from eligible trials.

Study reference	Intervention	QoL type	QoL	Short term summary	Moderate term summary	Long term summary
Nylande 2007	Control	Generic	SF-36	Significant improvements were seen in physical functioning and reported health transition.	Bodily pain and reported health transition were significantly improved	Only reported health transition domain was significantly improved
	ER			Only physical functioning domain was significantly improved. Remaining domains did not change	Bodily pain and reported health transition were significantly improved	Only reported health transition domain was significantly improved
	Control	Disease specific	CLAU-S	None of the domains significantly improved	Only severity of pain was significantly improved	Only pain during activity was significantly improved
	ER			Pain during activity and severity of pain significantly improved. Other domains including everyday life, pain related to sleep, social life, specific fears related to illness and psychological well-being did not change	Only pain during activity was significantly improved	Only pain during activity was significantly improved
Mazari 2017	ER	Generic	SF-36	NA	NA	None of the domains significantly improved
	SET			NA	NA	None of the domains significantly improved
	SET+ER			NA	NA	None of the domains significantly improved
	ER	Disease specific	Vascu QoL	NA	NA	None of the domains significantly improved
	SET			NA	NA	None of the domains significantly improved
	SET+ER			NA	NA	None of the domains significantly improved

Fakhry, 2013	SET	Generic	SF-36	NA	Physical function, bodily pain and general health significantly improved	General health domain significantly decreased
	ER			NA	Physical function, role physical and bodily pain significantly improved	Physical functioning, role physical and bodily pain significantly improved
	SET	Disease specific	Vascu QoL	NA	VascuQoL and rating score significantly improved	Only VascuQoL score significantly improved
	ER			NA	VascuQoL and rating score significantly improved	Only VascuQoL score significantly improved
Djerf 2019	ER	Generic	SF-36	Physical functioning and bodily pain significantly improved compared to baseline and control group	Domains including physical functioning, role physical and bodily pain significantly improved	None of the domains significantly improved
	Control			None of the domains significantly improved	Domains including physical functioning, role physical and bodily pain significantly improved	Only role physical domain was significantly improved
	ER	Disease specific	Vascu QoL	Domains including activities, symptoms, and emotional were significantly increased	All domains significantly improved	None of the domains significantly improved
	Control			None of the domains significantly improved	All domains significantly improved	None of the domains significantly improved
Lindgren 2018	ER	Generic	SF-36	NA	NA	Domains including physical functioning, bodily pain, vitality and physical component summary were significantly improved
	Control			NA	NA	None of the domains significantly improved
	ER	Generic	EQ5D	NA	NA	EQ5D did not significantly improve
	Control			NA	NA	EQ5D did not significantly improve
	ER		WIQ	NA	NA	WIQ scores significantly improved

	Control	Disease specific		NA	NA	WIQ scores significantly improved
Murphy 2015	Control	Generic	SF-12	NA	No significant improvement in SF-12 physical score	NA
	SET			NA	SF-12 physical score was significantly improved compared to control but no difference within intragroup	NA
	ER			NA	SF-12 physical score was significantly improved compared to control but no difference within intragroup	NA
	Control	Disease specific	WIQ	NA	No significant improvement in pain severity and walking distance	NA
	SET			NA	Pain severity and walking distance were significantly improved compared to control and baseline but no significance reported	NA
	ER			NA	Pain severity and walking distance were significantly improved compared to control and baseline but no significance reported	NA
	Control	Disease specific	PAQ	NA	No significant improvement in physical limitation, symptoms, QoL and summary	NA
	SET			NA	Only PAQ summary was significantly improved compared to baseline and control	NA

	ER			NA	Physical limitation, symptoms, QoL and summary improved compared to baseline and control. Physical limitation, QoL and summary were significantly improved compared to SET	NA
Greenhalgh 2008a	ER+SET	Generic	SF-36	NA	NA	None of the domains significantly improved
	SET			NA	NA	
Greenhalgh 2008b	ER+SET	Generic	SF-36	NA	NA	Physical score domains significantly improved compared to SET, but no significance reported comparing with baseline
	SET			NA	NA	
Gelin 2001	Control	Generic	NA	NA	NA	NA
	SET			NA	NA	NA
	ER			NA	NA	NA
Bo 2013	ER	Generic	SF-36	NA	Physical function, bodily pain and vitality were significantly different between the groups, but not reported against baseline.	NA
	SET+ER			NA		NA
	ER	Disease specific	CLAU-S	NA	Daily life domain showed a trend towards improvement but not statistically different. Other domains did not change.	NA
	SET+ER			NA		NA
Spronk 2009	ER	Generic	SF-36	None of the domains significantly improved	None of the domains significantly improved	NA
	SET			None of the domains significantly improved	None of the domains significantly improved	NA
	ER	Disease specific	Vascu QoL	None of the domains significantly improved	None of the domains significantly improved	NA

	SET			None of the domains significantly improved	None of the domains significantly improved	NA
Crowther 2008	Control	NA	NA	NA	NA	NA
	SET			NA	NA	NA
Cheetham 2004	HET	Generic	SF-36	NA	Physical functioning was significantly improved in SET compared to HET group	NA
	SET			NA		NA
	HET	Disease specific	ICQ	Scores improved but not significant	Scores significantly improved	NA
	SET					NA
Gardner 2002	Control	Disease specific	WIQ	Scores did not change between pre and post intervention	Scores did not change between pre and post intervention	NA
	SET			Scores did not change between pre and post intervention	Scores did not change between pre and post intervention	NA
Baker 2017	SET	NA	NA	NA	NA	NA
	Control			NA	NA	NA
Brass 2012	Cilostazol	NA	NA	NA	NA	NA
	Control			NA	NA	NA
Collins 2011	Control	Generic	SF-36	Only mental health domain significantly improved in HET compared to control group	NA	NA
	HET				NA	NA
	Control	Disease specific	WIQ	Walking speed domain significantly improved in HET compared to control group	NA	NA
	HET				NA	NA
Crowther 2012	SET	NA	NA	NA	NA	NA
	Control			NA	NA	NA
Dawson 2000	Cilostazol	Generic	MOS SF-36	None of the domains significantly improved	NA	NA

	Control			None of the domains significantly improved	NA	NA
	Cilostazol	Disease specific	WIQ	None of the domains significantly improved	NA	NA
	Control			None of the domains significantly improved	NA	NA
Fakhry 2015	SET+ER	Generic	SF-36	Physical functioning, bodily pain, physical role functioning score and general health perceptions were significantly improved	Physical functioning, bodily pain, physical role functioning score and general health perceptions were significantly improved	NA
	SET			Physical functioning, bodily pain, physical role functioning score and general health perceptions were significantly improved	Physical functioning, bodily pain, physical role functioning score and general health perceptions were significantly improved	NA
	SET+ER	Disease specific	Vascu QoL	VascuQoL and rating score significantly improved	VascuQoL and rating score significantly improved	NA
	SET			VascuQoL and rating score significantly improved	VascuQoL and rating score significantly improved	NA
Gardner 2001	SET	Generic	MOS SF-36	None of the domains significantly improved	None of the domains significantly improved	NA
	Control			None of the domains significantly improved	None of the domains significantly improved	NA
	SET	Disease specific	WIQ	None of the domains significantly improved	None of the domains significantly improved	NA
	Control			None of the domains significantly improved	None of the domains significantly improved	NA
Gardner 2014	SET	Generic	MOS SF-36	Physical function significantly increased compared to baseline	NA	NA
	HET			Physical function significantly increased compared to baseline	NA	NA

	Control			None of the domains significantly improved	NA	NA
	SET	Disease specific	WIQ	Walking economy and fractional utilization increased significantly from baseline in the supervised exercise group	NA	NA
	HET			Walking economy and fractional utilization increased significantly from baseline in the supervised exercise group	NA	NA
	Control			None of the domains significantly improved	NA	NA
Gardner 2012	SET	Disease specific	WIQ	Walking distance and speed significantly improved	NA	NA
	Control			None of the domains significantly improved	NA	NA
Gardner 2011	HET	Generic	MOS SF-36	Physical function score significantly improved	NA	NA
	SET			Physical function score significantly improved	NA	NA
	Control			None of the domains significantly improved	NA	NA
	HET	Disease specific	WIQ	Fractional utilization, walking distance, speed and stair climbing scores significantly increased	NA	NA
	SET			Walking economy, fractional utilization, walking distance, speed and stair climbing scores significantly increased	NA	NA
	Control			Fractional utilization significantly improved	NA	NA
	Control	NA	NA	NA	NA	NA

Hobbs 2006	ER			NA	NA	NA
	SET			NA	NA	NA
Hobbs 2007	SET	NA	NA	NA	NA	NA
	Cilostazol			NA	NA	NA
	SET + cilostazol			NA	NA	NA
	Control			NA	NA	NA
Hodges 2008	SET	NA	NA	NA	NA	NA
	Control			NA	NA	NA
Kakkos 2005	HET	Generic	SF-36	None of the domains significantly improved	Only mental health sub-domain significantly improved	NA
	SET			None of the domains significantly improved	Only mental health sub-domain significantly improved	NA
	HET	Disease specific	WIQ	None of the domains significantly improved	None of the domains significantly improved	None of the domains significantly improved
	SET			None of the domains significantly improved	None of the domains significantly improved	None of the domains significantly improved
Kruidenier 2011	ER	Generic	MOS SF-36	Domains including mental health, vitality and mental summary score were significantly improved in SET+ER as compared to ER only	NA	NA
	SET+ER				NA	NA
	ER	Disease specific	EuroQoL	Both total score and general health were similar in both treatment strategies	NA	NA
	SET+ER				NA	NA
Lamberti 2016	HET	Generic	MOS SF-36	physical component summary, bodily pain, emotional role, general health, mental component summary, mental health, physical functioning, physical role, social functioning and vitality were significantly improved	NA	NA

	ER			physical component summary, bodily pain, emotional role, physical functioning, physical role and vitality were significantly improved	NA	NA
Novakovic 2018	SET	Generic	SF-36	Physical functioning, bodily pain and physical component summary significantly improved	NA	NA
	Control			None of the domains significantly improved	NA	NA
Mauer 2015	SET	Disease specific	BASIC-Q	Change in BASIC score significantly improved	NA	NA
	HET				NA	NA
	Control			Scores did not change between pre and post intervention	NA	NA
Mays 2015	Control	Generic	SF-36	None of the domains significantly improved	NA	NA
	HET			None of the domains significantly improved	NA	NA
	Control	Disease specific	WIQ	Distance, speed and combined percentage significantly improved with intervention compared to control group	NA	NA
	HET			None of the domains significantly improved	NA	NA
Mika 2005	SET	NA	NA	NA	NA	NA
	HET			NA	NA	NA
Miika 2011	SET	NA	NA	NA	NA	NA
	Control			NA	NA	NA
O'Donnell 2009	Cilostazol	Generic	SF-36	Physical function and physical component summary were significantly improved. Physical function was significantly improved compared to control	NA	NA

	Control			None of the domains significantly improved	NA	NA
	Cilostazol	Disease specific	VascuQoL	Pain domain significantly improved	NA	NA
	Control			None of the domains significantly improved	NA	NA
Sandercock 2007	SET	NA	NA	NA	NA	NA
	HET			NA	NA	NA
	Control			NA	NA	NA
Schlager 2011	SET	NA	NA	NA	NA	NA
	Control			NA	NA	NA
Stewart 2008	SET	NA	NA	NA	NA	NA
	HET			NA	NA	NA
Strandness 2002	Cilostazol	Generic	SF-36	Significant improvement in physical function, and a trend towards improvement in bodily pain, role-physical and general health perception compared to placebo	NA	NA
	Control				NA	NA
	Cilostazol	Disease specific	WIQ	Walking distance score improved but significance not reported	NA	NA
	Control				NA	NA
Tew 2015	Control	Disease specific	WIQ	Superior improvement in WIQ speed, distance and stair-climbing scores compared to control, but significance not reported	NA	NA
	HET				NA	NA
	Control	Generic	EQ5D	None of the domains significantly improved	NA	NA
	HET			None of the domains significantly improved	NA	NA

Tsai 2002	SET	Generic	MOS SF-36	Significant improvement was seen in physical function, role limitations/physical, bodily pain, general health and vitality as compared to baseline and control	NA	NA
	Control			None of the domains significantly improved	NA	NA
	SET	Disease specific	WIQ	Significant improvement was seen in WIQ distance, speed and stairs walking compared to baseline. Only speed and stairs improved against control	NA	NA
	Control			None of the domains significantly improved	NA	NA
Zwierska 2005	SET	NA	NA	NA	NA	NA
	SET			NA	NA	NA
	Control			NA	NA	NA
Duscha 2018	HET	NA	NA	NA	NA	NA
	Control			NA	NA	NA
Bulinska 2016	SET (treadmill)	NA	NA	NA	NA	NA
	SET (NPW)			NA	NA	NA
Girold 2017	SET (NPW)	NA	NA	NA	NA	NA
	SET (Walking group)			NA	NA	NA
	HET	NA	NA	NA	NA	NA

Spafford 2014	HET (NPW)			NA	NA	NA

* Data compares intergroup only. Intragroup comparing against baseline not available.

BASIC-Q – Baltimore Activity Scale for Intermittent Claudication questionnaire; CLAU-S – Claudication scale; ICQ – Intermittent Claudication Questionnaire; ER – Endovascular revascularization; EQ5D – EuroQol-5D; HET – Home exercise therapy; MOS-SF36 – Medical Outcomes Study; NA – Not available; PAQ – Peripheral artery questionnaire; QoL – Quality of life; SET – Supervised exercise therapy; SF – Short Form; NPW – Nordic pole walking; VascuQoL – Vascular QoL

Table S4. Adverse events reported in all included trials.

Study reference	Treatment	Sample size	Follow-up (months)	MI	Stroke	Any hospital admissions	Lower limb revascularization procedures	Any other vascular procedures	Amputation	All-cause mortality
Nylande 2007	Control	28	24	NR	NR	NR	NR	NR	NR	0
Nylande 2007	ER	28	24	NR	NR	NR	NR	NR	NR	1
Mazari 2017	ER	60	60	4	2	NR	14	NR	1	14
Mazari 2017	SET	60	60	2	1	NR	10	NR	0	13
Mazari 2017	SET_ER	58	60	3	5	NR	6	NR	0	12
Fakhry, 2013	SET	75	84	NR	NR	NR	32	NR	2	17
Fakhry, 2013	ER	75	84	NR	NR	NR	17	NR	3	15
Djerf 2020	ER	79	60	NR	2	NR	22	NR	0	13
Djerf 2020	Control	79	60	NR	2	NR	20	NR	1	7
Lindgren 2018	ER	45	24	3	2	NR	10	NR	1	1
Lindgren 2018	Control	47	24	2	0	NR	7	NR	0	1
Murphy 2015	Control	22	18	1	NR	NR	0	NR	NR	0
Murphy 2015	SET	43	18	0	NR	NR	0	NR	NR	1
Murphy 2015	ER	46	18	0	NR	NR	1	NR	NR	0
Gelin 2001^	Control	89	12	NR	NR	NR	NR	NR	2	4
Gelin 2001^	SET	88	12	NR	NR	NR	NR	NR	0	5
Gelin 2001^	ER	87	12	NR	NR	NR	NR	NR	1	5
Bo 2013	ER	21	12	NR	NR	NR	6*	NR	NR	0
Bo 2013	SET_ER	29	12	NR	NR	NR		NR	NR	1
Spronk 2009	ER	75	12	1	NR	NR	2	0	NR	5
Spronk 2009	SET	75	12	0	NR	NR	4	3	NR	3
Crowther 2008	Control	11	12	NR	NR	NR	NR	NR	NR	NR
Crowther 2008	SET	10	12	NR	NR	NR	NR	NR	NR	NR
Gardner 2002	Control	14	18	NR	NR	NR	NR	NR	0	2

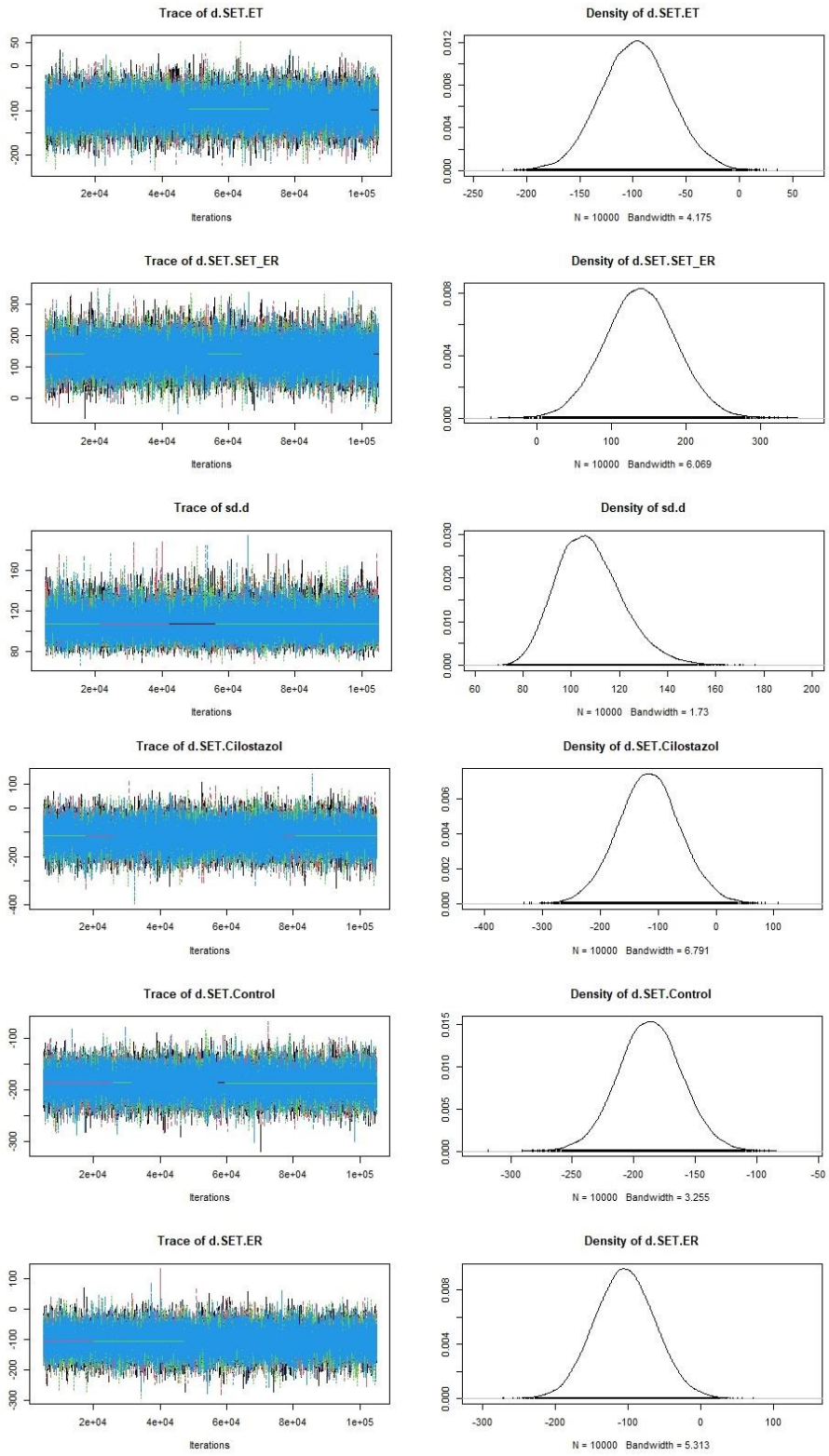
Gardner 2002	SET	17	18	NR	NR	NR	NR	NR	1	1
Baker 2017	SET	29	3	NR	NR	NR	NR	NR	NR	NR
Baker 2017	Control	35	3	NR	NR	NR	NR	NR	NR	NR
Brass 2012	Cilostazol	89	6.5	NR	1	NR	NR	NR	NR	1
Brass 2012	Control	87	6.5	NR	0	NR	NR	NR	NR	0
Collins 2011	Control	73	6	NR	NR	NR	NR	NR	NR	NR
Collins 2011	HET	72	6	NR	NR	NR	NR	NR	NR	NR
Crowther 2012	SET	11	6	NR	NR	NR	NR	NR	NR	NR
Crowther 2012	Control	11	6	NR	NR	NR	NR	NR	NR	NR
Spafford 2014	SET	28	3	0	NR	NR	NR	NR	NR	0
Spafford 2014	HET	24	3	1	NR	NR	NR	NR	NR	1
Dawson 2000	Cilostazol	227	6	NR	NR	NR	NR	NR	NR	2
Dawson 2000	Control	239	6	NR	NR	NR	NR	NR	NR	1
Fakhry 2015	SET_ER	106	12	NR	NR	NR	NR	NR	0	1
Fakhry 2015	SET	106	12	NR	NR	NR	NR	NR	2	3
Gardner 2001	SET	31	6	NR	NR	NR	NR	NR	NR	NR
Gardner 2001	Control	30	6	NR	NR	NR	NR	NR	NR	NR
Gardner 2014	SET	60	3	NR	1	NR	0	NR	NR	NR
Gardner 2014	HET	60	3	NR	0	NR	1	NR	NR	NR
Gardner 2014[#]	Control	60	3	1	1	NR	0	NR	NR	NR
Gardner 2012	SET	106	6	1*	3*	NR	NR	1*	1*	NR
Gardner 2012	Control	36	6			NR	NR			NR
Gardner 2011	HET	40	3	1	1	NR	1	NR	NR	NR
Gardner 2011	SET	40	3	0	1	NR	0	NR	NR	NR
Gardner 2011	Control	39	3	0	1	NR	1	NR	NR	NR
Hobbs 2006	Control	7	6	NR	NR	NR	NR	NR	NR	NR
Hobbs 2006	ER	9	6	NR	NR	NR	NR	NR	NR	NR
Hobbs 2006	SET	7	6	NR	NR	NR	NR	NR	NR	NR
Hobbs 2007	SET	9	6	NR	NR	NR	NR	NR	NR	NR

Hobbs 2007	Cilostazol	9	6	NR	NR	NR	NR	NR	NR	NR
Hobbs 2007	Control	9	6	NR	NR	NR	NR	NR	NR	NR
Hodges 2008	SET	14	3	NR	NR	NR	NR	NR	NR	NR
Hodges 2008	Control	14	3	NR	NR	NR	NR	NR	NR	NR
Kakkos 2005	HET	10	12	NR	NR	NR	NR	NR	NR	0
Kakkos 2005	SET	12	12	NR	NR	NR	NR	NR	NR	1
Kruidenier 2011	ER	35	6	NR	NR	NR	2	NR	NR	NR
Kruidenier 2011	SET_ER	35	6	NR	NR	NR	0	NR	NR	NR
Lamberti 2016	HET	18	4	NR	NR	NR	NR	NR	NR	NR
Lamberti 2016	ER	9	4	NR	NR	NR	NR	NR	NR	NR
Novakovic 2019	SET	12	4.5	NR	NR	NR	NR	NR	NR	NR
Novakovic 2019	Control	12	4.5	NR	NR	NR	NR	NR	NR	NR
Mauer 2015	SET	16	3	NR	NR	NR	NR	NR	NR	NR
Mauer 2015	Control	7	3	NR	NR	NR	NR	NR	NR	NR
Mays 2015	Control	10	3.5	NR	NR	NR	NR	NR	NR	NR
Mays 2015	HET	10	3.5	NR	NR	NR	NR	NR	NR	NR
Mika 2005	SET	49	3	NR	NR	NR	NR	NR	NR	NR
Mika 2005	HET	49	3	NR	NR	NR	NR	NR	NR	NR
Miika 2011	SET	34	3	NR	NR	NR	NR	NR	NR	NR
Miika 2011	Control	34	3	NR	NR	NR	NR	NR	NR	NR
Sandercock 2007	SET	13	3	NR	NR	NR	1	NR	NR	NR
Sandercock 2007	HET	15	3	NR	NR	NR	0	NR	NR	NR
Sandercock 2007	Control	15	3	NR	NR	NR	0	NR	NR	NR
Schlager 2011	SET	20	12	0	NR	NR	NR	NR	NR	0
Schlager 2011	Control	20	12	1	NR	NR	NR	NR	NR	1
Stewart 2008	SET	30	6	NR	1	NR	1	NR	NR	1
Stewart 2008	HET	30	6	NR	1	NR	0	NR	NR	0
Zwierska 2005	SET	37	6	NR	NR	NR	NR	NR	NR	3
Zwierska 2005	Control	33	6	NR	NR	NR	NR	NR	NR	

Greenhalgh 2008a	SET_ER	48	24	NR	2*	NR	NR	2*	NR	2
Greenhalgh 2008a	SET	45	24	NR		NR	NR		NR	2
Greenhalgh 2008b	SET_ER	19	24	NR	2*	NR	NR	0	NR	1
Greenhalgh 2008b	SET	15	24	NR		NR	NR	0	NR	2
Cheetham 2004	HET	30	12	NR	NR	NR	NR	NR	NR	2
Cheetham 2004	SET	29	12	NR	NR	NR	NR	NR	NR	2
O'Donnell 2009^	Cilostazol	39	6	NR	NR	NR	NR	NR	NR	NR
O'Donnell 2009^	Control	41	6	NR	NR	NR	NR	NR	NR	NR
Strandness 2002	Cilostazol	133	6	NR	NR	NR	NR	NR	NR	2
Strandness 2002	Control	128	6	NR	NR	NR	NR	NR	NR	0
Tew 2015	Control	9	1.5	NR	0	NR	NR	NR	NR	NR
Tew 2015	HET	14	1.5	NR	1	NR	NR	NR	NR	NR
Tsai 2002	SET	27	3	NR	NR	NR	NR	NR	NR	NR
Tsai 2002	Control	26	3	NR	NR	NR	NR	NR	NR	NR
Duscha 2018	HET	10	3	NR	NR	NR	NR	NR	NR	NR
Duscha 2018	Control	9	3	NR	NR	NR	NR	NR	NR	NR
Bullinska 2016	SET	31	1.5	NR	NR	NR	NR	NR	NR	NR
Bullinska 2016	HET	21	1.5	NR	NR	NR	NR	NR	NR	NR
Girold 2017	SET	21	1	NR	NR	NR	NR	NR	NR	NR
Girold 2017	HET	21	1	NR	NR	NR	NR	NR	NR	NR

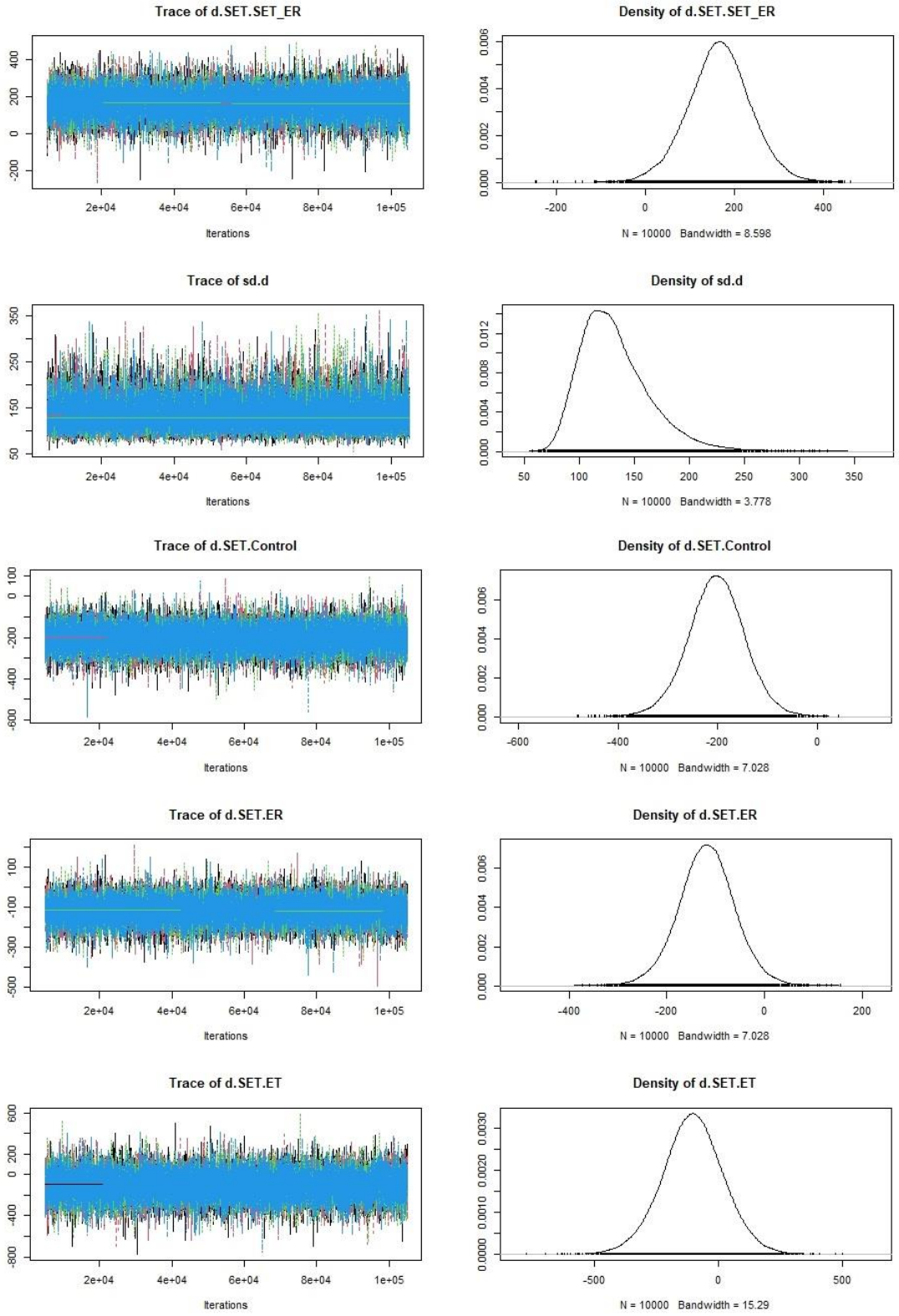
* Group-wise data not available; ^ Cardiovascular adverse events reported together with other events, but individual event numbers were not provided; # Cerebral vascular accidents was considered as stroke; ER – Endovascular revascularization; HET – Home exercise therapy; SET – Supervised exercise therapy; NR – Not reported; MI – Myocardial infarction.

Figure S1. Markov Chain Monte Carlo simulation showing the trace plots and corresponding density plots during short-term follow-up.



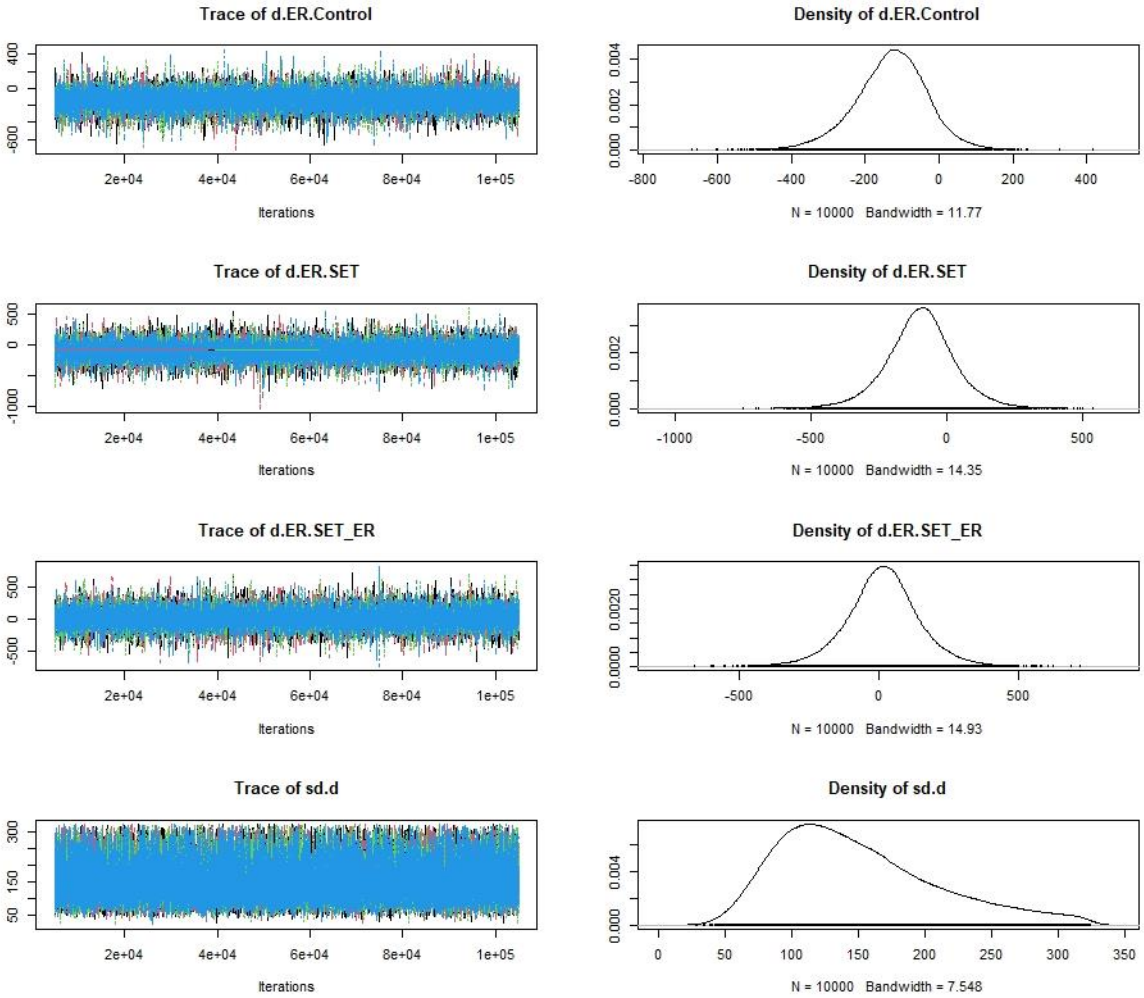
Convergence was achieved with higher iterations (100,000) and was suitable for the network model. HET – Home exercise therapy, SET – Supervised exercise therapy, ER – Endovascular revascularization, SD – Standard deviation

Figure S2. Markov Chain Monte Carlo simulation showing the trace plots and corresponding density plots during moderate follow-up.



Convergence was achieved with higher iterations (100,000) and was suitable for the network model. HET – Home exercise therapy, SET – Supervised exercise therapy, ER – Endovascular revascularization, SD – Standard deviation.

Figure S3. Markov Chain Monte Carlo simulation showing the trace plots and corresponding density plots during long-term follow-up.



Convergence was achieved with higher iterations (100,000) and was suitable for the network model. SET – Supervised exercise therapy, ER – Endovascular revascularization, SD – Standard deviation.