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SYSTEMATIC REVIEW

Combined Lower Limb Revascularisation and Supervised Exercise Training for Patients with Peripheral Arterial Disease: A Systematic Review of Randomised Controlled Trials

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Abstract

Background Both revascularisation and supervised exercise training improve functional outcomes and quality of life in patients with peripheral arterial disease (PAD). However, the value of combined therapy, where exercise therapy is delivered as an adjunct to revascularisation, is less clear.

Objective To systematically review evidence on the efficacy of lower limb revascularisation combined with supervised exercise training in patients with PAD.

Methods Parallel-group randomised controlled trials indexed in the Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, Embase, Scopus, CINAHL, SPORTDiscus and Web of Science were searched (up to Jan 2016). Outcome measures were pain-free and maximum walking distances, ankle-brachial index (ABI), leg blood flow and quality of life. Methodological quality was assessed using the Physiotherapy Evidence Database (PEDro) scale.

Result Eight trials were included that enrolled a total of 726 patients (mean age 66 ± 3 years, ABI 0.66 ± 0.05). Combined therapy led to greater improvements in pain-free (mean difference [MD] range 38–408 m) and maximal walking distances (MD range 82–321 m) compared with revascularisation or supervised training alone. Combined therapy had no added effect on resting ABI over revascularisation (MD range −0.05 to 0.13), and had a significantly greater effect than supervised exercise training alone (MD range 0.13–0.31). Limited evidence (one to three trials) also suggested that combined therapy led to greater improvements in leg blood flow and physical domains of quality of life than supervised exercise training alone, and that improvements in leg blood flow, as well as the physical and mental domains of quality of life were not different to that achieved with revascularisation alone.

Conclusion Current evidence suggests that PAD patients treated with combined therapy achieve greater functional benefits than those treated with revascularisation or supervised exercise training alone. Limited evidence also suggests that the effect of combined therapy on leg haemodynamics and quality of life may be superior to supervised exercise training alone, and similar to revascularisation alone.

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Key Points

Patients with PAD, including those with symptoms of intermittent claudication and more-severe critical limb ischaemia, benefit from the combination of revascularisation and supervised exercise therapy. Combined therapy leads to significant improvements in walking capacity over revascularisation or exercise therapy alone.

Improvements in walking capacity with combined therapy are achieved with no further improvement in leg blood flow compared with revascularisation alone. The mechanisms that underpin the benefits of the combined therapy approach remain to be determined.

Combining supervised exercise training as adjunct to revascularisation in patients with PAD is a promising treatment strategy. There is a need to define optimal and specific exercise training programs for PAD patients who have undergone revascularisation, as well as strategies to improve compliance with exercise programs.

1 Introduction

Peripheral arterial disease (PAD) is an atherosclerotic disease that leads to stenosis and occlusion of the arteries, most commonly affecting the lower extremities. PAD affects more than 200 million adults globally [1], and is associated with exercise intolerance, leading to impaired physical function [2–5] and quality of life [6–8]. Hospitalisation rates in patients with PAD are high and PAD is associated with high rates of cardiovascular events and revascularisation procedures [9].

Treatment for PAD aims to reduce cardiovascular risk, reduce leg symptoms and improve exercise tolerance [10, 11]. The recommended initial treatment for PAD comprises atherosclerotic risk factor modification with or without pharmacological therapy, and supervised exercise training [10, 11]. For patients who are unresponsive to exercise and pharmacological therapy, those with severe functional disability, or those with limb-threatening ischaemia, lower limb revascularisation, including endovascular and open surgical procedures, is indicated to improve limb circulation and for limb salvage [10, 11].

Revascularisation procedures and supervised exercise training have both independently been shown to improve functional outcomes and quality of life in patients with symptomatic PAD [12, 13]. Revascularisation procedures restore blood flow to the lower limbs and thereby improve muscle oxygen delivery and exercise capacity [14]. Conversely, exercise training leads to improvements in exercise capacity, usually without any significant gains in limb blood flow [15]. This raises the possibility that combining both therapies would result in greater improvements in exercise capacity compared to either revascularisation or exercise training alone. This combined treatment approach where exercise therapy is delivered as an adjunct to surgical procedures is commonly recommended for patients undergoing cardiac, thoracic or orthopaedic surgery in order to promote recovery and secondary prevention [16]. Given that the potential utility of this treatment strategy has been acknowledged for patients with PAD [11, 17], a better understanding of the benefits of combining revascularisation and exercise therapy would facilitate this approach being adopted into treatment guidelines and standard care for patients with more severe PAD. Therefore, we aimed to systematically review the available evidence of the effect of lower limb revascularisation combined with supervised exercise training in patients with PAD, on walking capacity, limb haemodynamics and quality of life.

2 Methods

This review was conducted according to the guidelines of the 2009 Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [18].

2.1 Search Strategy

The literature search was performed, with no language restrictions, using the electronic databases Cochrane Central Register of Controlled Trials (CENTRAL) (1996 to present), PubMed (1996 to present), Embase (1947 to present), Scopus (1966 to present), CINAHL (1980 to present), SPORTDiscus (1871 to present) and Web of Science (1900 to present). Databases were searched from the earliest records up to January 2016 (last search 04/01/2016). Bibliographies of all eligible primary studies were manually searched for additional studies. Search terms and strategies for each database are presented in Electronic Supplementary Material Tables S1–S7. This review was registered in the international database of prospectively registered systematic reviews in health and social care

(PROSPERO; CRD42015023983), publically available at http://www.crd.york.ac.uk/PROSPERO/.

2.2 Study Eligibility Criteria

Study populations consisted of atherosclerotic PAD patients who were considered eligible for both revascularisation and supervised exercise training therapy. This included the presence of target lesions suitable for revascularisation, intermittent claudication (IC) symptoms that were not improved with standard medical care and the absence of co-morbidities for which exercise is contraindicated. Only parallel-group randomised controlled trials including combined therapy of lower limb revascularisation plus supervised exercise training, and a comparison group of either revascularisation alone, supervised exercise training alone, standard medical therapy or no therapy (control) were eligible for inclusion in the present review. There was no restriction based on the stage of the disease and disease severity, the type of lower limb revascularisation procedure (surgical or endovascular), the site of the primary lesion, or the type of supervised exercise training performed.

The primary outcome measures were pain-free walking distance and maximal walking distance measured by a treadmill test. Studies using either incremental (graded) or constant-load treadmill walking tests were included, but the outcomes were considered separately based on test type. The secondary outcome measures were 6-min walking distance, ankle-brachial index (ABI), resting calf arterial blood flow (venous occlusion plethysmography) and quality of life (physical and mental health summary scores of the 36-item Short-Form Health Survey [SF-36]; 0 [severe limitation] to 100 [no limitation]). Trials were excluded if group allocation was not randomised, if they did not report primary outcome data or if group data were not presented separately. Non-peer-reviewed publications (e.g. conference abstracts) were excluded.

2.3 Study Selection and Data Extraction

One reviewer (ALM) conducted the literature search and the results from all databases were downloaded into bibliographic software (EndNote X6; Thompson Reuters, New York, USA). After eliminating duplicates, all papers identified by the search strategy were screened by title and abstract. Full-text evaluation was performed to confirm the suitability of the selected trials for inclusion in the review, and the bibliographies of all included studies were manually searched for additional studies. Papers where abstracts were published in languages other than English were evaluated by experienced researchers who were native-speakers of the particular language with the use of a standardised review template designed for this study. Quality assessment of all eligible papers was undertaken separately and in duplicate by two reviewers (ALM and RMR) using the Physiotherapy Evidence Database Scale for randomised controlled trials (PEDro) [19]. One reviewer (ALM) extracted the data from included studies and a second reviewer (CDA) checked the accuracy of extracted data. Disagreements between the reviewers were resolved by consensus or by a third reviewer when necessary.

Data extracted from each included trial consisted of: (1) characteristics of trial participants; (2) characteristics of the revascularisation procedure; (3) characteristics of the supervised exercise training intervention; (4) protocols for assessment of primary and secondary outcomes; and (5) between-group comparative data pre (baseline) and immediately post-intervention.

2.4 Data Analysis

Trials were divided into two groups: (1) combined therapy versus revascularisation alone, which assessed the added effect of exercise over revascularisation, and (2) combined therapy versus supervised exercise training alone, which assessed the added effect of revascularisation over exercise therapy. There were no other comparative treatment combinations identified in the literature. Due to the heterogeneity of protocols for the assessment of primary outcomes, a systematic review was conducted without meta-analysis. Where there were missing outcome data, or when data were not provided as mean and standard deviation (SD), corresponding authors were contacted. Where duplicate data were suspected, authors were contacted to clarify whether data were published across multiple papers. If partial data sets had been published previously, the more complete data sets were extracted for analysis.

Mean differences and between-group effect sizes (ES) were calculated for each trial using the pre-post intervention changes in mean and SD for each comparison group. Between-group ES, adjusted using Hedges' bias-correction for small sample sizes, and 95 % confidence intervals (CIs) were calculated for each outcome measure where applicable as: between-group ES = (Δtreatment − Δcontrol)/pooled baseline SD; where Δ indicates change. In some trials, the minimum outcome data required for ES calculation were not reported. Despite an attempt to request missing data, few of the data could be obtained. Therefore, where findings were presented as median, range, interquartile range or standard error, data were converted to derive means and SD prior to the calculation of the ES, as per Hozo [20]. ES were interpreted according to Cohen's classification of 'trivial' (<0.20), 'small' ($\geq$0.20 to <0.50), 'moderate' ($\geq$0.50 to <0.80) and 'large' ($\geq$0.80) [21]. ES

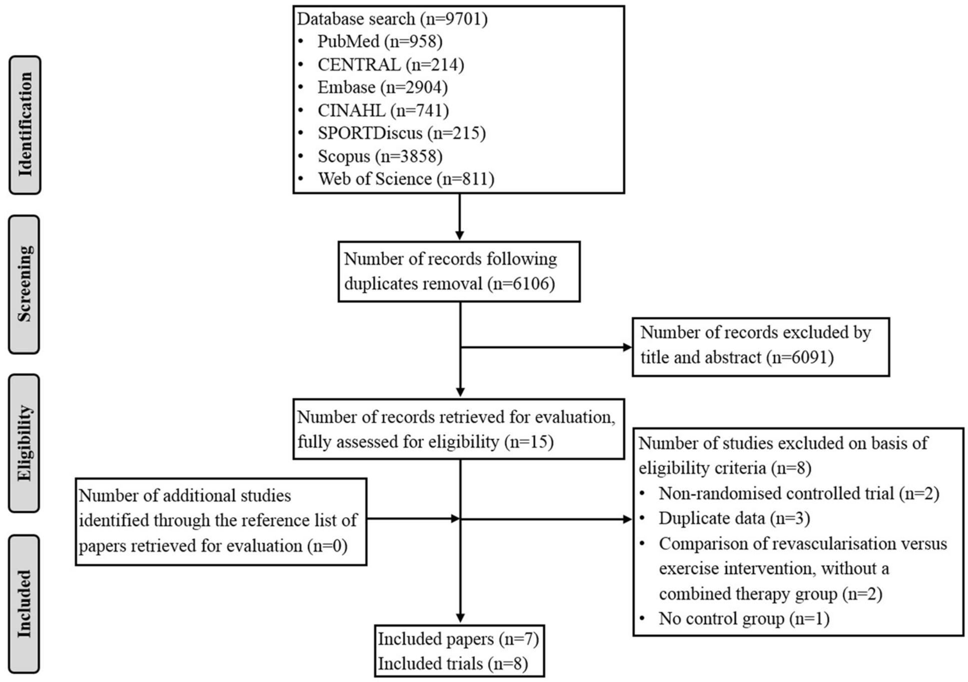

Fig. 1 Study flow diagram. *CENTRAL* Cochrane Central Register of Controlled Trials

and 95 % CIs were graphed as forest plots and the between-group ES for each study was deemed to have no statistical significance when the CI crossed the vertical midline (i.e. included zero) [22]. Values are presented as mean and SD and significance was set at $p < 0.05$.

3 Results

Results of the literature search are presented in Fig. 1. The search identified a total of 9701 citations. Fifteen studies were retrieved for full-text examination; however, eight trials did not meet inclusion criteria and were subsequently excluded [13, 23–29]. The reasons for the exclusion of studies are described in Electronic Supplementary Material Table S8. One study was divided into two trials as patients were stratified according to the anatomical site of revascularisation (femoropopliteal or aortoiliac) prior to randomisation [30]. Therefore, seven studies and a total of eight trials were included in the systematic review [30–36].

3.1 Quality Assessment

Overall quality of the included trials was modest, with an average of six of the ten quality criteria being present (mean ± SD 6 ± 2, range 3–8/10), as shown in Table 1. The most prevalent study limitation was related to the blinding of participants and research personnel (>75 %), which is somewhat expected considering the nature and design of these studies. Four trials (50 %) [30, 31, 33] presented insufficient information about allocation concealment. Six trials (75 %) [30, 33–36] reported an intention-to-treat analysis or stated that all participants received treatment or control conditions as originally allocated. Three trials (38 %) [30–32] measured key outcomes in less than 85 % of the participants initially allocated to a treatment group; therefore, a greater than 15 % drop-out rate may have disguised the true treatment effect of the intervention in these trials. Eligibility criteria (100 %), random allocation (100 %), baseline similarity (88 %), between-group statistics (100 %) and point measures and measures of variability (e.g. mean and SD) (100 %) were sufficiently reported by most studies. The consistency of outcomes listed in the clinical trials registries of included trials (when available) [30, 32, 34–36] were compared with their respective published results. For these studies, the registered outcome measures and time frames for outcome assessment were consistent with published outcome results.

3.2 Study Characteristics

A summary of the study and patient characteristics is presented in Table 2. The total number of patients screened for inclusion across all trials was 3791 (range 48 to 1401); of these, 726 were enrolled ($n = 253$ underwent revascularisation therapy alone; $n = 145$ underwent supervised exercise training alone and $n = 328$ underwent combined therapy). Included patients presented with a mean age of 66 ± 3 years, and a resting ABI of 0.66 ± 0.05. History of IC was an inclusion criterion for all trials, and two trials (25 %) [31, 35] also included patients with lower limb

Table 1 Assessment of methodological quality using the Physiotherapy Evidence Database (PEDro) rating scale for randomised controlled trials[a]

Study	Eligibility criteria specified[b]	Random allocation	Concealed allocation	Baseline similarity	Blinding of all participants	Blinding of all therapists	Blinding of all assessors	Dropout <15 %	Intention-to-treat analysis	Between group statistics	Point measures and measures of variability	Final score (/10)
Lundgren et al. [33][c]	Yes	Yes	No	Yes	No	No	No	Yes	Yes	Yes	Yes	6
Badger et al. [31][c]	Yes	Yes	No	No	No	No	No	No	No	Yes	Yes	3
Greenhalgh et al. [30][d]	Yes	Yes	No	Yes	No	No	No	Yes	Yes	Yes	Yes	6
Greenhalgh et al. [30][d]	Yes	Yes	No	Yes	No	No	No	No	Yes	Yes	Yes	5
Kruidenier et al. [35][c]	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes	7
Mazari et al. [32][c]	Yes	Yes	Yes	Yes	No	No	No	No	No	Yes	Yes	5
Bo et al. [34][c]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	8
Fakhry et al. [36]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	8

[a] Trials scored by members of the research team (ALM/RMR)

[b] Eligibility criteria item did not contribute to total score

[c] Scores are publically available at PEDro database (http://www.pedro.org.au/) [19]

[d] Greenhalgh et al. [30] was divided into two trials as patients were stratified according to the anatomical site of revascularisation (femoropopliteal or aortoiliac) prior to randomisation

ischaemic rest pain. Four trials (50 %) [30, 32, 34] stated that included patients had stable IC that had persisted for more than 3 months of standard medical care prior to study entry. Co-morbidities associated with PAD, including diabetes (22 ± 17 %), hypertension (62 ± 13 %), coronary artery disease (31 ± 10 %), as well as history of previous ischaemic events, were reported in most trials.

A summary of the intervention approaches used in the trials is presented in Table 3. Revascularisation was performed to treat femoropopliteal and/or aortoiliac artery stenoses or occlusions by endovascular (percutaneous transluminal angioplasty) or open surgical (e.g. bypass graft) procedures. Study outcomes were not assessed according to the site of revascularisation, with the exception of the study by Greenhalgh et al. [30] where patients were stratified to femoropopliteal or aortoiliac trials. In the combined therapy versus revascularisation trials [31–35], the treatment sites were reported as being similar across groups in four out of the five trials [31, 32, 34, 35], and not reported in the other [33]. Five trials (63 %) [30, 31, 34, 35] reported that standard post-operative care (drug therapy and cardiovascular risk factor control) and standard advice (e.g. smoking cessation, exercise, and diet) were provided for all patients during the subsequent exercise intervention or control period.

For patients undergoing combined therapy, the reported recovery time from revascularisation to the commencement of exercise training ranged from one [32] to 12 weeks [30]. For patients undergoing revascularisation therapy only, the reported time between recovery from revascularisation and post-intervention follow-up visit ranged between six [33] to 44 weeks [36]. Walking exercise was prescribed in all trials [30–36], which in some cases was performed in addition to upper/lower limb exercises incorporated into dance classes [34], or leg exercises as part of a circuit training [30, 32, 33]. The average duration of the supervised exercise training programs was 22 ± 13 weeks (ranged from 6 [31] to 48 weeks [36]). Exercise frequency ranged from 1 to 3 days per week, with each session lasting 22 min [32] to 60 min [34]. The prescribed exercise intensity was either beyond the onset of claudication pain [33] or to a submaximal [35, 36] or maximal pain threshold [30, 36]. One trial [34] prescribed exercise intensity (walking plus dance classes) as 15–17 on the Borg 6–20 perceived exertion scale, which equates to a vigorous to high intensity [37]. All exercise training programs were completely supervised, with the exception of one trial by Bo et al. [34] where participants performed one-third of the weekly sessions without supervision. Exercise programs were usually hospital-based [30–34]. Attendance at exercise training sessions (62 ± 13 %) was reported in four trials (50 %) [30, 32, 36], with only one trial [32] reporting a priori criteria for exercise compliance (≥85 %

Table 2 Study and patient characteristics

Study	Country	Patients inclusion criteria	Group	*N*	Gender (% male)	Age (years)	BMI (kg/m^2)	DM (%)	HTN (%)	CAD (%)	Dyslipidaemia (%)	Current smokers (%)	Previous ischaemic events (%)	Resting ABI
Lundgren et al. [33]	Sweden	IC	R	25	79	64 ± 10	NR	8	31	25	NR	93	MI (19); TIA (3)	0.55 ± 0.15
			SET	25		64 ± 5								0.59 ± 0.15
			R + SET	25		63 ± 10								0.59 ± 0.10
Badger et al. [31]	UK	IC and/or CLI	R	6	NR	73 ± 10	NR	68	85	16	32	82	CVA (0); MI (16)	NR
			R + SET	8		70 ± 10		38	50	38	25	88	CVA (12); MI (50)	
Greenhalgh et al. [30][a]	UK	IC	SET	45	58	69 ± 9	26.9 ± 4.5	NR	76	22	67	84	NR	0.69 ± 0.12
			R + SET	48	59	64 ± 9	27.0 ± 5.1		73	44	83	79		0.66 ± 0.14
Greenhalgh et al. [30][a]	UK	IC	SET	15	67	63 ± 10	25.2 ± 3.8	NR	53	40	80	100	NR	0.66 ± 0.11
			R + SET	19	62	64 ± 9	27.2 ± 3.6		58	26	58	89		0.68 ± 0.19
Kruidenier et al. [35]	The Netherlands	IC and/or CLI	R	35	60	60 ± 10	27.5 ± 4.9	14	69	20	89	60	CVA or TIA (6)	0.71 ± 0.18
			R + SET	35	63	65 ± 9	26.6 ± 3.4	26	71	37	86	51	CVA or TIA (11)	0.69 ± 0.21
Mazari et al. [32]	UK	IC	R	60	62	69 ± 25	NR	15	67	NR	78	30	NR	0.71 ± 0.25
			SET	60	62	70 ± 23		13	67		75	30		0.72 ± 0.22
			R + SET	58	57	70 ± 29		14	59		74	33		0.64 ± 0.24
Bo et al. [34]	Norway	IC	R	21	48	66 ± 8	27.4 ± 4.0	19	62	NR	91	43	MI (38); CVA (0)	0.63 ± 0.30
			R + SET	29	48	67 ± 7	27.2 ± 5.0	10	52		97	38	MI (28); CVA (3)	0.64 ± 0.30
Fakhry et al. [36]	The Netherlands	IC	SET	106	68	66 ± 10	26.2 ± 4.4	26	62	40	42	52	NR	0.68 ± 0.16
			R + SET	106	57	64 ± 9	27.0 ± 4.1	16	58	33	44	61		0.71 ± 0.18

Values are mean ± SD unless otherwise stated

IC intermittent claudication, *CLI* critical limb ischaemia, *R* revascularisation therapy, *SET* supervised exercise therapy, *R + SET* revascularisation plus supervised exercise therapy, *BMI* body mass index, *DM* diabetes mellitus, *HTN* hypertension, *CAD* coronary artery disease, *MI* myocardial infarction, *TIA* transient ischaemic attack, *CVA* cerebrovascular accident/stroke, *ABI* ankle-brachial index, *NR* not reported

[a] Greenhalgh et al. [30] was divided into two trials as patients were stratified according to the anatomical site of revascularisation (femoropopliteal or aortoiliac) prior to randomisation

Table 3 Intervention characteristics

Study	Revascularisation		Treadmill walking test protocol	Supervised exercise program						
	Site/method	Recovery time (weeks)		Length (weeks)	Frequency (days/week)	Duration (min/session)	Modality	Intensity	Progression	Supervision/settings
Lundgren et al. [33]	AI and/or FP Bypass	6	4 km/h; 0 % grade Max 15 min (1000 m)	≥24	3	30	Walking (in group) + heel-raising exercise + home walking advice	Beyond onset of pain	NR	All sessions Hospital-based
Badger et al. [31]	FD or FP[a,b] Bypass	4	3.2 km/h; 10 % grade Max 30 min (1600 m)	6	2	30	Treadmill walking 3.2 km/h, 10° grade	NR	NR	All sessions Hospital-based
Greenhalgh et al. [30][c]	FP[b] PTA (balloon)	≤12	4 km/h; 10 % grade Max 15 min (1000 m)	24	≥1	30	Treadmill walking interspersed with 7 leg exercises + advice to increase physical activity levels	Max pain	NR	All sessions Hospital-based
Greenhalgh et al. [30][c]	AI[b] PTA (balloon ± stent)	≤12	4 km/h; 10 % grade Max 15 min (1000 m)	24	≥1	30	Treadmill walking interspersed with 7 leg exercises + advice to increase physical activity levels	Max pain	NR	All sessions Hospital-based
Kruidenier et al. [35]	AI and/or FP[a,b] PTA (stent)	≤3	3.2 km/h; 0 % grade 2 % every 1 min up to 10 % Max 30 min (1600 m)	24	2–3	30	Intermittent walking (3–5 min bouts) + home walking advice	Submax pain	Frequency of sessions reduced according to patient's progress	All sessions Community-based
Mazari et al. [32]	FP[a] PTA (balloon)	1	2.5 km/h; 10 % grade Max 5 min (215 m)	12	3	22–50	Intermittent walking interspersed with 6 leg exercises	"Brisk walking"	Increment of 1 station per week from weeks 6–12	All sessions Hospital-based
Bo et al. [34]	AI or FP[a,b] PTA (balloon ± stent)	NR	3.2 km/h; 0 % grade 2 % every 1 min up to 10 % Max 30 min (1600 m)	12	2/3 Supervised 1/3 Unsupervised	60	Aerobic upper/lower exercise (dance) + walking + 1 home-based walking exercise session	15–17 Borg scale	NR	2/3 Hospital-based 1/3 Home-based (unsupervised)

Table 3 continued

Study	Revascularisation		Treadmill walking test protocol	Supervised exercise program						
	Site/method	Recovery time (weeks)		Length (weeks)	Frequency (days/week)	Duration (min/session)	Modality	Intensity	Progression	Supervision/settings
Fakhry et al. [36]	AI and/or FP PTA (balloon ± stent)	2–4	3.2 km/h; 0 % grade 2 % every 1 min up to 10 % Max 30 min (1600 m)	48	2–3 from week 0–12; ≥ 1 from week 12–24; 1 day each 4 weeks from week 24–48	30–45	Treadmill walking	Near-max pain	Frequency of sessions reduced according to patient's progress and preference	All sessions Physiotherapy clinics

PTA percutaneous transluminal angioplasty, *FD* femorodistal, *FP* femoropopliteal, *AI* aortoiliac, *Max* maximal, *NR* not reported

[a] Patient's treatment sites/procedures were similar across groups

[b] Post-operative care/standard care (drug therapy, cardiovascular risk factors control) and standard advice (smoking cessation, exercise, and diet) provided for all patients in the trial

[c] Greenhalgh et al. [30] was divided into two trials as patients were stratified according to the anatomical site of revascularisation (femoropopliteal or aortoiliac) prior to randomisation

completion of supervised exercise sessions), and three trials (38 %) reporting that exercise programs were not delivered as planned (<75 % attendance) [30, 36].

Complications following revascularisation occurred in most trials [30–33, 35, 36] and ranged from minor haematomas and sensory deficits to major complications requiring reinterventions such as persistent bleeding, graft occlusion, aortic rupture, contralateral leg embolism and toe amputations. One trial [36] reported that 2 % of the patients in the supervised exercise training group underwent minor amputation due to deterioration of claudication and progression of lower limb ischaemia. No complications related to exercise training were reported. Four trials (50 %) [32, 34–36] reported rates of reintervention (further invasive treatment required to manage complications, restenosis or for persistent/recurrent symptoms) across groups. Overall, rates of reintervention were similar in the groups of patients undergoing revascularisation alone (range 6–15 %), supervised exercise training alone (10 %) or combined therapy (range 0–14 %) over a follow-up period of 3–12 months. In one trial [36], reintervention rates were significantly lower (8 %) in the combined therapy group compared to supervised exercise training (23 %) at 1-year follow-up.

3.3 Outcome Measures

A complete dataset of the outcome measures, mean differences and ES are presented in Electronic Supplementary Material Tables S9–S15.

3.3.1 Pain-Free Walking Distance

The mean difference in pain-free walking distance between combined therapy and revascularisation therapy alone ranged from 38 to 391 m in favour of combined therapy (Fig. 2; Electronic Supplementary Material Table S9). Between-group ES were large (mean ES 1.28; range 0.45–1.73) and indicated a significant benefit of combined therapy over revascularisation alone, with the exception of one trial [33] where ES analysis revealed no significant differences between groups ($p = 0.14$). The mean difference between combined therapy and exercise training alone ranged from 51 to 408 m in favour of combined therapy. Between-group ES were again large (mean ES 1.14; range 0.61–1.65) and significant in favour of combined therapy ($p < 0.01$).

3.3.2 Maximal Walking Distance

The mean difference in maximal walking distance between combined therapy and revascularisation therapy alone ranged from 97 to 321 m in favour of combined therapy

Study	Control therapy Δ Mean ± SD	N	Combined therapy Δ Mean ± SD	N	Mean difference [95% CI]
Revascularisation versus combined therapy					
Constant load treadmill walking test					
Lundgren et al. 1989 [33]	320 ± 357	21	489 ± 380	22	169 [-58 to 396]
Mazari et al. 2012 [32]	45 ± 28	52	82 ± 28	47	38 [26 to 49]
Graded treadmill walking test					
Kruidenier et al. 2011 [35]	265 ± 223	27	656 ± 223	34	391 [276 to 506]
Bo et al. 2013 [34]	113 ± 123	20	317 ± 123	24	203 [128, 279]
Supervised exercise training versus combined therapy					
Constant load treadmill walking test					
Lundgren et al. 1989 [33]	120 ± 215	21	489 ± 380	22	369 [178 to 560]
Greenhalgh et al. 2008 [30][a]	UTC		UTC		UTC
Greenhalgh et al. 2008 [30][b]	UTC		UTC		UTC
Mazari et al. 2012 [32]	31 ± 30	46	82 ± 30	47	51 [39 to 64]
Graded treadmill walking test					
Fakhry et al. 2015 [36]	712 ± 640	106	1120 ± 675	106	408 [230 to 586]

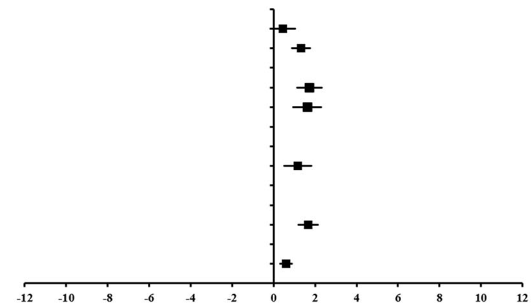

Fig. 2 Pain-free walking distance (m): change in walking distance with revascularisation alone/exercise training alone (control) versus combined therapy of revascularisation plus exercise training. [a,b]Greenhalgh et al. 2008 [30] was divided into two trials as patients were stratified according to the anatomical site of revascularisation (femoropopliteal or aortoiliac) prior to randomisation. Forest plot detailing between-group effect size and 95 % confidence intervals (CIs) of each trial. Δ change from baseline, *UTC* unable to calculate

Study	Control therapy Δ Mean ± SD	N	Combined therapy Δ Mean ± SD	N	Mean difference [95% CI]
Revascularisation versus combined therapy					
Constant load treadmill walking test					
Lundgren et al. 1989 [33]	361 ± 335	21	474 ± 380	22	113 [-108 to 334]
Badger et al. 2007 [31]	UTC		UTC		UTC
Mazari et al. 2012 [32]	33 ± 74	52	130 ± 74	47	97 [67 to 127]
Graded treadmill walking test					
Kruidenier et al. 2011 [35]	342 ± 221	27	663 ± 221	34	321 [207 to 435]
Bo et al. 2013 [34]	161 ± 243	27	259 ± 243	26	98 [-46 to 242]
Supervised exercise training versus combined therapy					
Constant load treadmill walking test					
Lundgren et al. 1989 [33]	276 ± 302	21	474 ± 380	22	198 [-14 to 410]
Greenhalgh et al. 2008 [30][a]	UTC		UTC		UTC
Greenhalgh et al. 2008 [30][b]	UTC		UTC		UTC
Mazari et al. 2012 [32]	48 ± 71	46	130 ± 71	47	82 [52 to 111]
Graded treadmill walking test					
Fakhry et al. 2015 [36]	955 ± 663	106	1237 ± 703	106	282 [97 to 467]

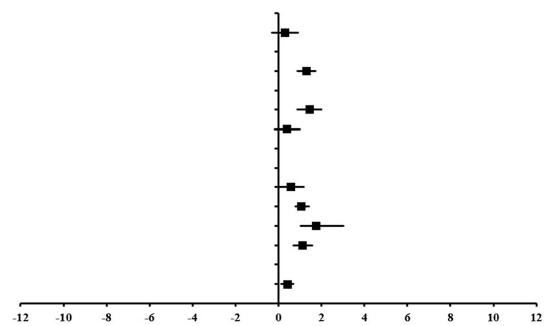

Fig. 3 Maximal walking distance (m): change in walking distance with revascularisation alone/exercise training alone (control) versus combined therapy of revascularisation plus exercise training. Forest plot detailing between-group effect size (ES) and 95 % confidence intervals (CIs) of each trial. [a,b]Greenhalgh et al. 2008 [30] was divided into two trials as patients were stratified according to the anatomical site of revascularisation (femoropopliteal or aortoiliac) prior to randomisation. Greenhalgh et al. 2008 [30][a] and Greenhalgh et al. 2008 [30][b] did not report post-intervention data (standard deviation) for each comparison group but did report between-group ES data. Δ change from baseline, *UTC* unable to calculate

(Fig. 3; Electronic Supplementary Material Table S10). Between-group ES were large (mean ES 0.86; range 0.31–1.44), with ES analysis revealing a large and significant ES ($p < 0.01$) in favour of combined therapy over revascularisation in two trials [32, 35], and non-significant ES ($p > 0.05$) in another two trials [33, 34]. Combined therapy was generally superior to exercise training alone with a mean difference that ranged from 82 to 282 m, and a large and significant between-group ES (mean ES 0.98; range 0.41–1.75), except for one trial [33] where the ES did not reach significance ($p = 0.07$).

3.3.3 Six-min Walking Distance

Only one trial measured 6-min walking distance [34]. The mean difference between combined therapy and revascularisation therapy alone was 7 m (95 % CI −48 to 63). The between-group ES was trivial with no significant difference between groups (ES 0.08, 95 % CI −0.49 to 0.64; $p = 0.79$; Electronic Supplementary Material Table S11).

3.3.4 Resting Ankle-Brachial Index

The mean difference in ABI between combined therapy and revascularisation therapy alone ranged from −0.05 to 0.13, and the between-group ES were mostly trivial (mean ES 0.06; range −0.35 to 0.53) with no significant difference between groups (Fig. 4; Electronic Supplementary Material Table S12), with the exception of one trial [32], which reported a significant effect in favour of combined therapy ($p = 0.01$). The mean difference in ABI between

Study	Control therapy Δ Mean ± SD	N	Combined therapy Δ Mean ± SD	N	Mean difference [95% CI]
Revascularisation versus combined therapy					
Lundgren et al 1989 [33]	0.35 ± 0.14	21	0.30 ± 0.14	22	-0.05 [-0.14 to 0.04]
Badger et al. 2007 [31]	UTC		UTC		UTC
Kruidenier et al. 2011 [35]	0.22 ± 0.20	33	0.19 ± 0.20	30	-0.03 [-0.13 to 0.07]
Mazari et al. 2012 [32]	0.21 ± 0.25	52	0.34 ± 0.25	47	0.13 [0.03 to 0.23]
Bo et al. 2013 [34]	0.19 ± 0.30	18	0.26 ± 0.30	26	0.07 [-0.12 to 0.26]
Supervised exercise training versus combined therapy					
Lundgren et al. 1989 [33]	0.04 ± 0.14	21	0.30 ± 0.14	22	0.26 [0.17 to 0.35]
Greenhalgh et al. 2008 [30][a]	UTC		UTC		UTC
Greenhalgh et al. 2008 [30][b]	UTC		UTC		UTC
Mazari et al. 2012 [32]	0.03 ± 0.23	46	0.34 ± 0.23	47	0.31 [0.22 to 0.40]
Fakhry et al. 2015 [36]	0.03 ± 0.20	106	0.16 ± 0.03	106	0.13 [0.08 to 0.18]

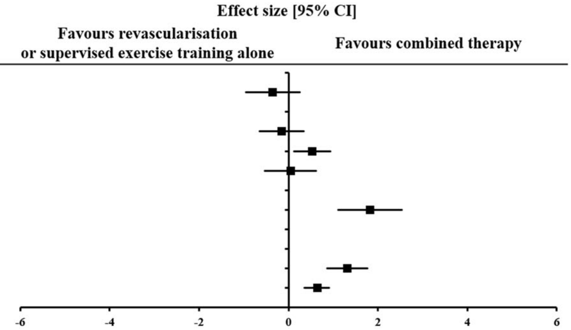

Fig. 4 Resting ankle-brachial index (ABI): change in ABI with revascularisation alone/exercise training alone (control) versus combined therapy of revascularisation plus exercise training. Forest plot detailing between-group effect size (ES) and 95% confidence intervals (CIs) of each trial. [a,b]Greenhalgh et al. 2008 [30] was divided into two trials as patients were stratified according to the anatomical site of revascularisation (femoropopliteal or aortoiliac) prior to randomisation. Greenhalgh et al. 2008 [30][a] and Greenhalgh et al. 2008 [30][b] reported only 2-year follow-up data, which revealed a significant effect in favour of combined therapy over supervised exercise training in both trials (Greenhalgh et al. 2008 [30][a] ES 0.11, 95 % CI 0.03–0.20; $p = 0.01$; Greenhalgh et al. 2008 [30][b] ES 0.14, 95 % CI 0.03–0.26; $p = 0.02$). Δ change from baseline, *UTC* unable to calculate

Study	Control therapy Δ Mean ± SD	N	Combined therapy Δ Mean ± SD	N	Mean difference [95% CI]
Revascularisation versus combined therapy					
Badger et al. 2007 [31]	UTC		UTC		UTC
Kruidenier et al. 2011 [35]	13 ± 8	29	11 ± 8	32	-2 [-6 to 3]
Mazari et al. 2012 [32]	6 ± 45	46	50 ± 45	47	44 [25 to 62]
Bo et al. 2013 [34]	-2 ± 9	21	1 ± 9	25	3 [-2 to 8]
Supervised exercise training versus combined therapy					
Greenhalgh et al. 2008 [30][a]	UTC		UTC		UTC
Greenhalgh et al. 2008 [30][b]	UTC		UTC		UTC
Mazari et al. 2012 [32]	25 ± 42	52	50 ± 42	47	25 [8 to 42]

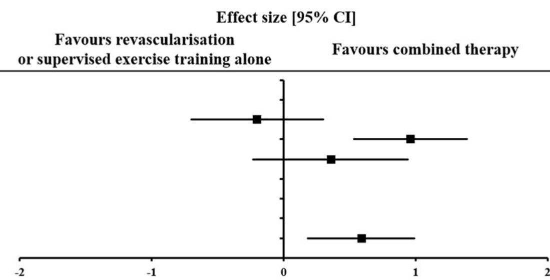

Fig. 5 Quality of life (SF-36 Physical Health): change in scores with revascularisation alone/exercise training alone (control) versus combined therapy of revascularisation plus exercise training. Forest plot detailing between-group effect size (ES) and 95 % confidence intervals (CIs) of each trial. [a,b]Greenhalgh et al. 2008 [30] was divided into two trials as patients were stratified according to the anatomical site of revascularisation (femoropopliteal or aortoiliac) prior to randomisation. Greenhalgh et al. 2008 [30][a] and Greenhalgh et al. 2008 [30][b] reported only 2-year follow-up data, which revealed that combined therapy had no added effect over supervised exercise training in the femoropopliteal trial (Greenhalgh et al. 2008 [30][a] ES −0.4, 95 % CI −4.2 to 3.4; $p = 0.82$), and a significant effect in favour of combined therapy in the aortoiliac trial (Greenhalgh et al. 2008 [30][b] ES 7.8, 95 % CI 1.5–14.1; $p = 0.02$). Δ change from baseline, *UTC* unable to calculate

combined therapy and exercise training alone ranged from 0.13 to 0.31. Between-group ES were large (mean ES 1.26; range 0.64–1.82) and significant in favour of combined therapy ($p < 0.01$).

3.3.5 Resting Calf Arterial Blood Flow

Resting calf arterial blood flow was only reported in one study by Lundgren et al. [33]. The mean difference in resting calf blood flow between combined therapy and revascularisation therapy was 2.30 ml·100 ml^{-1}·min^{-1} (95 % CI −3.48 to 8.08), which resulted in a small and non-significant between-group ES (ES 0.24, 95 % CI −0.36 to 0.84; $p = 0.43$; Electronic Supplementary Material Table S13) [33]. The mean difference between combined therapy and exercise training alone was 6.90 ml·100 ml^{-1}·min^{-1} (95 % CI 1.40–12.40). The between-group ES was moderate (ES 0.76, 95 % CI 0.14–1.38) and significant in favour of combined therapy ($p = 0.02$).

3.3.6 Health-Related Quality of Life

The mean difference between combined therapy and revascularisation in the scores of the physical health component of quality of life ranged from −2 to 44 (Fig. 5; Electronic Supplementary Material Table S14). Between-group ES were mostly negligible and non-significant (mean ES 0.00; range −0.20 to 0.96), except for one trial [32] where the ES revealed a large and significant effect in favour of combined therapy ($p < 0.01$). Based on this single trial [32], combined therapy had a greater effect on scores of physical domains of quality of life with a mean difference of 25 (95 % CI 8–42) and a moderate between-group ES (ES 0.59, 95 % CI 0.18–0.99; $p < 0.01$) over exercise training alone.

Study	Control therapy Δ Mean ± SD	N	Combined therapy Δ Mean ± SD	N	Mean difference [95% CI]
Revascularisation versus combined therapy					
Badger et al. 2007 [31]	UTC		UTC		UTC
Kruidenier et al. 2011 [35]	-5 ± 12	29	0 ± 12	32	5 [-1 to 11]
Mazari et al. 2012 [32]	33 ± 143	46	33 ± 143	47	0 [-59 to 59]
Bo et al. 2013 [34]	-2 ± 9	21	1 ± 9	25	3 [-3 to 8]
Supervised exercise training versus combined therapy					
Greenhalgh et al. 2008 [30][a]	UTC		UTC		UTC
Greenhalgh et al. 2008 [30][b]	UTC		UTC		UTC
Mazari et al. 2012 [32]	67 ± 104	52	33 ± 104	47	-33 [-75 to 8]

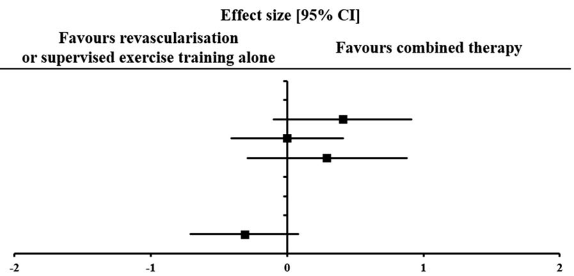

Fig. 6 Quality of life (SF-36 Mental Health): change in scores with revascularisation alone/exercise training alone (control) versus combined therapy of revascularisation plus exercise training. Forest plot detailing between-group effect size (ES) and 95% confidence intervals (CIs) of each trial. [a,b]Greenhalgh et al. 2008 [30] was divided into two trials as patients were stratified according to the anatomical site of revascularisation (femoropopliteal or aortoiliac) prior to randomisation. Greenhalgh et al. 2008 [30][a] and Greenhalgh et al. 2008 [30][b] reported 2-year follow-up data, which revealed that combined therapy had no added effect over supervised exercise training in both trials (Greenhalgh et al. 2008 [30][a] ES 2.4, 95% CI −1.7 to 6.5; $p = 0.25$; Greenhalgh et al. 2008 [30][b] ES 4.9, 95% CI −1.3 to 11.1; $p = 0.12$). Δ change from baseline, *UTC* unable to calculate

The mean difference between combined therapy and the revascularisation therapy in the scores of the mental health component of quality of life ranged from 0 to 5 (Fig. 6; Electronic Supplementary Material Table S15). Between-group ES were small (mean ES 0.23; range 0.00–0.41) with no significant difference between groups ($p > 0.05$). The mean difference in scores between combined therapy and exercise training, calculated for one trial [32], was −33 (95 % CI −75 to 8). The between-group ES was negative and small, with no significant difference between groups (ES −0.31, 95 % CI −0.71 to 0.08; $p = 0.12$).

4 Discussion

This review identified a total of eight randomised controlled trials investigating the effect of combined therapy of revascularisation and supervised exercise training in patients with PAD and symptoms of IC. The summary of findings indicate that combined therapy leads to greater improvements in pain-free and maximal walking distances compared with revascularisation or supervised exercise training alone. Combined therapy improved ABI to a similar extent as revascularisation, and to a greater extent than supervised exercise training. In addition, findings from a small number of trials suggest that: (1) combined therapy may lead to greater improvements in leg blood flow than supervised exercise training (one trial), and no added effect compared to revascularisation alone (one trial); and (2) combined therapy may lead to greater gains in physical quality of life than supervised exercise training (one trial), with no further improvements in the physical and mental domains of quality of life than revascularisation alone (three trials).

There has previously been significant interest in comparing the effects of revascularisation with exercise therapy for patients with PAD, and reviews of this literature generally conclude that both forms of treatment are equally beneficial for improving walking ability [38, 39]. Our current systematic review offers a new perspective by showing that patients with PAD, including those with symptoms of more severe disease, benefit from the combination of revascularisation and supervised exercise therapy, with an additional mean difference of 38 to 408 m in treadmill walking distances over revascularisation or supervised exercise training alone. It is possible that the benefits of combined therapy are sustained over the longer term, as evidence suggests that within 1–2 years of the completion of interventions, patients treated with combined therapy maintain greater pain-free and maximal walking distances compared with patients treated with revascularisation [34] or supervised exercise training alone [30]. However, further study is required as the trial by Mazari et al. [32] showed that revascularisation therapy, exercise therapy and the combined therapy approach were equally effective in improving walking distances, with no significant difference between groups 1 year after the completion of interventions.

It is noteworthy that the single study that measured 6-min walking distance [34] failed to find a significant difference between combined therapy and revascularisation, which is in contrast with the generally large differences observed for pain-free and maximal treadmill walking distances found in the current review. While large and clinically meaningful changes in 6-min walk distance (>50 m) [40] were observed with combined therapy and revascularisation, there was no difference in the effect between the groups. This study also assessed treadmill walking distances, and there was a significant gain in pain-free walking distance with combined therapy over revascularisation alone (MD 203 m, $p < 0.01$). However, the effect for maximal walking distance was not significantly different between groups (MD 98 m, $p = 0.18$), which is somewhat consistent with the 6-min walk test finding.

The data presented here suggest that combined therapy leads to large gains in walking capacity over revascularisation or exercise therapy alone, and it does so over revascularisation alone without any further improvement in lower limb haemodynamics. While it is well established that lower limb revascularisation achieves improvements in walking capacity and ABI by restoring arterial patency and improving limb blood flow capacity [33, 41, 42], increases in walking capacity with exercise training occur with negligible changes in lower limb blood flow and ABI [15]. Thus, the significant effect of combined therapy compared with revascularisation alone on walking capacity indicates that exercise has an additive effect, and reinforces the notion that revascularisation and exercise therapy improve walking capacity via different mechanisms [43]. Although the primary pathology of PAD is impaired blood flow, other factors such as altered skeletal muscle phenotype, also contribute to patients' poor exercise tolerance [44]. Exercise training induces adaptive changes in skeletal muscle phenotype, which include increases in muscle cross-sectional area [45], alterations in metabolic activity [46] and enhanced capillary supply [47, 48], thus potentially improving the ability of the working muscles to optimise the utilisation of the limited oxygen delivered to the lower limbs. These intramuscular changes, in conjunction with the haemodynamic benefits of revascularisation, likely explain the significant improvements in walking capacity achieved with combined therapy over exercise or revascularisation therapy alone. This is somewhat speculative as the current understanding of the mechanisms that underpin the improvements in exercise tolerance with exercise training is limited to studies of patients with IC who have not undergone a previous revascularisation intervention. Whether the mechanism of the improvement with exercise therapy differs following revascularisation (i.e. where limb blood flow has been restored) remains to be determined.

Based on our findings, it appears that patients undergoing either revascularisation alone or combined therapy perceive greater improvements in their physical and mental health than patients undergoing exercise therapy alone. This may be explained by the fact that patients are more likely to perceive improvements in quality of life as a result of immediate improvements in IC and other symptoms after revascularisation, compared with more gradual improvements that result from exercise therapy [36, 42]. It is known that exercise-induced leg pain is the most prevalent barrier to physical activity in patients with IC [49]. It is plausible to suggest that revascularisation may increase the patient's ability to walk independently by providing symptom relief, and thereby enhance their confidence and motivation to engage in exercise and lifestyle change [50]. From a clinical perspective, given that physical activity is strongly associated with overall physical function [51] and all-cause and cardiovascular mortality in patients with PAD [52, 53], it is possible that the improvement in walking capacity achieved with combined therapy, in comparison with either revascularisation or exercise alone, would not only enhance the capacity to undertake activities of daily living, but would also be associated with a better patient prognosis as a result of increased physical activity.

With the advancement of revascularisation techniques and devices, the rates of lower limb interventions in patients with PAD have rapidly increased [54]. However, revascularisation therapy is associated with a substantial risk of complications and associated reinterventions due to initial and subsequent treatment failure [55]. Only four (50 %) trials reported reintervention rates [32, 34–36], and these limited data suggested that the need for reintervention associated with combined therapy was comparable, or even lower, than that for revascularisation alone or supervised exercise training alone. Combined therapy may improve the durability of revascularisation, which would have substantial social and cost-benefits. Fakhry et al. [36] reported that one-third of the patients undergoing combined therapy developed restenosis of their initially revascularised lesion at one-year follow-up, yet only 4 % of these patients required a secondary intervention because of recurrent symptoms. A cost-effectiveness analysis of the Mazari et al. [32] trial showed that, within 1 year, the cost per quality-adjusted life-year (QALY) was significantly higher for the group of patients undergoing revascularisation (€11,777.00), compared with supervised exercise training (€6147.04) or combined therapy (€10,649.74) [56]. Secondary interventions following revascularisation contributed significantly to the total cost of care in this study, supporting the suggestion that supervised exercise training should be offered to patients undergoing revascularisation with the aim of reducing potential reintervention costs in the long-term [56].

Supervised exercise therapy is a well-established effective treatment for improving walking capacity in patients with IC [57, 58]. While there is strong evidence to support current recommendations for the prescription of exercise as part of the initial treatment of patients with IC [57, 59, 60], there are currently no recommendations for exercise prescription in patients with more severe disease undergoing revascularisation. Further research is needed to establish whether the current exercise recommendations for patients with IC are also suitable for use post-operatively. For instance, although the majority of the included trials prescribed aerobic interval exercise at a moderate-high level of IC pain, the use of pain as a marker of intensity may not always be appropriate in post-surgical patients because it is expected that revascularisation would relieve symptoms [36, 42], and therefore enable patients to exercise with little or no ischaemic leg pain. There does not seem to be a clear relationship between exercise program length and improvement in outcomes. Fakhry et al. [36] found that the mean differences in walking distances and ABI between combined therapy and supervised training remained significant in favour of the combined therapy at the beginning (1 month), midpoint (6 months) and at completion of 12 months of the exercise program, but decreased in magnitude over time. This may be explained by the fact that the prescribed volume of exercise was reduced after the first 6 months of training, which is a somewhat unconventional approach as the goal of exercise prescription is usually to gradually progress the intensity and/or volume of exercise towards levels that can be maintained for the longer term. While the heterogeneity of exercise prescribed in the current trials make it difficult to provide guidelines on exercise prescription at this time, the observed improvements in pain-free and maximal walking distance across a range of exercise interventions would suggest that exercise training should be routine care post revascularisation. Further research is needed to develop optimal and specific exercise training programs for PAD patients who have undergone revascularisation, including guidance on the ideal time to commence exercise following revascularisation, as well as on the progression of exercise following revascularisation. These trials should aim to clarify how each component of exercise, such as intensity, frequency and duration of exercise sessions, contributes to improvements in exercise tolerance.

Exercise attendance rates were only reported in four (50 %) [30, 32, 36] of the trials included in this review, and therefore it is unclear whether exercise programs were always delivered as planned. Incomplete description of exercise attendance is highly prevalent in the PAD literature [61], and this has negative implications for the interpretation of results, investigation of dose-response effects, and replication of protocols in future studies. Low exercise attendance in one of the trials was reported to be associated with lack of motivation, working commitments, insurance-related issues and orthopaedic co-morbidities [35]. Future research is needed to identify barriers that should be addressed to enhance delivery/attendance of post-operative exercise interventions for PAD. For example, structured post-operative home-based exercise programs may be effective as an alternative to hospital-based programs or as an extended maintenance phase of such programs [62].

The efficacy of the combined therapy approach should be considered in light of potential biases associated with exercise testing procedures. First, only three of the included trials [34–36] used a graded-test protocol, which is considered the more reliable treadmill protocol for determining walking capacity in patients with PAD [63]. Despite differences in the treadmill protocols used between studies, the present review demonstrates improvements with combined therapy in both pain-free and maximal walking distances. Uniformity in the assessment of walking distance is desirable in future research to facilitate comparison of study outcomes through meta-analyses. Second, none of the included trials reported that patients were familiarised with the walking tests prior to baseline assessments. The introduction of any learning effect, particularly in patients who performed treadmill walking as part of the therapy program, has the potential to overestimate the true therapy effect [64, 65]. Third, in all of the included studies, a cap was placed on the duration of treadmill walking tests, ranging from 5 min (215 m) to 30 min (1600 m). It is likely that such caps limit the ability to accurately assess walking distances, and possibly contribute to an underestimation of the treatment effect. For example, Greenhalgh et al. [30] reported that walking distances in patients who improved beyond the allocated cap of 1000 m were taken as equal to 1000 m. Similarly, Kruidenier et al. [35] reported that 11 patients in the combined therapy group and one patient in the revascularisation group improved beyond the allocated cap of 30 min. Therefore, the implementation of open-ended, maximal graded test protocols for the assessment of walking distances should be considered in future studies [66]. The 6-min walking test is also a valid and reliable alternative for the assessment of walking capacity, and has been shown to be representative of mobility loss among patients with PAD [67, 68]. In addition, it is not associated with a learning effect when repeat testing is performed [67]. Despite its widespread use in clinical practice, only one of the included trials assessed patient's self-paced walking ability using the 6-min walking test. Therefore, future studies should consider inclusion of the six-minute walk test as an additional outcome measure.

This review has some limitations. As expected, the protocols for the assessment of primary outcomes were not uniform across studies, and the small number of trials within each outcome subgroup precluded the ability to undertake a meta-analysis. Non-peer-reviewed publications, such as conference abstracts, were excluded from the current review, and there was no attempt to identify registered clinical trials that have not been published. Therefore, we cannot fully exclude the possibility of publication bias. Despite an attempt to request missing data, few of the data could be obtained, and therefore, analyses proceeded for continuous variables using data that were converted from median/range and standard error/confidence intervals using established estimates [20, 69]. In most instances authors reported that they were no longer able to access the study data, which was not unexpected considering that results from five of the nine trials were published >5 years ago. Whether this reveals selective reporting and whether the use of pooled data contributed to the variance in ES is unclear. The mean ES calculated for each outcome did not consider the grade of evidence for each outcome or any differences in the sample size of each study, which differs from the overall (weighted) ES generated through a meta-analysis approach. Future studies examining the effects of combined therapy should clearly report between-group comparative data and effects in accordance with standard recommendations [69].

5 Conclusion

This systematic review found that patients with PAD and symptoms of IC treated with combined therapy achieve greater improvements in walking distance than those treated with either revascularisation or exercise therapy alone. The combination of revascularisation with supervised exercise training appears to be as beneficial as revascularisation alone for improving leg haemodynamics. The limited number of studies to date makes it difficult to conclude whether combined therapy may yield better results than revascularisation or supervised exercise training alone for health-related quality of life.

The use of supervised exercise training as an adjunct to revascularisation in patients with PAD is a promising treatment strategy and the improvements in walking distance suggest that exercise training should be routine care post revascularisation. Future research is needed to investigate whether the benefits achieved with combined therapy are sustained, and whether combined therapy is cost-effective in the long-term. There is also a need to define optimal and specific exercise training programs for PAD patients who have undergone revascularisation, as well as strategies to improve compliance with exercise programs. Uniformity in the assessment of outcomes, such as treadmill walking distance, is desirable in future research to facilitate comparison of study outcomes. Revascularisation and exercise therapy appear to have an additive effect, whereby independent mechanisms possibly contribute to the improvements in walking capacity when these treatments are combined. Further research is required to fully understand the mechanisms of this beneficial effect.

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Compliance with Ethical Standards

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Conflict of interest Annelise Meneses, Raphael Ritti-Dias, Belinda Parmenter, Jonathan Golledge and Christopher Askew declare that they have no conflicts of interest relevant to the content of this review.

References

1. Fowkes FG, Rudan D, Rudan I, et al. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis. Lancet. 2013;382:1329–40.
2. Meneses AL, Farah BQ, Ritti-Dias RM. Muscle function in individuals with peripheral arterial obstructive disease: a systematic review. Motricidade. 2012;8:86–96.
3. Gardner AW, Skinner JS, Vaughan NR, et al. Comparison of treadmill walking and stair climbing over a range of exercise intensities in peripheral vascular occlusive disease. Angiology. 1993;44:353–60.
4. Gardner AW, Montgomery PS, Scott KJ, et al. Patterns of ambulatory activity in subjects with and without intermittent claudication. J Vasc Surg. 2007;46:1208–14.
5. Atkins LM, Gardner AW. The relationship between lower extremity functional strength and severity of peripheral arterial disease. Angiology. 2004;55:347–55.
6. Regensteiner JG, Hiatt WR, Coll JR, et al. The impact of peripheral arterial disease on health-related quality of life in the Peripheral Arterial Disease Awareness, Risk, and Treatment: New Resources for Survival (PARTNERS) Program. Vasc Med. 2008;13:15–24.
7. Meneses AL, Lima AHRA, Farah BQ, et al. Correlation between physical fitness and indicators of quality of life of individuals with intermittent claudication. Rev Bras Med Sporte. 2011;17:175–8.
8. Cooper KM, Bilbrew D, Dubbert PM, et al. Health barriers to walking for exercise in elderly primary care. Geriatr Nurs. 2001;22:258–62.
9. Mahoney EM, Wang K, Keo HH, et al. Vascular hospitalization rates and costs in patients with peripheral artery disease in the United States. Circ Cardiovasc Qual Outcomes. 2010;3:642–51.
10. Anderson JL, Halperin JL, Albert NM, et al. Management of patients with peripheral artery disease (compilation of 2005 and 2011 ACCF/AHA guideline recommendations): a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation. 2013;127:1425–43.
11. Conte MS, Pomposelli FB, Clair DG, et al. Society for Vascular Surgery practice guidelines for atherosclerotic occlusive disease of the lower extremities: management of asymptomatic disease and claudication. J Vasc Surg. 2015;61:1S.
12. Spronk S, Bosch JL, den Hoed PT, et al. Cost-effectiveness of endovascular revascularization compared to supervised hospital-based exercise training in patients with intermittent claudication: a randomized controlled trial. J Vasc Surg. 2008;48:1472–80.

13. Fakhry F, Rouwet EV, Den Hoed PT, et al. Long-term clinical effectiveness of supervised exercise therapy versus endovascular revascularization for intermittent claudication from a randomized clinical trial. Br J Surg. 2013;100:1164–71.
14. Amarteifio E, Krix M, Wormsbecher S, et al. Dynamic contrast-enhanced ultrasound for assessment of therapy effects on skeletal muscle microcirculation in peripheral arterial disease: pilot study. Eur J Radiol. 2013;82:640–6.
15. Parmenter BJ, Raymond J, Fiatarone Singh MA. The effect of exercise on haemodynamics in intermittent claudication: a systematic review of randomized controlled trials. Sports Med. 2010;40:433–47.
16. Hoogeboom TJ, Dronkers JJ, Hulzebos EH, et al. Merits of exercise therapy before and after major surgery. Curr Opin Anaesthesiol. 2014;27:161–6.
17. Olin JW, White CJ, Armstrong EJ, et al. Peripheral artery disease: evolving role of exercise, medical therapy, and endovascular options. J Am Coll Cardiol. 2016;67:1338–57.
18. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009;339:b2535.
19. Maher CG, Sherrington C, Herbert RD, et al. Reliability of the PEDro scale for rating quality of randomized controlled trials. Phys Ther. 2003;83:713–21.
20. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol. 2005;5:13.
21. Cohen J. Statistical power analysis for the behavioural sciences. New York: Academic Press; 1977.
22. Maxwell L, Santesso N, Tugwell PS, et al. Method guidelines for Cochrane Musculoskeletal Group systematic reviews. J Rheumatol. 2006;33:2304–11.
23. Franco A, Legrand E, Guidicelli H, et al. Results of the physiotherapy of arterial disease at the stage of intermittent claudication by programmed efforts training (author's transl). J Mal Vasc. 1980;5:185–9.
24. Mazari FA, Gulati S, Rahman MN, et al. Early outcomes from a randomized, controlled trial of supervised exercise, angioplasty, and combined therapy in intermittent claudication. Ann Vasc Surg. 2010;24:69–79.
25. Jakubseviciene E, Vasiliauskas D, Velicka L, et al. Effectiveness of a new exercise program after lower limb arterial blood flow surgery in patients with peripheral arterial disease: a randomized clinical trial. Int J Environ Res Public Health. 2014;11:7961–76.
26. Bo E, Bergland A, Stranden E, et al. Effects of 12 weeks of supervised exercise after endovascular treatment: a randomized clinical trial. Physiother Res Int. 2014;20:147–57.
27. Matsuo T, Sakaguchi T, Ishida A, et al. Effect of in-hospital physical activity on cardiovascular prognosis in lower extremity bypass for claudication. J Phys Ther Sci. 2015;27:1855–9.
28. Nordanstig J, Gelin J, Hensäter M, et al. Walking performance and health-related quality of life after surgical or endovascular invasive versus non-invasive treatment for intermittent claudication—a prospective randomised trial. Eur J Vasc Endovasc Surg. 2011;42:220–7.
29. Lundgren F, Dahllof AG, Schersten T, et al. Muscle enzyme adaptation in patients with peripheral arterial insufficiency: spontaneous adaptation, effect of different treatments and consequences on walking performance. Clin Sci (Lond). 1989;77:485–93.
30. Greenhalgh RM, Belch JJ, Brown LC, et al. The adjuvant benefit of angioplasty in patients with mild to moderate intermittent claudication (MIMIC) managed by supervised exercise, smoking cessation advice and best medical therapy: results from two randomised trials for stenotic femoropopliteal and aortoiliac arterial disease. Eur J Vasc Endovasc Surg. 2008;36:680–8.
31. Badger SA, Soong CV, O'Donnell ME, et al. Benefits of a supervised exercise program after lower limb bypass surgery. Vasc Endovasc Surg. 2007;41:27–32.
32. Mazari FA, Khan JA, Carradice D, et al. Randomized clinical trial of percutaneous transluminal angioplasty, supervised exercise and combined treatment for intermittent claudication due to femoropopliteal arterial disease. Br J Surg. 2012;99:39–48.
33. Lundgren F, Dahllof AG, Lundholm K, et al. Intermittent claudication-surgical reconstruction or physical training? A prospective randomized trial of treatment efficiency. Ann Surg. 1989;209:346–55.
34. Bø E, Hisdal J, Cvancarova M, et al. Twelve-months follow-up of supervised exercise after percutaneous transluminal angioplasty for intermittent claudication: a randomised clinical trial. Int J Environ Res Public Health. 2013;10:5998–6014.
35. Kruidenier LM, Nicola SP, Rouwet EV, et al. Additional supervised exercise therapy after a percutaneous vascular intervention for peripheral arterial disease: a randomized clinical trial. J Vasc Interv Radiol. 2011;22:961–8.
36. Fakhry F, Spronk S, van der Laan L, et al. Endovascular revascularization and supervised exercise for peripheral artery disease and intermittent claudication: a randomized clinical trial. JAMA. 2015;314:1936–44.
37. Norton K, Norton L, Sadgrove D. Position statement on physical activity and exercise intensity terminology. J Sci Med Sport. 2010;13:496–502.
38. Frans FA, Bipat S, Reekers JA, et al. Systematic review of exercise training or percutaneous transluminal angioplasty for intermittent claudication. Br J Surg. 2012;99:16–28.
39. Jones WS, Schmit KM, Vemulapalli S, et al. Treatment strategies for patients with peripheral artery disease. Rockville: Agency for Healthcare Research and Quality (US); 2013.
40. Perera S, Mody SH, Woodman RC, et al. Meaningful change and responsiveness in common physical performance measures in older adults. J Am Geriatr Soc. 2006;54:743–9.
41. Creasy TS, McMillan PJ, Fletcher EW, et al. Is percutaneous transluminal angioplasty better than exercise for claudication? Preliminary results from a prospective randomised trial. Eur J Vasc Surg. 1990;4:135–40.
42. Murphy TP, Cutlip DE, Regensteiner JG, et al. Supervised exercise versus primary stenting for claudication resulting from aortoiliac peripheral artery disease: six-month outcomes from the claudication: exercise versus endoluminal revascularization (CLEVER) study. Circulation. 2012;125:130–9.
43. Green S. Haemodynamic limitations and exercise performance in peripheral arterial disease. Clin Physiol Funct Imaging. 2002;22:81–91.
44. Askew CD, Green S, Walker PJ, et al. Skeletal muscle phenotype is associated with exercise tolerance in patients with peripheral arterial disease. J Vasc Surg. 2005;41:802–7.
45. McDermott MM, Guralnik JM, Ferrucci L, et al. Physical activity, walking exercise, and calf skeletal muscle characteristics in patients with peripheral arterial disease. J Vasc Surg. 2007;46:87–93.
46. Hiatt WR, Regensteiner JG, Wolfel EE, et al. Effect of exercise training on skeletal muscle histology and metabolism in peripheral arterial disease. J Appl Physiol. 1985;1996(81):780–8.
47. Duscha BD, Robbins JL, Jones WS, et al. Angiogenesis in skeletal muscle precede improvements in peak oxygen uptake in peripheral artery disease patients. Arterioscler Thromb Vasc Biol. 2011;31:2742–8.
48. McGuigan MR, Bronks R, Newton RU, et al. Resistance training in patients with peripheral arterial disease: effects on myosin isoforms, fiber type distribution, and capillary supply to skeletal muscle. J Gerontol A Biol Sci Med Sci. 2001;56:B302–10.

49. Barbosa JP, Farah BQ, Chehuen M, et al. Barriers to physical activity in patients with intermittent claudication. Int J Behav Med. 2014;22:70–6.
50. Wann-Hansson C, Rahm Hallberg I, Klevsgard R, et al. The long-term experience of living with peripheral arterial disease and the recovery following revascularisation: a qualitative study. Int J Nurs Stud. 2008;45:552–61.
51. Gardner AW, Montgomery PS, Scott KJ, et al. Association between daily ambulatory activity patterns and exercise performance in patients with intermittent claudication. J Vasc Surg. 2008;48:1238–44.
52. Chang P, Nead KT, Olin JW, et al. Effect of physical activity assessment on prognostication for peripheral artery disease and mortality. Mayo Clin Proc. 2015;90:339–45.
53. Gardner AW, Montgomery PS, Parker DE. Physical activity is a predictor of all-cause mortality in patients with intermittent claudication. J Vasc Surg. 2008;47:117–22.
54. Egorova NN, Guillerme S, Gelijns A, et al. An analysis of the outcomes of a decade of experience with lower extremity revascularization including limb salvage, lengths of stay, and safety. J Vasc Surg. 2010;51:878–85.
55. Sussman M, Mallick R, Friedman M, et al. Failure of surgical and endovascular infrainguinal and iliac procedures in the management of peripheral arterial disease using data from electronic medical records. J Vasc Interv Radiol. 2013;24:378–91.
56. Mazari FAK, Khan JA, Carradice D, et al. Economic analysis of a randomized trial of percutaneous angioplasty, supervised exercise or combined treatment for intermittent claudication due to femoropopliteal arterial disease. Br J Surg. 2013;100:1172–9.
57. Parmenter BJ, Dieberg G, Smart NA. Exercise training for management of peripheral arterial disease: a systematic review and meta-analysis. Sports Med. 2015;45:231–44.
58. Lane R, Ellis B, Watson L, et al. Exercise for intermittent claudication. Cochrane Database Syst Rev. 2014;7:CD000990.
59. Gardner AW, Poehlman ET. Exercise rehabilitation programs for the treatment of claudication pain: a meta-analysis. JAMA. 1995;274:975–80.
60. Askew CD, Parmenter B, Leicht AS, et al. Exercise & Sports Science Australia (ESSA) position statement on exercise prescription for patients with peripheral arterial disease and intermittent claudication. J Sci Med Sport. 2014;17:623–9.
61. Tew GA, Brabyn S, Cook L, et al. The completeness of intervention descriptions in randomised trials of supervised exercise training in peripheral arterial disease. PLoS One. 2016;11:e0150869.
62. Lamberti N, Malagoni AM, Ficarra V, et al. Structured home-based exercise versus invasive treatment: a mission impossible? A pilot randomized study in elderly patients with intermittent claudication. Angiology. 2015;67:772–80.
63. Nicolaï SPA, Viechtbauer W, Kruidenier LM, et al. Reliability of treadmill testing in peripheral arterial disease: a meta-regression analysis. J Vasc Surg. 2009;50:322–9.
64. Wu G, Sanderson B, Bittner V. The 6-minute walk test: how important is the learning effect? Am Heart J. 2003;146:129–33.
65. Hiatt WR, Hirsch AT, Regensteiner JG, et al. Clinical trials for claudication. Assessment of exercise performance, functional status, and clinical end points. Vascular Clinical Trialists. Circulation. 1995;92:614–21.
66. Nicolaï SPA, Leffers P, Kruidenier LM, et al. Extending the range of treadmill testing for patients with intermittent claudication. Med Sci Sports Exerc. 2010;42:640–5.
67. McDermott MM, Guralnik JM, Criqui MH, et al. Six-minute walk is a better outcome measure than treadmill walking tests in therapeutic trials of patients with peripheral artery disease. Circulation. 2014;130:61–8.
68. Montgomery PS, Gardner AW. The clinical utility of a six-minute walk test in peripheral arterial occlusive disease patients. J Am Geriatr Soc. 1998;46:706–11.
69. Higgins J, Green S. Cochrane handbook for systematic reviews of interventions. The Cochrane Collaboration. 2011. http://www.cochrane-handbook.org. Accessed 30 Aug 2016.