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[Intervention Protocol]

Effects of additional exercise therapy after a successful vascular intervention for patients with symptomatic peripheral arterial disease

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ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To analyse the effects of a supervised exercise programme following successful lower limb revascularisation compared with standard care following lower limb revascularisation in patients with symptomatic peripheral artery disease (PAD).

BACKGROUND

Description of the condition

Peripheral artery disease (PAD) refers to the obstruction or narrowing of the large arteries of the lower limbs, usually caused by atheromatous plaque (Gerhard-Herman 2016). The resulting stenosis or occlusion, if severe enough, can result in impairment of oxygen delivery and supply to the tissues of the leg. The major risk factors for PAD are similar to those for coronary artery disease, namely smoking, diabetes, dyslipidaemia, and hypertension. Patients with PAD are at increased risk of morbidity and mortality from cardiovascular events, including myocardial infarction and stroke (Dormandy 1999; Fowkes 2008; Hooi 2004; Pande 2011).

Although in many cases less severely diseased patients can be asymptomatic, the major clinical manifestations of PAD are intermittent claudication (IC) and critical limb ischaemia (CLI). IC typically presents as reproducible exercise-induced ischaemic pain in the leg muscles, from which relief is generally gained by rest. If underlying arterial stenosis continues to progress, blood flow may become inadequate to meet the resting metabolic demands of the tissues of the leg, and CLI will develop. A patient with CLI will experience (often extreme) pain in the foot at rest, while the skin and other tissues of the affected limb may become more susceptible to ulceration and poor wound healing, including the development of gangrene. This progression from asymptomatic disease is often categorised using the Fontaine classification criteria (Fontaine 1954); see Table 1.

The prevalence of PAD increases with age and is more common in men than women (Dormandy 2000). In Scotland, the prevalence of IC in 2010 ranged from 0.7% to 1.7% in people aged 16 to 54 years, and was 7.4% in people aged over 74 years (Bromley 2011). Globally, an estimated 202 million people live with PAD (Fowkes 2013), which represents an increase of 28.7% in low- and middle-income countries and 13.1% in higher-income countries compared with the preceding 10 years (Fowkes 2013).

Diagnosis and treatment

Guidelines addressing the diagnosis and management of PAD have been produced by several bodies, including the National Institute for Health and Care Excellence (NICE 2012), the American Heart Association (Hirsch 2006; Gerhard-Herman 2016), the European Society of Cardiology (Tendera 2011), and the Society for Vascular Surgery (SVS 2015), and these organisations broadly agree on the overall diagnosis and management of PAD. Following a thorough clinical history and physical examination of the lower limbs, including the peripheral pulses, a diagnosis of PAD may be confirmed using the ankle-brachial index (ABI) (an ABI of less than 0.90 is suggestive of PAD) or non-invasive imaging (or both). Doppler ultrasound of the lower limbs can establish the extent of atherosclerosis, and magnetic resonance angiography or computerised tomography angiography may be undertaken to provide additional information on the anatomy of stenosis or occlusion if required prior to revascularisation (Gerhard-Herman 2016; NICE 2012; Tendera 2011).

Initial treatment of PAD for those with IC involves reduction of cardiovascular risk factors, including the use of statins and antiplatelet medication (Hirsch 2006; NICE 2012; Tendera 2011). This reduces cardiovascular and mortality risk, as well as progression of disease requiring surgical revascularisation procedures (Gargiulo 2012; Wong 2011). Patients should also be offered access to a supervised exercise programme (Lane 2017; NICE 2012), though access to these programmes and patient engagement is limited (Ahimastos 2011; Dua 2020; Shalhoub 2009). In patients in whom symptoms do not improve with exercise and risk factor management, revascularisation procedures may be offered if the patient's symptoms are severe enough to outweigh the risks of intervention. In the first instance, patients are offered angioplasty (Fakhry 2018), or stenting (Bachoo 2010), with bypass grafting being a further treatment option for patients where this is unsuccessful or unsuitable (Antoniou 2017). If revascularisation surgery is declined, some national guidelines suggest medical management using pharmacological interventions such as cilostazol (Hirsch 2006; Tendera 2011), naftidrofuryl (NICE 2012; Tendera 2011) and pentoxifylline (Hirsch 2006; Tendera 2011). However, there is a degree of uncertainty as to which, if any, of these medications provides most clinical benefit (Bedenis 2014; de Backer 2012; Salhiyyah 2012).

Patients with CLI are more urgently considered for possible revascularisation after thorough assessment by a vascular multidisciplinary team, adequate pain management (NICE 2012), and management of cardiovascular risk factors. Finally, in those with established gangrene, or disease which is not amenable to revascularisation procedures, amputation may be needed.

Description of the intervention

Conservative treatment strategies for patients with PAD are based on secondary prevention of cardiovascular disease, medical management, and exercise therapy. Exercise therapy, especially supervised walking exercise, is considered to be the first clinical choice for the management of IC symptoms in patients with PAD (Hirsch 2006; NICE 2012). A Cochrane Review found high-quality evidence that supervised exercise programmes are more beneficial than placebo or usual care in improving the pain-free walking distance (PFWD) and maximum walking distance (MWD) (Lane 2017). In addition, some exercise programmes have improved other parameters of physical function (muscle strength, walking speed, stair climbing ability, physical activity) (Treat-Jacobson 2019), health-related quality of life (Saxton 2011), and cardiovascular function in patients with PAD (Chehuen 2017; Correia 2020; Ritti-Dias 2019).

Despite the known benefits of supervised exercise, revascularisation surgery is sometimes a good option for patients with significant disability or impaired activities of daily life (SVS 2015), those with no satisfactory improvement following conservative management (NICE 2012), and those with CLI (Gerhard-Herman 2016). Previous evidence suggests that revascularisation in symptomatic PAD leads to improvements in haemodynamics, functional capacity, and quality of life in the short term (Fakhry 2018). However, over the longer term, patients can present with recurrence of IC symptoms and a need to perform a second intervention (re-intervention) (Hirsch 2006; Venermo 2019). Some studies have suggested that revascularisation for IC may not bring significantly greater benefits than supervised exercise alone in respect of improved physical function and quality of life, however it is still recommended for patients where supervised exercise has failed, or for those with CLI. An option for optimising the benefit patients receive from lower limb revascularisation

treatment for PAD could be to include supervised exercise training as an adjunctive treatment. This would potentially give patients the opportunity to benefit from the proven efficacy of a supervised exercise programme in addition to surgical revascularisation, which may have benefits beyond either treatment alone.

How the intervention might work

As the main aim of revascularisation in PAD is to improve local blood flow to the lower limbs, the possible advantage of adding exercise therapy after the surgical procedure is that it could not only augment the improvement in lower-limb blood flow response following surgery but would also help to increase walking ability through improvement in several mechanisms, such as reduced levels of inflammatory markers, increased capillary density of the gastrocnemius muscle, and altered skeletal muscle metabolism through an increase on muscular enzymatic oxidative capacity (Haas 2012). Moreover, adding exercise therapy after the surgical procedure could also improve cardiovascular profile due to better blood pressure control (Chehuen 2017), improve autonomic cardiovascular function (Chehuen 2017; Ritti-Dias 2019), and increase engagement with exercise programmes, which may also be improved following reduction in IC symptoms after lower limb revascularisation (Fakhry 2015).

Why it is important to do this review

Previous studies have shown that both exercise therapy and lower limb revascularisation are effective for improving PFWD and MWD in patients with symptomatic PAD (Fowkes 2008; Lane 2017). However, there are no systematic reviews examining the effectiveness of additional supervised exercise therapy following a vascular intervention for patients with symptomatic PAD. This review aims to identify the possible benefits from adding a supervised exercise regimen following revascularisation compared to usual care. Our results will allow assessment of the quality of the included studies and the direction of observed effects. This may support a change in standard management for patients with symptomatic PAD undergoing lower limb revascularisation, or may identify a need for further randomised controlled trials in this field.

OBJECTIVES

To analyse the effects of a supervised exercise programme following successful lower limb revascularisation compared with standard care following lower limb revascularisation in patients with symptomatic peripheral artery disease (PAD).

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs) which compare supervised exercise training following lower limb revascularisation with standard care following lower limb revascularisation. We will include all relevant RCTs, regardless of language or publication status.

Types of participants

We will include participants aged 18 years and older, diagnosed with PAD of any level (Fontaine Classifications II, IIA, IIB, III, and IV, or Rutherford Class 2 to 6; Fontaine 1954; Rutherford 1997), diagnosed by a clinician using a combination of general and systemic examination and diagnostic tools (ankle-brachial index (ABI), toe pressure index (TPI), doppler scan), following successful lower limb revascularisation by either open surgery or endovascular procedures. We consider lower limb revascularisation to be successful when patients are able to participate in supervised exercise programmes after the surgical procedure.

Types of interventions

We will include studies that investigate the chronic effects of any form of supervised exercise training following lower limb revascularisation compared to standard care following lower limb revascularisation. Exercise training may be performed individually or in a group setting, set in an exercise facility or at home, and use any exercise modality, such as aerobic exercise, strength training, circuit training (or combined-modality exercise training programmes). We will define four weeks as the minimum duration of the exercise programme for inclusion in our review. Standard care may involve drug therapy, smoking cessation, and any non-supervised exercise advice. We expect both study arms will receive equal conservative treatment before and after vascular surgery (Aboyans 2018). If they do not, we will investigate further using subgroup and sensitivity analysis.

The possible comparisons are as follows.

- Exercise training (individual or group; facility- or home-based; using any modality or combined-modality training programme) compared to standard care.
- Exercise training (individual or group; facility- or home-based; using any modality or combined-modality training programme) plus standard care compared to standard care alone.

Types of outcome measures

Primary outcomes

- Changes in objective measurements of physical function. These can include:
  - maximum walking distance or time (MWD/T) on treadmill;
  - six-minute walk test (6MWT) total distance; or
  - pain-free walking distance or time (PFWD/T) on treadmill.

Secondary outcomes

- Changes in ABI
- Changes in health-related quality-of-life scores, measured by generic or disease-specific tools (or both)
- Reintervention rates
- All-cause mortality
- Changes in subjective measures of physical function. These can include:
  - Walking Impairment Questionnaire (WIQ); or
  - Walking Estimated-Limitation Calculated by History (WELCH (Tew 2014)).
- Patient adherence and acceptability of exercise training following lower limb revascularisation programmes, as reported by the study investigators

For all outcomes, we will include the time points reported by the individual studies. Clinically relevant time points will be baseline,

(pre-surgery or post-surgery, or both) and post-intervention at any point of time (e.g. three, six, nine, and 12 months).

Search methods for identification of studies

Electronic searches

The Cochrane Vascular Information Specialist aims to identify all relevant RCTs regardless of language or publication status (published, unpublished, in press, or in progress).

The Information Specialist will search the following databases for relevant trials.

- The Cochrane Vascular Specialised Register via the Cochrane Register of Studies (CRS-Web).
- The Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Register of Studies Online (CRSO).
- MEDLINE (Ovid MEDLINE® Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE®) (1946 onwards).
- Embase Ovid (from 1974 onwards).
- CINAHL Ebsco (from 1982 onwards).
- Scopus (from 1966 onwards).
- SPORTDiscus (1871 onwards).
- Web of Science (1900 onwards).

The Information Specialist will search the following trial registries.

- The World Health Organization International Clinical Trials Registry Platform (who.int/trialsearch).
- ClinicalTrials.gov (clinicaltrials.gov).

Searching other resources

We will also search internal reports and conference proceedings and contact study authors to solicit additional information about completed or ongoing studies.

Data collection and analysis

Selection of studies

Two review authors (GC, RMR) will independently assess the titles and abstracts of each study to identify those that meet the inclusion criteria. We will retrieve the full text of the studies identified as potentially relevant by at least one review author. The same two review authors will independently screen the full-text articles retrieved for inclusion or exclusion. If necessary, a third review author (JS) will resolve any disagreements between reviewers by discussion. We will illustrate the study selection process in a PRISMA diagram (Liberati 2009). We will list all articles excluded after full-text assessment in a 'Characteristics of excluded studies' table and will provide the reasons for their exclusion.

Data extraction and management

Two review authors (GC, RMR) will independently extract data from the eligible studies using an adapted data extraction form provided by Cochrane Vascular. We will enter the data into Review Manager 5 (RevMan Web 2019; Review Manager 2020). If necessary, the third review author (JS) will resolve any disagreements by discussion with the two reviewers (GC, RMR).

We will extract data from each included study on the following parameters.

- Study participant inclusion/exclusion criteria.
- Country where the research was conducted.
- Participants' gender and age.
- Study design, duration, randomisation processes, allocation concealment.
- Analysis used (intention-to-treat or per-protocol).
- Funding source and declarations of interest of the study authors.
- Recruitment rates.
- Description of vascular surgery.
- Descriptions of exercise interventions (type, length, intensity).
- Intervention settings (home, hospital, gym).
- Number of participants in each trial arm, withdrawals.
- Exclusions post-randomisation, dropouts, and loss to follow-up.
- Outcome measures and times outcomes were assessed.

Assessment of risk of bias in included studies

Two review authors (GC, RMR) will independently assess the risk of bias for every included study using the criteria recommended by the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). The tool assesses bias in seven different domains (random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selective outcome reporting; other potential sources of bias). Each domain will be categorised as being at high, low, or unclear risk of bias, depending on each review author's judgement. A third review author (JS) will adjudicate disagreements. If necessary, we will contact study authors to clarify further information about the possible risk of bias identified.

Measures of treatment effect

We will use risk ratio with corresponding 95% confidence intervals (CIs) to measure the treatment effects for dichotomous data; and we will calculate the mean difference (MD) and standard deviation (SD) with corresponding 95% CIs for continuous outcome measures. We will use standardised mean difference (SMD) with 95% CIs to combine data from trials that measure the same outcome using different scales.

Unit of analysis issues

The unit of analysis will be participants, as randomised to the intervention and control groups (Higgins 2019).

Dealing with missing data

We will contact study authors to request missing data. We will report levels of loss to follow-up and assess this as a source of potential bias. We will use sensitivity analysis to explore the impact of including studies with missing data in the overall assessment of results.

Assessment of heterogeneity

We will assess the degree of heterogeneity by visually inspecting the forest plots and we will calculate Chi^2 and I^2 tests to measure the amount of heterogeneity. The values of I^2 will be interpreted as follows, using the guidance from Higgins 2019. We will take the levels of heterogeneity into account when interpreting results.

- I^2 less than 50%: low heterogeneity.
- I^2 between 50% and 75% moderate heterogeneity.
- I^2 greater than 75%: substantial heterogeneity.

Assessment of reporting biases

We will investigate publication bias using funnel plots if 10 or more studies meet the inclusion criteria of the review, as recommended by the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019)

Data synthesis

We will assess clinical heterogeneity (e.g. PAD grade, presence of risk factors, age, gender, ethnic background, socioeconomic status) and methodological heterogeneity (e.g. type of revascularisation, type of intervention, exercise modality, type of control and follow-up period) across studies to define the effect model. We will use the fixed-effect model when there is no or low heterogeneity. If there is clinical heterogeneity (where the Chi^2 test P value is greater than 0.01, or the I^2 test has a value of 75% or more), we will use random-effects meta-analyses. If we identify clinical, methodological, or statistical heterogeneity across included trials sufficient to cause concerns, we will not report pooled results from the meta-analysis but will instead use a narrative approach to data synthesis. The statistical analyses will be performed using Review Manager 5 (Review Manager 2020).

Subgroup analysis and investigation of heterogeneity

We will consider the reasons for any heterogeneity detected. We intend to perform the following subgroup analyses.

- Severity of ischaemia (Fontaine score of II or IV or a Rutherford score of 2 to 6).
- Types of lower limb revascularisation (open or endovascular).
- Types of intervention (supervised, unsupervised, or home-based exercise).
- Type of exercise modality (walking, resistance training, combined exercise).
- Type of control or standard care.
- Follow-up period (three, six, nine, or 12 months).

Sensitivity analysis

We will repeat the analyses after excluding studies at a high risk for bias to assess their impact (sensitivity analysis). We will consider studies at high risk of bias when more than three of the seven domains in the Cochrane 'Risk of bias' tool are assessed as being at high risk of bias, or if studies are at high risk of bias regarding their random sequence generation (Higgins 2011). If missing data are believed to introduce a risk of bias, we will explore the impact of including such studies in the overall assessment of results using sensitivity analysis.

Summary of findings and assessment of the certainty of the evidence

We will create a 'Summary of findings' table to present the main findings for supervised exercise programme following lower limb revascularisation versus standard care following lower limb revascularisation, using GRADEpro GDT software (GRADEpro GDT 2015). We will include the following outcomes.

- Changes in MWD/T.
- Changes in 6MWT.
- Changes in PFWD/T.
- Changes in ABI.
- Changes in health-related quality-of-life scores measured by generic or disease-specific tools (or both).
- Reintervention rates.
- All-cause mortality.

We will assess the certainty of the evidence for each outcome as high, moderate, low, or very low, based on the five GRADE considerations of risk of bias, inconsistency, indirectness, imprecision, and publication bias, using the GRADE approach (Schünemann 2019). We will base the tables on methods described in the *Cochrane Handbook for Systematic Reviews of Interventions*, and will justify any departures from the standard methods (Atkins 2004; Higgins 2019). Two review authors (GC, RMR) will independently judge the certainty of the evidence and, if required, will resolve any disagreements by consensus or discussion with a third review author (JS). We will justify all decisions to downgrade the evidence using footnotes and we will make comments to aid the reader's understanding of the review where necessary. We have included a draft 'Summary of findings' table in this protocol (Table 2).

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ADDITIONAL TABLES

Table 1. Fontaine Classification of peripheral arterial disease (Fontaine 1954)

Stage	Description
I	Asymptomatic
II	Mild claudication pain
IIa	Claudication distance > 200 metres
IIb	Claudication distance < 200 metres
III	Rest pain (especially at night)
IV	Ulceration and/or gangrene of the limb

Table 2. Example 'Summary of findings' table

Supervised exercise programme following lower limb revascularisation compared with standard care following lower limb revascularisation

Patient or population: patients with symptomatic PAD

Settings: hospital, home, or clinical setting

Intervention: supervised exercise programme following lower limb revascularisation

Comparison: standard care following lower limb revascularisation[a]

Outcomes	Anticipated absolute effects * (95% CI)		Relative effect (95% CI)	No of participants (RCTs)	Certainty of the evidence (GRADE)	Comments
	Risk with standard care following lower limb revascularisation	Risk with supervised exercise programme following lower limb revascularisation				
MWD/T [follow-up]	The mean MWD/T ranged across control groups from [value][measure]	The mean MWD/T in the intervention groups was **[value] [lower/higher]** [(value to value lower/higher)]		[value] ([value])	⊕⊖⊖⊖ **very low** ⊕⊕⊖⊖ **low** ⊕⊕⊕⊖ **moderate** ⊕⊕⊕⊕ **high**	
6MWT [follow-up]	The mean 6MWT total distance ranged across control groups from [value][measure]	The mean 6MWT total distance in the intervention groups was **[value] [lower/higher]** [(value to value lower/higher)]		[value] ([value])	⊕⊖⊖⊖ **very low** ⊕⊕⊖⊖ **low** ⊕⊕⊕⊖ **moderate** ⊕⊕⊕⊕ **high**	
PFWD/T [follow-up]	The mean PFWD/T ranged across control groups from [value][measure]	The mean PFWD/T in the intervention groups was **[value] [lower/higher]** [(value to value lower/higher)]		[value] ([value])	⊕⊖⊖⊖ **very low** ⊕⊕⊖⊖ **low** ⊕⊕⊕⊖ **moderate** ⊕⊕⊕⊕ **high**	
ABI [follow-up]	The mean ABI ranged across control groups from [value][measure]	The mean ABI in the intervention groups was **[value] [lower/higher]** [(value to value lower/higher)]		[value] ([value])	⊕⊖⊖⊖ **very low** ⊕⊕⊖⊖ **low** ⊕⊕⊕⊖ **moderate**	

Table 2. Example 'Summary of findings' table *(Continued)*

					⊕⊕⊕⊕ **high**
Quality of life (measured on validated quality-of-life scale) [follow-up]	The mean quality of life ranged across control groups from [value][measure]	The mean quality of life in the intervention groups was **[value] [lower/higher]** [(value to value lower/higher)]		[value] ([value])	⊕⊝⊝⊝ **very low** ⊕⊕⊝⊝ **low** ⊕⊕⊕⊝ **moderate** ⊕⊕⊕⊕ **high**
Reintervention rates [follow-up]	**Study population** **[value] per 1000**	**[value] per 1000** ([value] to [value])	**RR [value]** ([value] to [value])	[value] ([value])	⊕⊝⊝⊝ **very low** ⊕⊕⊝⊝ **low** ⊕⊕⊕⊝ **moderate** ⊕⊕⊕⊕ **high**
All-cause mortality [follow-up]	**Study population** **[value] per 1000**	**[value] per 1000** ([value] to [value])	**RR [value]** ([value] to [value])	[value] ([value])	⊕⊝⊝⊝ **very low** ⊕⊕⊝⊝ **low** ⊕⊕⊕⊝ **moderate** ⊕⊕⊕⊕ **high**

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low certainty: we have very little confidence and true effect is likely to be substantially different from the estimate of effect

6MWT: six-minute walking test; **ABI**: ankle-brachial index; **CI**: confidence interval; **MWD/T**: maximum walking distance/time; **PFWD/T**: pain-free walking distance/time; **RCT**: randomised controlled trial; **RR**: risk ratio

[a] Any other control intervention without exercise training

APPENDICES

Appendix 1. MEDLINE search strategy

1 Intermittent Claudication/

2 exp Peripheral Vascular Diseases/

3 exp Peripheral Arterial Disease/

4 exp Arterial Occlusive Diseases/

5 exp Leg/bs

6 Iliac Artery/

7 Popliteal Artery/

8 Femoral Artery/

9 Tibial Arteries/

10 (PVD or PAOD or PAD).ti,ab.

11 ((arter* or vascular or vein* or veno* or peripher*) adj3 (occlus* or steno* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)).ti,ab.

12 (peripheral adj3 dis*).ti,ab.

13 claudic*.ti,ab.

14 arteriopathic.ti,ab.

15 dysvascular*.ti,ab.

16 (leg adj3 (occlus* or steno* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)).ti,ab.

17 (limb adj3 (occlus* or steno* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)).ti,ab.

18 (lower adj3 extrem* adj3 (occlus* or steno* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)).ti,ab.

19 ((iliac or femoral or popliteal or femoro* or fempop* or crural or tibial) adj3 (occlus* or steno* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)).ti,ab.

20 or/1-19

21 exp Endovascular Procedures/

22 exp Stents/

23 exp Vascular Surgical Procedures/

24 exp Blood Vessel Prosthesis/

25 exp Blood Vessel Prosthesis Implantation/

26 exp Angioplasty/

27 endovasc*.ti,ab.

28 endostent*.ti,ab.

29 endoluminal.ti,ab.

30 endoprosthe*.ti,ab.

31 graft.ti,ab.

32 endograft*.ti,ab.

33 percutaneous*.ti,ab.

34 stent*.ti,ab.

35 (Palmaz or Zenith or Dynalink or Hemobahn or Luminex* or Memotherm or Wallstent or Viabahn or Nitinol or Intracoil or Tantalum).ti,ab.

36 EVAR.ti,ab.

37 (surger* or surgic* or repair).ti,ab.

38 Angioplasty.ti,ab.

39 or/21-38

40 20 and 39

41 exp Exercise/

42 exp Exercise Therapy/

43 exp Walking/

44 Dancing/

45 (physical adj (exercise* or exertion or endurance or therapy or conditioning or activity or activities or fitness or training)).ti,ab.

46 (exercise adj (training or intervention or programme or therapy or activity or regime)).ti,ab.

47 (fitness adj (training or intervention or protocol or programme or therapy or activity or regime)).ti,ab.

48 ((training or conditioning) adj (circuit or intervention or protocol or programme or activity or regime or resistance or strength)).ti,ab.

49 (walk or walking or run or running or treadmill or aerobic or swim or swimming or dance or dancing or cycling or cyclist).ti,ab.

50 kinesiotherap*.ti,ab.

51 ((endurance or aerobic or cardio*) adj (fitness or training or intervention or protocol or program* or therapy or activity or regime)).ti,ab.

52 or/41-51

53 40 and 52

54 randomized controlled trial.pt.

55 controlled clinical trial.pt.

56 randomized.ab.

57 placebo.ab.

58 drug therapy.fs.

59 randomly.ab.

60 trial.ab.

61 groups.ab.

62 or/54-61

63 exp animals/ not humans.sh.

64 62 not 63

65 53 and 64

CONTRIBUTIONS OF AUTHORS

GC: designed and drafted the protocol. For the review GC will acquire trial reports, select trials, extract data, perform data analysis and interpretation, and draft the review future review updates
DP: designed and drafted the protocol. For the review DP will draft the review and future review updates
RMR: designed and drafted the protocol. For the review RMR will acquire trial reports, select trials, extract data, perform data analysis and interpretation, and draft review and future review updates
JS: designed and drafted the protocol. For the review JS will assist with data interpretation, and draft the review and future review updates

DECLARATIONS OF INTEREST

GC: none known
DP: none known
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JS: none known

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NOTES

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