Supervised exercise therapy and revascularization for intermittent claudication: network meta-analysis of randomized controlled trials

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STRUCTURED ABSTRACT

Objectives: This study sought to perform a comprehensive meta-analysis comparing all therapeutic modalities for intermittent claudication (IC), including: Best Medical Therapy (BMT) alone, Percutaneous Angioplasty (PTA), Supervised Exercise Therapy (SET), or PTA combined with SET, to establish the optimal IC first-line treatment.

Background: IC is a common health-problem which limits physical activity, results in decreased Quality of Life (QoL) and is associated with poor cardiovascular outcomes. Previous meta-analyses have attempted to combine data from randomized trials; however, none have combined data from all possible treatment combinations or synthesized QoL outcomes.

Methods: Following a systematic literature review (December 2018) which identified 37 published randomized trials, a network meta-analysis was performed combining all possible IC treatment strategies.

Results: Overall, 2,983 claudicants were included (mean weighted age: 68 years, 54.5% males). Comparisons were performed between: BMT (688 patients, 28 arms) vs. SET (1,189 patients, 35 arms) vs. PTA (511 patients, 12 arms) vs. PTA plus SET (395 patients, 8 arms). Mean weighted follow-up was 12 months (95% Confidence Interval: 9-23 months). Compared with BMT alone, PTA plus SET outperformed other treatment strategies, with a Maximum Walking Distance (MWD) gain of 290 meters (95% Credible Interval: 180-390 meters, $p<0.001$). A variety of QoL assessments using validated tools were reported in 15 trials; PTA plus SET was superior to other treatments (Cohen's d 1.8, 95% Credible Interval: 0.21-3.4).

Conclusions: In addition to BMT, PTA combined with SET seems to be the optimal first-line treatment strategy for claudicants in terms of MWD and QoL improvement.

CONDENSED ABSTRACT

Intermittent Claudication (IC) is the commonest manifestation of Peripheral Arterial Disease (PAD) and constitutes an important health problem, associated with poor Quality of Life (QoL) and future cardiovascular events. Several randomized trials have performed head-to-head comparisons between the main therapeutic modalities for IC: Best Medical Therapy (BMT), Percutaneous Angioplasty (PTA), Supervised Exercise Therapy (SET), or PTA with SET. Unfortunately, no literature synthesis to date has combined all these treatment arms in a comprehensive meta-analysis. Furthermore, the vast majority of previous meta-analyses in this clinical area have not synthesized QoL outcomes. In this comprehensive network meta-analysis, Maximum Walking Distance (MWD) and QoL outcomes, were combined from all available treatment arms in published randomized studies relating to IC. The optimal treatment strategy was PTA with SET, shown to improve both MWD and QoL outcomes. Clinicians should not consider PTA without SET as first-line treatment in IC.

List of abbreviations:

PAD: Peripheral Arterial Disease

IC: Intermittent Claudication

QoL: Quality of Life

PFWD: Pain-Free Walking Distance

MWD: Maximum Walking Distance

SET: Supervised Exercise Therapy

BMT: Best Medical Therapy

PTA: Percutaneous Angioplasty

CrI: Credible Interval

INTRODUCTION

It is estimated that more than 200 million people have Peripheral Arterial Disease (PAD) worldwide, with a spectrum of symptoms from none to severe(1). Intermittent Claudication (IC) is the most frequent presentation of PAD(2). It profoundly limits physical activity and results in ambulatory dysfunction and poor Quality of Life (QoL)(3-5).

A considerable body of evidence suggests that exercise therapy should have a central role in the management of IC. Exercise may improve Pain-Free Walking Distance (PFWD), Maximum Walking Distance (MWD) and reduce the risk of future major cardiovascular events in patients with IC(6). Supervised Exercise Therapy (SET) in particularis considered more effective than unsupervised exercise therapy(7,8). Unfortunately, SET is not readily available in all institutions and patient uptake or

adherence can be suboptimal(9). The cost of setting-up and maintaining SET services can also be a barrier in terms of offering SET to all claudicants(10). Some clinicians may therefore advocate Percutaneous Angioplasty (PTA) as an attractive initial treatment(11).

Multiple trials have compared the efficacy and effectiveness of SET, PTA, or Best Medical Therapy (BMT) using a plethora of different designs. The vast majority of trials consisted of two treatment arms directly comparing one therapeutic modality to the other. Previous systematic literature syntheses have suggested that SET may be superior to BMT or early PTA. The most recent meta-analyses have suggested that SET combined with PTA may be the optimal initial treatment strategy(6). These meta-analyses, however, mostly included studies with head-to-head comparisons between two specific treatment arms (e.g. PTA vs. SET) or used an approach that did allow the inclusion and direct comparison of all potential treatments in the context of IC(6). Using this approach to perform a synthesis of the available literature means that a significant body of evidence may have been overlooked. Furthermore, previous meta-analytical attempts in this area have not included all available QoL assessments in their reporting due to the fact that various different tools have been used in claudication trials across the years.

To address this, the current study sought to perform a network meta-analysis, comparing all possible therapeutic modalities in patients with IC against each other, aiming to establish which mode of treatment is the most appropriate in this clinical setting. Contrary to previous meta-analyses, our approach ensured that all QoL

assessments, regardless of the QoL tool used in each study, were included in the literature syntheses.

METHODS

The search strategy, study selection and analyses were carried out in accordance with the PRISMA statement for systematic reviews and meta-analyses (Figure 1).

Search strategy

An electronic search of the MEDLINE, EMBASE, AMED and Scopus databases was performed (December 2018) using the following key terms: claudication OR "peripheral arterial disease" OR "peripheral artery disease", exercise. The search was limited to human studies published after 1970; no language restrictions were applied.

Study selection

Upon completion of the electronic search, a list of all relevant abstracts was collated and reviewed to identify published clinical trials comparing the efficacy of any form of contemporary treatment (SET, BMT, PTA or surgical intervention) in patients presenting with ischaemic IC. All abstracts were screened independently by two authors. The senior author was advised in case of disagreement regarding potential inclusion of a study. Studies included in this analysis were required to have: 1) a randomized controlled trial design; 2) data on baseline symptom status of study participants; 3) clearly defined intervention and control group; and 4) objective

measures of exercise capacity at the end of the study. The references cited in all the trials that fulfilled the inclusion criteria were also examined to identify additional studies. No anatomical exclusion criteria were applied. Trials presented at conferences which had not published full results in the form of a peer-reviewed manuscript were not included. All identified trials that fulfilled the four aforementioned criteria were included in the final synthesis.

Data extraction and risk of bias assessment

Data extraction was performed independently by two authors. Presentation, clinical characteristics, target lesion location, type of intervention offered, outcomes measured at baseline and end of study, follow-up duration and clinical events were extracted from individual studies onto an electronic database. Discrepancies were resolved through discussion with the senior author. Risk of bias was assessed using the Cochrane risk of bias assessment tool and the relevant studies were classified as "low", "moderate", or "high-risk"(12). Publication bias was assessed using a funnel plot. Quantitative quality assessment was performed through use of the PEDro scale, a validated tool in the context of clinical trials(13). The PEDro scale provides 11 different criteria (potential scores 0 to 11) to assess whether a trial is likely to be internally valid and could have sufficient statistical information to make the results interpretable.

Outcomes of interest

Primary outcome of interest

The primary outcome of interest was Maximum Walking Distance (MWD) improvement at latest available follow-up.

Secondary outcome of interest

The secondary outcome of interest was patient-reported QoL at latest available follow-up, using a validated QoL reporting tool.

Statistical analysis

Following identification of studies suitable for inclusion in the analysis, the following distinct treatment arms were identified: BMT (alone), SET, PTA as well as PTA combined with SET. A network graph summarizing the various interventions assessed in the trials included in the meta-analysis is included (Figure 2). A funnel plot was used to assess overall reporting bias (Figure 3). Lines signify that interventions are compared in at least one study with thicker lines signifying that interventions have been compared in multiple studies. A network meta-analysis was performed(14,15). This type of analysis, also known as mixed treatment comparison, allows the combined direct and indirect comparison of all relevant data to allow complex healthcare decisions. A Bayesian network approach was used, which can be applied in multi-arm trials and allows the incorporation of study-level covariates for adjustments, to combine and compare all the aforementioned treatment arms in this specific clinical setting. Homogeneity of effect estimates in each pairwise meta-analysis was tested using Cochrans' Q and the I^2 statistic(16,17). A random effect model was used due to heterogeneity between all treatment arms, when comparing results between different modes of treatment. The primary meta-analytical endpoint

was the average benefit in MWD measured in meters (continuous variable). The MWD was expressed in absolute mean value and 95% Credible Intervals (CrI). The secondary endpoint was the reported gain in QoL indexes. The latter were combined and reported using Cohen's d – which is the difference between two means divided by a standard deviation. Cohen's d can take values ranging between 0.01 and 2.0, which correspond to an overall effect size ranging from "very small" (0.01) to "huge" (2.0), and is a popular effect measure in qualitative contexts. The GeMTC GUI and ADDIS software were used for the network meta-analysis (https://drugis.org/software). Continuous variables (age) were combined between studies and a weighted mean is reported with 95% Confidence Interval (CI), where applicable. For categorical variables (sex), proportions were again combined and a weighed percentage is reported with 95% CI. These analyses were performed using R (version 3.5.1) for Windows. A p value <0.05 was considered statistically significant in all cases.

RESULTS

Overall, a total of 37 clinical trials (39 publications, 5 were multi-arm trials; 1 trial reported results in 2 publications) with 2,983 patients diagnosed with IC were included in the analysis(18-55) (Figure 1 – PRISMA flow diagram). No trials were eventually excluded based on the quality assessment score as all fulfilled the four inclusion criteria described under "Methods". The "Adjuvant benefit of angioplasty in patients with mild to moderate intermittent claudication" (MIMIC) trial (32) reported separately for those with aorto-iliac and femoro-popliteal disease. A total of 15 angioplasty treatment arms were identified in 14 of which patients received endovascular treatment in the femoro-popliteal segment and 1 (MIMIC trial) in the

aorto-iliac segment. No below-the-knee (distal angioplasty) treatment arms were identified. Furthermore, results from the "Comparing Exercise Therapy with Angioplasty for Claudication" (CETAC) trial were reported in two different publications (2009 and 2013) and the latest available follow-up events were extracted from the two publications and entered in the analyses both for MWD and QoL assessments(22,31). The baseline, demographic, and clinical characteristics of the study participants are summarised in Table 1, including the trial quality assessment using the PEDro scale(13). One study(55) was identified as "high-risk" based on the Cochrane risk of bias assessment tool; all other studies were of "moderate-risk". None of the studies were double blind due to the nature of intervention. No sham control trials were identified.

Comparisons were performed between the following treatment arms: BMT (688 patients, 28 arms) vs. SET (1,189 patients, 35 arms) vs. PTA (511 patients, 12 arms) vs. PTA plus SET (395 patients, 8 arms) (Figure 2). Patients in the SET, PTA, and PTA combined with SET arms were on BMT.

The mean weighted age of the participants was 68 years (95% CI: 66-71 years, I^2=0%) and the weighted proportion of male patients was 54.5% (95% CI: 45-65, I^2=0%). The mean weighted follow-up in the studies included in the meta-analysis was 12 months (95% CI: 9-23 months). Given the lack of individual patient level data, no comparisons were possible between treatment arms with regards to cardiovascular risk-factors or other parameters of interest. The mean weighted duration of SET was reported in 24 treatment arms and was 24 weeks (95% CI: 14-40 weeks, I^2=42%); the mean weighted number of SET sessions per week was reported in 12 treatment arms and was 3 sessions per week (95% CI: 3-4, I^2=0%). In all but 3

treatment arms included in the final synthesis, SET consisted of walking on a treadmill; in 2 SET treatment arms(36,47) patients were only asked to walk whilst in 1 study patients were offered pole-striding(43).

Primary outcome of interest

Compared with BMT alone, PTA plus SET outperformed all other treatment strategies, with a MWD gain of 290 meters (95% CrI: 180-390 meters, $p<0.001$) or a 141% proportional gain (95% CrI: 86.85-188.3%, $p<0.001$) over the 12 month average follow-up. Similarly, compared to SET, PTA plus SET again outperformed the other treatment modalities, with a MWD gain of 110 meters (95% CrI: 16-200 meters, $p<0.001$) or a 66% proportional gain (95% CrI: 9.66-121%, $p<0.001$) (Figure 4). SET (MWD gain of 180 meters, 95% CrI: 130-230 meters; 87% proportional gain, 95% CrI: 63-111%) was found to be superior to PTA but inferior to SET plus PTA in terms of improving MWD. Results relating to quantitative findings in all trials are summarized in Table 2.

Secondary outcome of interest

A variety of QoL and health-related assessments were reported in 15 trials, as summarised in Table 3. The 36-item Short Form (SF-36) QoL survey was the most commonly used tool. Details regarding the validity and format of the QoL tools used in the 15 trials are discussed elsewhere(56); all 15 trials used a QoL reporting tool that had previously been validated as their main reporting criterion for QoL-related outcomes(56). Overall, PTA plus SET was superior to all other treatment modalities in terms of QoL improvement (using the criterion reported by each study), as detailed in Figure 5. More specifically, when comparing modalities to BMT alone, the

reported effect size using Cohen's d for PTA plus SET was 1.8 (95% CrI: 0.21-3.4) vs. 0.63 (95% CrI: -0.59-1.8) for SET vs. 0.90 (-0.47-2.3) for PTA (p<0.001). When compared to SET, again PTA plus SET outperformed the other treatment modalities with a combined Cohen's d effect size of 1.2 (95% CrI: -0.0092-2.4).

DISCUSSION

This up to date comprehensive systematic review and network meta-analysis has shown that Percutaneous Angioplasty (PTA) combined with Supervised Exercise Therapy (SET) seems to be the preferred first-line treatment for patients presenting with Intermittent Claudication (IC). There was a significant difference in terms of Maximum Walking Distance (MWD) over a one year average follow-up with an average gain of 110 meters if SET was combined with PTA compared to SET without PTA and a gain of 290 meters compared to BMT . Furthermore, PTA plus SET was superior in terms of gain in QoL outcomes. Overall, both in terms of MWD and QoL, SET plus PTA (with BMT) was the most effective treatment, followed by SET (with BMT), PTA (with BMT), and BMT alone with no adjunct.

These findings have important implications for clinical practice. All patients with IC should be offered BMT, given the overwhelming evidence that BMT prevents future cardiovascular events and improves limb-related outcomes(57,58). Adjunctive treatment modalities such as SET and PTA should, however, be also considered, to improve walking distance and QoL. This current meta-analysis strongly suggests that SET with PTA should be the preferred first-line treatment (always in the context of

BMT), followed by SET (with BMT). Offering PTA without SET should be avoided where possible.

Intermittent claudication is a common diagnosis in middle and high income countries, especially amongst the elderly(2,59). It shares common risk-factors with Coronary Heart Disease (CHD) and in fact represents a systemic manifestation of atherosclerosis. Patients with IC will therefore often have established CHD and will be at high-risk of developing cardiovascular events(7,60,61). In fact, CHD and cerebrovascular disease are the main determinants of future morbidity in this patient group(7,60-62). As per current national guidance in the USA and the UK, patients with IC should all receive BMT in the form of blood pressure control, lipid control (statin therapy), an antiplatelet(7,8) and smoking cessation. The value of these interventions has been established, especially in terms of cardiovascular prevention, in several well-conducted studies and is currently beyond any reasonable doubt(57,58). Besides cardiovascular prevention, however, patients with IC experience significant lifestyle limitations with an impact on their QoL. Subsequently, SET and/or PTA should play a significant role in their treatment pathway.

The Cochrane collaboration has been regularly updating a systematic review and meta-analysis regarding the role of exercise therapy in IC(63). Several trials have already shown that exercise programmes provide important benefits to this population compared with placebo or usual care in improving both pain-free and MWD. Even though exercise may not improve ankle-brachial pressure index or impact on overall mortality, it does improve QoL. Supervised exercise therapy, where patients exercise under close supervision by a healthcare professional, is even more effective (64). Adding PTA to SET may be beneficial and in fact many centres will offer PTA as the initial treatment strategy due to lack of SET programmes locally(64). Poor

uptake/adherence to SET, poor patient fitness and patient preference have also been used by the advocates of a “PTA first” strategy as reasons for offering this type of initial therapeutic intervention in IC(9,64). As pointed out by the Cochrane collaborators, contemporary trials investigating treatment modalities in IC have begun to include SET vs. SET alongside PTA(63). This supports the assumption that clinicians treating IC view PTA as an adjunct to the established treatments consisting of BMTand SET.

Previous meta-analyseshave compared head-to-head BMT vs. SET (or unsupervised exercise) vs. angioplasty, given that most relevant trials consisted of two patient arms. Network meta-analyses have also been attempted; however the endpoints used (e.g. compassion of SET only vs. other treatments) did not allow the inclusion of all published treatment arms(65). This means that a significant amount of the available patient data may have been overlooked, especially when assessing angioplasty as an adjunct to SET or vice-versa. Furthermore, previous meta-analyses have failed to include all available QoL outcomes in their syntheses, due to the fact that different trials use different reporting tools. In this study we attempted to address these issues and provide the most thorough review to date by performing a network meta-analysis which included all potential treatment arms in the studies that have reported to date. It also allowed us to perform a synthesis of QoL outcomes using all QoL criteria reported in each study by employing the Cohen’s d effect size. A previous meta-analysis published in 2015 focussed on different therapeutic modalities for IC and used a mixed-treatment comparison approach similar to the network meta-analytical approach used in this current study(65). The authors reported that evidence was at the time insufficient to determine treatment superiority for improving QoL and MWD in

IC patients. It is important to note that this meta-analysis included alternative pharmaceutical treatments of IC such as cilostazol, pentoxifylline and inositol nicotinate, which were beyond the scope of our review. A review by the National Institute of Health and Care Excellence (NICE) in 2011 on the use of such medications in the context of IC concluded against their use as first-line treatments(66). The scope of our meta-analysis was to identify the best initial treatment strategy rather than a pharmaceutical adjunct in patients unfit for any treatment, hence we did not focus on these "therapies".

The findings of this current study have important implications for future patient care in the setting of IC. These patients should be offered BMT and angioplasty should be combined with SET, if the patient can have exercise. Angioplasty as a first line treatment without the availability of SET should be discouraged.

Limitations

Patient level data were not available, hence meta-regression or in-depth analyses investigating interaction between risk factors could not be performed. Several trials did not report QoL outcomes; however, among those which did report QoL and health assessments there was good consistency in the use of validated tools. The SF-36 tool was used in most instances (Table 3). For obvious reasons, the trials included in this meta-analysis are not double-blinded and no sham control trials could be identified. Hence, the quality assessments of the trials have suffered; however, we did use two different tool to assess the studies both in terms of bias and using a quantitative scale. Finally, we cannot comment on whether PTA after SET should be offered or vice

versa. Individual patient level data of high validity and precision are required in order to perform a meta-regression that could assess this.

Conclusion

In addition to BMT, PTA combined with SET appears to be the optimal initial treatment strategy for patients presenting with IC in terms of MWD and improvement in QoL.

CLINICAL PERSPECTIVE

What's known? Intermittent claudication is a common health-problem which limits physical activity, results in decreased quality of life and is associated with poor cardiovascular outcomes. Previous meta-analyses have attempted to combine data from randomized trials to assess which is the best initial treatment strategy in patients with claudication; however, none have combined data from all possible treatment combinations or synthesized all possible quality of life outcomes.

What's new? This network meta-analysis has shown that in addition to best medical therapy, angioplasty combined with supervised exercise appears to be the optimal initial treatment strategy for patients presenting with claudication.

What's next? Healthcare providers should invest in supervised exercise therapy alongside angioplasty as this appears to be the optimal strategy in order to improve walking distance and quality of life of individuals with claudication.

REFERENCES

1. Shu J, Santulli G. Update on peripheral artery disease: Epidemiology and evidence-based facts. Atherosclerosis 2018;275:379-381.
2. Fowkes FG, Aboyans V, Fowkes FJ, McDermott MM, Sampson UK, Criqui MH. Peripheral artery disease: epidemiology and global perspectives. Nat Rev Cardiol 2017;14:156-170.
3. Spronk S, White JV, Bosch JL, Hunink MG. Impact of claudication and its treatment on quality of life. Semin Vasc Surg 2007;20:3-9.
4. Mehta T, Venkata Subramaniam A, Chetter I, McCollum P. Disease-specific quality of life assessment in intermittent claudication: review. Eur J Vasc Endovasc Surg 2003;25:202-8.
5. Spronk S, Bosch JL, Veen HF, den Hoed PT, Hunink MG. Intermittent claudication: functional capacity and quality of life after exercise training or percutaneous transluminal angioplasty--systematic review. Radiology 2005;235:833-42.
6. Klaphake S, Buettner S, Ultee KH, van Rijn MJ, Hoeks SE, Verhagen HJ. Combination of endovascular revascularization and supervised exercise therapy for intermittent claudication: a systematic review and meta-analysis. J Cardiovasc Surg (Torino) 2018;59:150-157.
7. Layden J, Michaels J, Bermingham S, Higgins B, Guideline Development G. Diagnosis and management of lower limb peripheral arterial disease: summary of NICE guidance. Bmj 2012;345:e4947.
8. Gerhard-Herman MD, Gornik HL, Barrett C et al. 2016 AHA/ACC Guideline on the Management of Patients With Lower Extremity Peripheral Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation 2017;135:e726-e779.
9. Harwood AE, Broadbent E, Totty JP, Smith GE, Chetter IC. "Intermittent claudication a real pain in the calf"-Patient experience of diagnosis and treatment with a supervised exercise program. J Vasc Nurs 2017;35:131-135.
10. Fanari Z, Weintraub WS. Cost-effectiveness of medical, endovascular and surgical management of peripheral vascular disease. Cardiovasc Revasc Med 2015;16:421-5.
11. Frans FA, Bipat S, Reekers JA, Legemate DA, Koelemay MJ. Systematic review of exercise training or percutaneous transluminal angioplasty for intermittent claudication. Br J Surg 2012;99:16-28.
12. Higgins JP, Altman DG, Gotzsche PC et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. Bmj 2011;343:d5928.
13. de Morton NA. The PEDro scale is a valid measure of the methodological quality of clinical trials: a demographic study. Aust J Physiother 2009;55:129-33.
14. Lu GA, A.E. Assessing Evidence Inconsistency in Mixed Treatment Comparisons. Journal of the American Statistical Association 2006;101:12.
15. Lumley T. Network meta-analysis for indirect treatment comparisons. Stat Med 2002;21:2313-24.
16. Sedgwick P. Meta-analyses: what is heterogeneity? Bmj 2015;350:h1435.
17. Hunter JP, Saratzis A, Sutton AJ, Boucher RH, Sayers RD, Bown MJ. In meta-analyses of proportion studies, funnel plots were found to be an

inaccurate method of assessing publication bias. J Clin Epidemiol 2014;67:897-903.
18. Nordanstig J, Taft C, Hensater M, Perlander A, Osterberg K, Jivegard L. Two-year results from a randomized clinical trial of revascularization in patients with intermittent claudication. Br J Surg 2016;103:1290-9.
19. 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.
20. Murphy TP, Cutlip DE, Regensteiner JG et al. Supervised exercise, stent revascularization, or medical therapy for claudication due to aortoiliac peripheral artery disease: the CLEVER study. J Am Coll Cardiol 2015;65:999-1009.
21. Bo 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.
22. Fakhry F, Rouwet EV, den Hoed PT, Hunink MG, Spronk S. 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.
23. 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.
24. Leicht AS, Crowther RG, Golledge J. Influence of peripheral arterial disease and supervised walking on heart rate variability. J Vasc Surg 2011;54:1352-9.
25. Kruidenier LM, Nicolai SP, Rouwet EV, Peters RJ, Prins MH, Teijink JA. 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.
26. Schlager O, Giurgea A, Schuhfried O et al. Exercise training increases endothelial progenitor cells and decreases asymmetric dimethylarginine in peripheral arterial disease: a randomized controlled trial. Atherosclerosis 2011;217:240-8.
27. Mika P, Wilk B, Mika A, Marchewka A, Nizankowski R. The effect of pain-free treadmill training on fibrinogen, haematocrit, and lipid profile in patients with claudication. Eur J Cardiovasc Prev Rehabil 2011;18:754-60.
28. Gardner AW, Parker DE, Montgomery PS, Scott KJ, Blevins SM. Efficacy of quantified home-based exercise and supervised exercise in patients with intermittent claudication: a randomized controlled trial. Circulation 2011;123:491-8.
29. Nicolai SP, Hendriks EJ, Prins MH, Teijink JA, group Es. Optimizing supervised exercise therapy for patients with intermittent claudication. J Vasc Surg 2010;52:1226-33.
30. Treat-Jacobson D, Bronas UG, Leon AS. Efficacy of arm-ergometry versus treadmill exercise training to improve walking distance in patients with claudication. Vasc Med 2009;14:203-13.
31. Spronk S, Bosch JL, den Hoed PT, Veen HF, Pattynama PM, Hunink MG. Intermittent claudication: clinical effectiveness of endovascular

revascularization versus supervised hospital-based exercise training--randomized controlled trial. Radiology 2009;250:586-95.
32. 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.
33. Stewart AH, Smith FC, Baird RN, Lamont PM. Local versus systemic mechanisms underlying supervised exercise training for intermittent claudication. Vasc Endovascular Surg 2008;42:314-20.
34. Crowther RG, Spinks WL, Leicht AS, Sangla K, Quigley F, Golledge J. Effects of a long-term exercise program on lower limb mobility, physiological responses, walking performance, and physical activity levels in patients with peripheral arterial disease. J Vasc Surg 2008;47:303-9.
35. Hodges LD, Sandercock GR, Das SK, Brodie DA. Randomized controlled trial of supervised exercise to evaluate changes in cardiac function in patients with peripheral atherosclerotic disease. Clin Physiol Funct Imaging 2008;28:32-7.
36. Hobbs SD, Marshall T, Fegan C, Adam DJ, Bradbury AW. The effect of supervised exercise and cilostazol on coagulation and fibrinolysis in intermittent claudication: a randomized controlled trial. J Vasc Surg 2007;45:65-70; discussion 70.
37. Nylaende M, Abdelnoor M, Stranden E et al. The Oslo balloon angioplasty versus conservative treatment study (OBACT)--the 2-years results of a single centre, prospective, randomised study in patients with intermittent claudication. Eur J Vasc Endovasc Surg 2007;33:3-12.
38. Hobbs SD, Marshall T, Fegan C, Adam DJ, Bradbury AW. The constitutive procoagulant and hypofibrinolytic state in patients with intermittent claudication due to infrainguinal disease significantly improves with percutaneous transluminal balloon angioplasty. J Vasc Surg 2006;43:40-6.
39. Zwierska I, Walker RD, Choksy SA, Male JS, Pockley AG, Saxton JM. Upper- vs lower-limb aerobic exercise rehabilitation in patients with symptomatic peripheral arterial disease: a randomized controlled trial. J Vasc Surg 2005;42:1122-30.
40. Mika P, Spodaryk K, Cencora A, Unnithan VB, Mika A. Experimental model of pain-free treadmill training in patients with claudication. Am J Phys Med Rehabil 2005;84:756-62.
41. Tsai JC, Chan P, Wang CH et al. The effects of exercise training on walking function and perception of health status in elderly patients with peripheral arterial occlusive disease. J Intern Med 2002;252:448-55.
42. Gardner AW, Katzel LI, Sorkin JD, Goldberg AP. Effects of long-term exercise rehabilitation on claudication distances in patients with peripheral arterial disease: a randomized controlled trial. J Cardiopulm Rehabil 2002;22:192-8.
43. Langbein WE, Collins EG, Orebaugh C et al. Increasing exercise tolerance of persons limited by claudication pain using polestriding. J Vasc Surg 2002;35:887-93.
44. Gelin J, Jivegard L, Taft C et al. Treatment efficacy of intermittent claudication by surgical intervention, supervised physical exercise training

compared to no treatment in unselected randomised patients I: one year results of functional and physiological improvements. Eur J Vasc Endovasc Surg 2001;22:107-13.
45. Gardner AW, Katzel LI, Sorkin JD et al. Exercise rehabilitation improves functional outcomes and peripheral circulation in patients with intermittent claudication: a randomized controlled trial. J Am Geriatr Soc 2001;49:755-62.
46. Gibellini R, Fanello M, Bardile AF, Salerno M, Aloi T. Exercise training in intermittent claudication. Int Angiol 2000;19:8-13.
47. Tisi PV, Hulse M, Chulakadabba A, Gosling P, Shearman CP. Exercise training for intermittent claudication: does it adversely affect biochemical markers of the exercise-induced inflammatory response? Eur J Vasc Endovasc Surg 1997;14:344-50.
48. Whyman MR, Fowkes FG, Kerracher EM et al. Is intermittent claudication improved by percutaneous transluminal angioplasty? A randomized controlled trial. J Vasc Surg 1997;26:551-7.
49. Perkins JM, Collin J, Creasy TS, Fletcher EW, Morris PJ. Exercise training versus angioplasty for stable claudication. Long and medium term results of a prospective, randomised trial. Eur J Vasc Endovasc Surg 1996;11:409-13.
50. Hiatt WR, Wolfel EE, Meier RH, Regensteiner JG. Superiority of treadmill walking exercise versus strength training for patients with peripheral arterial disease. Implications for the mechanism of the training response. Circulation 1994;90:1866-74.
51. Mannarino E, Pasqualini L, Innocente S, Scricciolo V, Rignanese A, Ciuffetti G. Physical training and antiplatelet treatment in stage II peripheral arterial occlusive disease: alone or combined? Angiology 1991;42:513-21.
52. Jansen T, Weiss T, Amendt K, Hsu E, Hubsch-Muller C, Diehm C. [Effect of a 2-year ambulatory vascular sports program on walking distance in claudication patients--a controlled study]. Vasa Suppl 1991;33:175.
53. Hiatt WR, Regensteiner JG, Hargarten ME, Wolfel EE, Brass EP. Benefit of exercise conditioning for patients with peripheral arterial disease. Circulation 1990;81:602-9.
54. Lundgren F, Dahllof AG, Lundholm K, Schersten T, Volkmann R. Intermittent claudication--surgical reconstruction or physical training? A prospective randomized trial of treatment efficiency. Ann Surg 1989;209:346-55.
55. Dahllof AG, Bjorntorp P, Holm J, Schersten T. Metabolic activity of skeletal muscle in patients with peripheral arterial insufficiency. Eur J Clin Invest 1974;4:9-15.
56. Conijn AP, Jens S, Terwee CB, Breek JC, Koelemay MJ. Assessing the quality of available patient reported outcome measures for intermittent claudication: a systematic review using the COSMIN checklist. Eur J Vasc Endovasc Surg 2015;49:316-34.
57. Arya S, Khakharia A, Binney ZO et al. Association of Statin Dose With Amputation and Survival in Patients With Peripheral Artery Disease. Circulation 2018;137:1435-1446.
58. Committee CS. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. Lancet 1996;348:1329-39.
59. Criqui MH, Aboyans V. Epidemiology of peripheral artery disease. Circ Res 2015;116:1509-26.

60. 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.
61. Diehm C, Allenberg JR, Pittrow D et al. Mortality and vascular morbidity in older adults with asymptomatic versus symptomatic peripheral artery disease. Circulation 2009;120:2053-61.
62. Sabatine MS, Giugliano RP, Keech AC et al. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. N Engl J Med 2017;376:1713-1722.
63. Lane R, Harwood A, Watson L, Leng GC. Exercise for intermittent claudication. Cochrane Database Syst Rev 2017;12:CD000990.
64. Harwood AE, Smith GE, Cayton T, Broadbent E, Chetter IC. A Systematic Review of the Uptake and Adherence Rates to Supervised Exercise Programs in Patients with Intermittent Claudication. Ann Vasc Surg 2016;34:280-9.
65. Vemulapalli S, Dolor RJ, Hasselblad V et al. Comparative Effectiveness of Medical Therapy, Supervised Exercise, and Revascularization for Patients With Intermittent Claudication: A Network Meta-analysis. Clin Cardiol 2015;38:378-86.
66. Shalhoub J, Davies AH. Adjunctive pharmacotherapies for intermittent claudication--NICE guidance. Heart 2012;98:244-5.

TABLES

Table 1: Characteristics of the studies included in the meta-analysis

Study	Year	Country	Male %	Age	Follow-up	Treatment*	Control	PEDro score
Dahllof (55)	1974	Sweden	100	NA	6 months	SET	BMT	3
Lundgren(54)	1989	Sweden	NA	NA	13 months	PTA or PTA+SET	SET	4
Hiatt(53)	1990	USA	100	60 (SD:12)	3 months	SET	BMT	4
Jansen(52)	1991	Germany	NA	NA	24 months	SET	BMT	4
Mannarino(51)	1991	Italy	90	NA	6 months	SET	BMT	5
Hiatt(50)	1994	USA	100	67 (SD: 6)	3 months	SET	BMT	5
Perkins(49)	1996	UK	NA	NA	15 months	PTA	SET	4
Tisi(47)	1997	UK	69	68 (SD: NA)	12 months	SET	BMT	5
Whyman(48)	1997	UK	82	61.4 (range: 44-78)	24 months	PTA	BMT	6
Gibellini(46)	2000	Italy	90	67 (SD: 7)	6 months	SET	BMT	3
Gelin(44)	2001	Sweden	67	67 (SD: NA)	12 months	PTA or PTA+SET	BMT	4
Gardner(45)	2001	USA	91	71 (SD: 1)	6 months	SET	BMT	6
Gardner(42)	2002	USA	NA	72 (SD: 1)	18 months	SET	BMT	4
Langbein(43)	2002	USA	98	76 (SD: 9)	6 months	Polestriding (SET)	BMT	5
Tsai(41)	2002	Taiwan	83	76 (SD: 4)	3 months	SET	BMT	5
Mika(40)	2006	Poland	83	61 (SD: 6)	3 months	SET	BMT	5
Hobbs (EXACT)(38)	2006	UK	71	72 (SD: NA)	6 months	3-arms	3-arms	5
Hobbs (INEXACT)(36)	2007	UK	79	67 (range: 63-72)	6 months	SET +/- cilostazol (2x2 design)	BMT (2x2 design)	5
Nylaende (OBACT)(37)	2007	Norway	56	69 (range: 56-75)	24 months	PTA	BMT	6
Hodges(35)	2008	Germany	NA	68 (SD:8)	3 months	SET	BMT	3
Crowther(34)	2008	USA	47	69 (SD: 8)	12 months	SET	BMT	5
Greenhalgh (MIMIC FEM-POP)(32)	2008	UK	65	65 (SD: 9)	24 months	PTA+SET	SET	6
Greenhalgh (MIMIC AORTO-ILIAC)(32)	2008	UK	65	63 (SD: 9)	24 months	PTA+SET	SET	6
Stewart(33)	2008	UK	NA	NA	6 months	SET	BMT	4
Treat-Jacobson(30)	2009	USA	71	67 (SD: 10)	6 months	SET	BMT	5
Spronk (CETAC)(31)	2009	Netherlands	40	66 (SD: 10)	12 months	PTA	SET	5
Nicolai (EXITPAD)(29)	2010	Netherlands	62	66 (SD: 9)	12 months	SET	BMT	5
Schlager(26)	2011	Austria	60	69 (SD: 10)	12 months	SET	BMT	7

Leicht(24)	2011	Australia	56	67 (SD: 8)	12 months	SET	BMT	5
Gardner(28)	2011	USA	49	66 (SD: 11)	3 months	SET	BMT	6
Mika(27)	2011	Poland	88	63 (SD: 7)	3 months	SET	BMT	5
Zwierska(39)	2011	UK	80	69 (range: 50-85)	18 months	SET	BMT	5
Kruidenier(25)	2011	Netherlands	NA	NA	6 months	PTA+SET	PTA	4
Majari(23)	2012	UK	61	70 (range: NA)	12 months	PTA+SET	PTA	5
Bo(21)	2013	Norway	48	66 (SD: 8)	12 months	PTA+SET	PTA	5
Fakhry (CETAC long-term results)(22)	2013	Netherlands	NA	NA	12 months	PTA+SET	PTA	4
Fakhry (ERASE)(19)	2015	Netherlands	66	65 (SD: 10)	12 months	PTA+SET	SET	5
Murphy (CLEVER)(20)	2015	USA	62	64 (SD: 9.5)	18 months	SET	PTA or BMT	5
Nordanstig (IRONIC)(18)	2016	Sweden	53	68 (SD: 8)	12 months	PTA	BMT	5

**Patients having PTA and/or SET were offered BMT*.

NA: not available in the study; SD: standard deviation; SET: supervised exercise therapy; BMT: best medical therapy; PTA: percutaneous angioplasty

Table 2: Main outcomes reported in the studies included in the meta-analysis

Study	BMT			SET			PTA			PTA+SET			QoL
	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	
Dahllof (55)	8	0.0	357.8	10	324.0	219.3	NA	NA	NA	NA	NA	NA	NA
Lundgren(54)	NA	NA	NA	25	276.0	66.0	25	361.0	73.0	25	474.0	81.0	NA
Hiatt(53)	9	58.7	187.9	10	400.0	207.5	NA	NA	NA	NA	NA	NA	NA
Jansen(52)	24	26.0	29.7	24	129.0	56.8	NA	NA	NA	NA	NA	NA	NA
Mannarino(51)	10	31.6	45.7	10	93.7	48.7	NA	NA	NA	NA	NA	NA	NA
Hiatt(50)	8	-6.0	227.4	10	274.0	497.3	NA	NA	NA	NA	NA	NA	NA
Perkins(49)	NA	NA	NA	28	335.0	77.8	28	68.0	67.7	NA	NA	NA	NA
Tisi(47)	17	15.5	62.8	22	70.5	127.9	NA	NA	NA	NA	NA	NA	NA
Whyman(48)	32	417.0	450.3	NA	NA	NA	30	439.00	476.69	NA	NA	NA	YES
Gibellini(46)	20	-4.1	165.0	20	161.3	187.5	NA	NA	NA	NA	NA	NA	NA
Gelin(44)	89	-11.0	201.4	88	-11.0	180.2	87	70.0	241.1	NA	NA	NA	NA
Gardner(45)	24	46.0	390.0	28	306.0	349.8	NA	NA	NA	NA	NA	NA	NA
Gardner(42)	14	-5.0	310.8	17	375.0	466.2	NA	NA	NA	NA	NA	NA	NA
Langbein(43)	25	-4.8	704.7	27	878.4	1013.7	NA	NA	NA	NA	NA	NA	NA
Tsai(41)	26	21.3	265.0	27	272.0	286.7	NA	NA	NA	NA	NA	NA	YES
Mika(40)	28	19.0	92.7	27	201.0	92.8	NA	NA	NA	NA	NA	NA	NA
Hobbs (EXACT)(38)	7	102.0	288.3	7	60.0	240.6	9	428.5	592.2	NA	NA	NA	NA
Hobbs (INEXACT)(36)	9	5.0	80.0	9	84.5	218.0	NA	NA	NA	NA	NA	NA	NA
Nylaende (OBACT)(37)	28	54.1	280.5	NA	NA	NA	28	215.3	272.8	NA	NA	NA	YES
Hodges(35)	14	43.6	431.9	14	275.6	379.5	NA	NA	NA	NA	NA	NA	NA
Crowther(34)	11	46.5	205.1	10	348.2	331.8	NA	NA	NA	NA	NA	NA	NA
Greenhalgh (MIMIC FEM-POP)(32)	NA	NA	NA	45	29.0	153.1	NA	NA	NA	48	112.0	214.3	YES
Greenhalgh (MIMIC AORTO-ILIAC)(32)	NA	NA	NA	15	42.0	159.1	NA	NA	NA	19	240.0	360.7	YES
Stewart(33)	30	40.4	45.2	30	99.2	267.7	NA	NA	NA	NA	NA	NA	NA
Treat-Jacobson(30)	8	73.3	65.5	11	294.4	162.2	NA	NA	NA	NA	NA	NA	NA
Spronk (CETAC)(31)	NA	NA	NA	75	1034.0	56.3	75	826.0	61.0	NA	NA	NA	YES
Nicolai (EXITPAD)(29)	102	110.0	222.2	109	310.0	629.6	NA	NA	NA	NA	NA	NA	YES
Schlager(26)	20	16.0	107.2	20	53.2	113.1	NA	NA	NA	NA	NA	NA	NA
Leicht(24)	9	88.6	203.9	8	191.4	159.1	NA	NA	NA	NA	NA	NA	NA
Gardner(28)	30	-8.9	156.4	33	191.1	184.0	NA	NA	NA	NA	NA	NA	YES
Mika(27)	31	-35.0	108.5	30	297.0	83.5	NA	NA	NA	NA	NA	NA	NA
Zwierska(39)	33	0.0	34.0	37	97.7	17.3	NA	NA	NA	NA	NA	NA	YES

Kruidenier(25)	NA	NA	NA	NA	NA	NA	27	341.7	399.7	34	662.9	525.8	YES
Majari(23)	NA	NA	NA	60	95.8	34.5	60	63.6	40.5	58	83.7	34.3	YES
Bo(21)	NA	NA	NA	NA	NA	NA	21	232.3	109.1	26	477.4	125.8	YES
Fakhry (CETAC long-term results)(22)	NA	NA	NA	75	1041.0	75.8	75	739.0	79.1	NA	NA	NA	YES
Fakhry (ERASE)(19)	NA	NA	NA	106	955.0	65.6	NA	NA	NA	106	1237.0	69.9	YES
Murphy (CLEVER)(20)	22	10.7	112.0	43	266.7	288.0	46	170.7	250.7	NA	NA	NA	YES
Nordanstig (IRONIC)(18)	NA	NA	NA	79	36.0	182.8	NA	NA	NA	79	32.0	169.3	YES

NA: not available in the study; SD: standard deviation; SET: supervised exercise therapy; BMT: best medical therapy; PTA: percutaneous angioplasty; QoL: quality of life

Table 3: Quality of Life (QoL) measures used in the studies included in the meta-analysis

Study	**Follow-up**	**QoL & health assessment tools**
Whyman	24 months	Nottingham
Tsai	3 months	SF-36, WIQ
Nylaende (OBACT)	24 months	SF-36, CLAU-S, VAS pain scale
Greenhalgh (FIC) – fem-pop & iliac arms	24 months	SF-36
Spronk (CETAC)	12 months	SF-36, EQ-5D
Nicolai (EXITPAD)	12 months	SF-36, WIQ
Zwierska	18 months	SF-36, EQ-VAS, WIQ
Kruidenier	6 months	SF-36, EQ-5D, WIQ
Gardner	3 months	SF-36, BASIC score, WIQ
Majari	12 months	SF-36, VascuQoL
Bo	12 months	SF-36, CLAU-S
Fakhry	12 months	SF-36, VascuQoL
Fakhry (ERASE)	12 months	SF-36, VascuQoL
Murphy (CLEVER)	18 months	SF-12, PAQ, WIQ
Nordanstig (IRONIC)	24 months	SF-36, VascuQoL

QoL: quality of life; SF-36 or 12: 36-item or 12-item short form QoL survey; WIQ: walking impairment questionnaire; CLAU-S: claudication scale QoL questionnaire; VAS: visual analogue pain scale; EQ-5D: European QoL questionnaire; EQ-VAS: European QoL visual analogue scale; PAQ: physical activity questionnaire; VascuQoL: vascular QoL questionnaire. Details regarding the validity and format of the QoL tools used in these trials are discussed elsewhere(56).

FIGURES

Figure 1 title: PRISMA Diagram

Figure 1 legend: Transparent reporting of systematic reviews and meta-analyses (PRISMA) flow diagram

Figure 2 title: Network graph

Figure 2 legend: Network graph summarising all interventions included in the meta-analysis

Figure 3 title: Funnel plot

Figure 3 legend: Funnel plot of all included trials

Figure 4 title: Mean walking distance gains

Figure 4 legend: Meta-analysis of Mean Walking Distance (MWD) at the end of follow-up in 37 randomized trials reporting weighted MWD and 95% Credible Interval (CrI)

Figure 5 title: Quality of life gains

Figure 5 legend: Meta-analysis of Quality of Life (QoL) reported outcomes in trials reporting at least on QoL parameter at the end of follow-up (compared to baseline) – synthesised using Cohen's d effect size, reported with 95% Credible Interval (CrI)