Functional status and quality of life after treatment of peripheral arterial disease

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Systematic review of exercise training or percutaneous transluminal angioplasty for intermittent claudication

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‘Inter utrumque tene’
ABSTRACT

Background
The aim was to summarize the results of all randomized clinical trials (RCTs) comparing percutaneous transluminal angioplasty (PTA) with (supervised) exercise therapy ((S)ET) in patients with intermittent claudication (IC) to obtain the best estimates of their relative effectiveness.

Methods
A systematic review was performed of relevant RCTs identified from the MEDLINE, Embase and Cochrane Library databases. Eligible RCTs compared PTA with (S)ET, included patients with IC due to suspected or known aorto-iliac and/or femoro-popliteal artery disease, and compared their effectiveness in terms of functional outcome and/or quality of life (Qol).

Results
Eleven of 258 articles identified (reporting data on eight randomized clinical trials) met the inclusion criteria. One trial included patients with isolated aorto-iliac artery obstruction, three trials studied those with femoro-popliteal artery obstruction and five included those with combined lesions. Two trials compared PTA with advice on ET, four PTA with SET, two PTA plus SET with SET and two PTA plus SET with PTA. Although the endpoints in most trials comprised walking distances and Qol, pooling of data was impossible owing to heterogeneity. Generally, the effectiveness of PTA and (S)ET was equivalent, although PTA plus (S)ET improved walking distance and some domains of Qol scales compared with (S)ET or PTA alone.

Conclusion
As IC is a common healthcare problem, defining the optimal treatment strategy is important. A combination of PTA and exercise (SET or ET advice) may be superior to exercise or PTA alone, but this needs to be confirmed.
INTRODUCTION
Ability to walk is impaired in patients with intermittent claudication (IC) due to peripheral arterial disease (PAD). One of the aims of care for patients with IC is to increase walking distance, and subsequently improve quality of life (QoL). Drugs, exercise therapy (ET), percutaneous transluminal angioplasty (PTA) or surgery can relieve symptoms. Exercise programmes and PTA are widely accepted therapies for IC. Two systematic reviews demonstrated the superiority of supervised exercise therapy (SET) over standard care or unsupervised ET in increasing both pain-free and maximum walking distance (MWD). PTA is attractive as an initial therapy as it is instantly effective and durable, especially in patients with iliac artery disease. A Cochrane review summarizing the results of two randomized clinical trials (RCTs) found more short term benefit from PTA than conservative management (medication or ET), but this was not sustained after 1–2 years. Another review found that medical treatment (a home or supervised exercise programme, as well as risk factor modification) resulted in a longer walking distance than PTA at 1–2 years. Thus, the optimal treatment for symptom relief, PTA, ET or both, is still unknown. Given that six additional RCTs have compared PTA and exercise in the past 5 years, an update on this topic is required in order to provide recommendations. The aim of this systematic review was to summarize the results of all RCTs comparing PTA with (S)ET to obtain the best estimates of their relative effectiveness.

METHODS
This review was done according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement, which has been updated to address several conceptual and practical advances for performing a systematic review of RCTs.

Literature search
A clinical librarian provided assistance with a computer-assisted search of the MEDLINE, Embase and Cochrane databases to identify RCTs on (S)ET versus PTA for IC published between January 1966 and September 2010. Medical Subject Headings (MeSH) terms were used, and accompanying entry terms for the patient group, interventions and outcomes. The keywords ‘angioplasty’, ‘intermittent Claudication’, ‘exercise therapy’ were used, along with their synonyms (Table 1). There was no language restriction. Reference lists of all eligible articles were checked for other relevant studies. Conference proceedings were not searched, and experts in the field were not contacted.
### Table 1. The search strategy

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient</strong></td>
<td>artery stenosis[tw] OR claudication OR peripheral arterial diseases[mh] OR peripheral arterial disease*</td>
<td>peripheral occlusive artery disease</td>
<td>claudication in All Fields</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td>angioplasty OR revascularization OR revascularisation</td>
<td>angioplasty OR revascularization OR revascularisation.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]</td>
<td>angioplasty OR revascularization OR revascularisation in All Fields</td>
</tr>
<tr>
<td><strong>Comparison</strong></td>
<td>exercise OR physical activity OR physical training OR physical therapy OR walking training[tw] OR walking therapy[tw]</td>
<td>exp exercise OR (physical activity or physical training or physical therapy OR walking training OR walking therapy).mp.</td>
<td>exercise OR physical activity OR physical training OR physical therapy OR walking training[tw] OR walking therapy[tw] in All Fields</td>
</tr>
</tbody>
</table>
**Study selection**
Titles and abstracts were screened by two reviewers independently to identify potentially relevant articles. Discrepancies in judgement were resolved after discussion and, when necessary, after mediation by a third reviewer. Agreement between both observers for study selection was good ($\kappa = 0.64$). The full text of all potentially relevant articles was retrieved for further analysis. Studies were included if they met the following criteria: the patients had IC due to PAD and were allocated randomly to S(ET) or PTA with or without stent insertion. The arterial lesions could be localized in the aorto-iliac and/or the femoro-popliteal tract. Studies on PTA for treatment of critical limb ischaemia were excluded. If the same cluster of investigators reported their results in various journals, the papers were scanned for similarity and completeness, and the results combined in the review.

**Quality assessment**
The methodological quality of the included studies was assessed using the Cochrane checklist. The following items were assessed: randomization; allocation concealment; blinding of patients, clinicians and assessors to the received treatment; similarity in baseline characteristics; completeness of follow-up of a sufficient number of included patients; intention-to-treat analysis; and similarity of other treatment, aside from the allocated treatment.

**Data extraction**
Recorded study characteristics included: inclusion and exclusion criteria, total number of patients included and excluded, age, sex distribution, single-centre or multicentre design, intervention type, duration of follow-up, time of randomization, description of PTA technique and complications, secondary prevention, description of the treadmill test (speed, incline and duration), description of the exercise programme (frequency, duration, content) and Qol questionnaires used. Recorded outcome measures included: MWD in metres (total walking distance until intolerable claudication pain forced the patient to stop), initial claudication distance (ICD) in metres (walking distance until onset of claudication pain), ankle:brachial pressure index (ABPI) at rest and Qol scores.

**Data analysis**
As it was anticipated that the interventions for (S)ET would be heterogeneous, a meta-analysis was planned in which the data would be pooled according to a random effects model, as long as clinical heterogeneity between studies was limited. Pooled estimates of
Table 2. The study design characteristics of the included trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Creasy&lt;sup&gt;13&lt;/sup&gt;</th>
<th>Whyman&lt;sup&gt;15&lt;/sup&gt;</th>
<th>Hobbs&lt;sup&gt;18&lt;/sup&gt;</th>
<th>Nylænde&lt;sup&gt;15&lt;/sup&gt;</th>
<th>Greenhalgh&lt;sup&gt;11&lt;/sup&gt;</th>
<th>Spronk&lt;sup&gt;22,23&lt;/sup&gt;</th>
<th>Mazari&lt;sup&gt;24&lt;/sup&gt;</th>
<th>Kruidenier&lt;sup&gt;25&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Was the assignment of patients to treatments randomized?</td>
<td>?</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>2 Was the person randomizing the patients blind to randomization</td>
<td>?</td>
<td>Y</td>
<td>?</td>
<td>?</td>
<td>Y</td>
<td>Y</td>
<td>?</td>
<td>Y</td>
</tr>
<tr>
<td>sequence?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 Were the patients kept “blind” to which treatment was being received?</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>4 Were the clinicians kept “blind” to which treatment was being received?</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>5 Were the assessors kept “blind” to which treatment was being received?</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>6 Were the groups similar at the start of the trial?</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>7 Was the complete follow-up available of a sufficient number of included patients?</td>
<td>N</td>
<td>Y</td>
<td>?</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>8 Were all patients who entered the trial accounted for? – and were they analyzed in the groups to which they were randomized?</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>?</td>
<td>Y</td>
</tr>
<tr>
<td>9 Aside from the allocated treatment, were groups treated equally?</td>
<td>N</td>
<td>?</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
</tbody>
</table>

Y= Yes  
N= No  
?= Unclear
effect were to be expressed as weighted mean differences including 95 per cent confidence intervals (c.i.) for continuous outcome measures, and odds ratios with 95 per cent c.i. for dichotomous outcome measures. Analyses were prespecified for symptoms due to arterial obstructions in different anatomical regions (aorto-iliac, femoro-popliteal or mixed) and for different time points (baseline and follow-up).

RESULTS
Some 257 articles were identified from the databases and one unpublished trial from a thesis, giving a total of 258 papers (Fig. 1). Twenty-four papers were eligible after reading the title and abstract, and were retrieved as a full text for further analysis. Finally, 12 articles reporting data on eight RCTs fulfilled the inclusion criteria. One paper was excluded because it reported 6-year follow-up of a trial that was already included, with 6- and 12-month results reported in another paper. Another reason for exclusion of this paper was incomplete follow-up for a substantial number of patients. The remaining 11 studies were used for data extraction and analysis.

Study and baseline characteristics
Results of the methodological assessment of the eight RCTs are presented in Table 2. The overall methodological study quality was mediocre, and there was only one trial of high quality. Four trials were terminated prematurely, and five were probably underpowered, or at least conducted without a power calculation.

Table 3 shows the inclusion and exclusion criteria for each trial, demonstrating the heterogeneity of study populations. Table 4 lists the number of patients screened and finally included in each trial, baseline characteristics, allocation of treatment, and the timing and nature of outcome assessments. Several trials included only a small proportion of the screened patients (range 6.2–51.4 per cent). A total of 702 patients were included in the eight trials. The mean age of these patients was 65.3 (range 61.6–69.5) years and the majority were men (62.5 per cent).

Interventions
Two trials compared PTA plus ET advice with ET advice alone, four compared PTA with SET, two compared PTA plus SET with SET and two compared PTA plus SET with PTA (Table 4). Table 5 summarizes the diverse exercise programmes varying from home-based exercise without supervision to SET programmes.
Table 3. Inclusion and Exclusion criteria

<table>
<thead>
<tr>
<th>Trial</th>
<th>Inclusion</th>
<th>Exclusion</th>
</tr>
</thead>
</table>
| Creasy et al, 1990    | 1. stable unilateral claudication, with failure of conservative treatment for at least 3 months  
2. A treadmill claudication distance of less than 375 m  
3. Angiographically significant lesion(s) suitable for treatment by angioplasty, as agreed by both surgeon and radiologist | 1. Previous angioplasty or arterial surgery to the symptomatic leg  
2. Myocardial infarction within the previous 6 months  
3. Patients taking oral anti-coagulants  
4. Duration of symptoms less than 1 month  
5. inability to manage the treadmill test  
6. Any psychiatric illness or other reason that would make follow-up difficult |
| Whyman et al, 1956-1977 | 1. Predominantly unilateral IC  
2. Suitable for unilateral infrainguinal PTA and participation in a dedicated, trial-funded, supervised exercise class | 1. Significant aortoiliac disease  
2. Equally severe bilateral symptoms (and therefore were unsuitable for unilateral angioplasty)  
3. Previous ipsilateral infrainguinal intervention  
4. Unable to exercise to ACD on the treadmill (eg. limited by shortness of breath) |
| Hobbs et al, 2006     | 1. Clinically and hemodynamically confirmed mild to moderate IC due to infrainguinal disease as their exercise-limiting diagnosis  
2. Suitable for unilateral infrainguinal PTA and participation in a dedicated, trial-funded, supervised exercise class | 1. Previous vascular or endovascular surgery  
2. Suffering from diabetic ulcer or renal insufficiency (defined as s-creatinine> 150 µmol/l  
3. Were on oral anti-coagulant medication  
4. Were suffering from a physical or mental disorder expecting to impede compliance and follow-up |
| Nyläende et al, 2007  | 1. < 80 years old  
2. Symptomatic IC > 3 months prior to evaluation  
3. ABI< 0.9 without rest pain and/or ulcers  
4. Subjective PFWD< 400m  
5. Were able to exercise on a treadmill | 1. Previous vascular or endovascular surgery  
2. Suffering from diabetic ulcer or renal insufficiency (defined as s-creatinine> 150 µmol/l  
3. Were on oral anti-coagulant medication  
4. Were suffering from a physical or mental disorder expecting to impede compliance and follow-up |
| Greenhalgh et al, 2008 | 1. A positive outcome on the Edinburgh Claudication Questionnaire  
2. ABPI<0.9 or >0.9 with a positive stress test (a fall of >30 mmHg in Doppler blood pressure following a treadmill test at 4km/h, 10°slope for 1 min)  
3. an aortoiliac or femoro-popliteal target lesion amenable to PTA as demonstrated by duplex scanning or diagnostic arteriography | 1. Symptoms were too mild to consider angioplasty or so severe that intervention was mandatory  
2. Patients with critical limb ischemia (absolute Doppler blood pressure < 50 mmHg or presence of ulcers or gangrene with a Doppler pressure>50mmHg)  
3. Concomitant disease such as musculoskeletal or cardiac which was prohibitive to exercise |
| Spronk et              | 1. Rutherford category 1,2, or 3 ≥ 3 months                                                   | 1. Abdominal aortic aneurysm                                                |
### Spronk et al, 22-23 2008-2009

1. Rutherford category 1,2, or 3 ≥ 3 months  
2. Maximum PFWD of < 350 m during a treadmill test  
3. ABI< 0.9 at rest, ABI with a decrease of >0.15 after the treadmill test  
4. Vascular stenoses of >50% diameter reduction at the iliac or femoro-popliteal level  
5. Informed consent  

1. Abdominal aortic aneurysm  
2. Life-incapacitating cardiac disease (NYHA classification III and higher, i.e., patients had marked limitation of physical activity, comfortable at rest, but less than ordinary activity cause fatigue, palpitation, or dyspnoea))  
3. Multilevel disease, which could have made multiple revascularization (endovascular and/or surgical) procedures necessary (i.e., same side stenoses at both the iliac and femoral levels, requiring multiple revascularization procedures)  
4. Isolated tibial artery disease  
5. Lesions deemed unsuitable for revascularization (iliac or femoro-popliteal TASC-type D and some TASC type-B/C lesions)  
6. Prior treatment for the same lesion (including exercise training)

### Mazari et al, 24 2010

Symptomatic unilateral IC  
Angioplastable lesion  
Femoro-popliteal lesion  
> 3 months on OMT  

Critical Ischemia  
Severe limitations of physical activity due to systemic disease  
Inability to tolerate treadmill testing (unrelated to limb ischemia)  
Significant ischemic ECG during treadmill testing  
Ipsilateral surgery, previous 6 months  
Ipsilateral angioplasty, previous 6 months

### Kruidenier et al, 25 2010

1. PAD Rutherford stage 1-4  
2. Planned for a PVI  
3. Maximum Walking Distance post-PVI less than 1600 m as measured by a standardized treadmill test  

1. History of or current participation in a SET program  
2. Serious cardiopulmonary co-morbidity (NYHA 3-4)  
3. Other serious co-morbidity preventing physical activity  
4. Insufficient knowledge of the Dutch language  
5. No insurance for SET  
6. Major amputation or tissue loss

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IC= Intermittent Claudication  
OMT= Optimal Medical Therapy  
PFWD= Pain Free Walking Distance  
ACD= Absolute Claudication Distance  
PVI= Percutaneous Vascular Intervention
### Table 4. Trial characteristics

<table>
<thead>
<tr>
<th>Trial</th>
<th>Included</th>
<th>Excluded</th>
<th>Supervised Exercise therapy</th>
<th>PTA</th>
<th>Supervised Exercise therapy + PTA</th>
<th>OMT</th>
<th>OMT + PTA</th>
<th>BMT alone</th>
<th>Mean age (Yrs)</th>
<th>Sex distribution F:M</th>
<th>Follow-up (months)</th>
<th>Single/multicenter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creasy&lt;sup&gt;13&lt;/sup&gt;</td>
<td>36</td>
<td>?</td>
<td>16</td>
<td>20</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>62.9</td>
<td>9:27</td>
<td>3+6+9+12</td>
<td>Single</td>
</tr>
<tr>
<td>Whyman&lt;sup&gt;15-14&lt;/sup&gt;</td>
<td>62</td>
<td>363</td>
<td></td>
<td></td>
<td></td>
<td>32</td>
<td>30</td>
<td></td>
<td>61.6</td>
<td>11:51</td>
<td>6+24</td>
<td>Single</td>
</tr>
<tr>
<td>Hobbs&lt;sup&gt;18&lt;/sup&gt;</td>
<td>23</td>
<td>349</td>
<td>7</td>
<td>9</td>
<td></td>
<td></td>
<td></td>
<td>7</td>
<td>67</td>
<td>7:16</td>
<td>3+6</td>
<td>Multi</td>
</tr>
<tr>
<td>Nylaende&lt;sup&gt;15-20&lt;/sup&gt;</td>
<td>56</td>
<td>?</td>
<td></td>
<td></td>
<td></td>
<td>28</td>
<td>28</td>
<td></td>
<td>68.5</td>
<td>25:31</td>
<td>3+12+24</td>
<td>Single</td>
</tr>
<tr>
<td>Greenhalgh&lt;sup&gt;21&lt;/sup&gt;</td>
<td>127</td>
<td>1274</td>
<td>60</td>
<td>67</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>64.7</td>
<td>46:81</td>
<td>6+12+24</td>
<td>Multi</td>
</tr>
<tr>
<td>Sprock&lt;sup&gt;21,23&lt;/sup&gt;</td>
<td>150</td>
<td>142</td>
<td>75</td>
<td>75</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>65.5</td>
<td>67:83</td>
<td>6+12</td>
<td>Single</td>
</tr>
<tr>
<td>Mazari&lt;sup&gt;24&lt;/sup&gt;</td>
<td>178</td>
<td>979</td>
<td>60</td>
<td>60</td>
<td>58</td>
<td></td>
<td></td>
<td></td>
<td>69.5</td>
<td>71:107</td>
<td>1+3</td>
<td>?</td>
</tr>
<tr>
<td>Kruidenier&lt;sup&gt;25&lt;/sup&gt;</td>
<td>70</td>
<td>261</td>
<td>35</td>
<td>35</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>62.4</td>
<td>27:43</td>
<td>3+6</td>
<td>Single</td>
</tr>
<tr>
<td>Total</td>
<td>702</td>
<td>218</td>
<td>199</td>
<td>160</td>
<td>58</td>
<td>7</td>
<td>58</td>
<td>60</td>
<td>65.3</td>
<td>283:439</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

OMT: Optimal Medical Therapy, including advice on nutrition, smoking and exercise therapy (ET) advice. *BMT: Best medical therapy. All patients in the other two arms also got BMT.
The exercise programme included dynamic leg exercises\textsuperscript{13}, exercise advice\textsuperscript{15,16,19,20}, a walking circuit\textsuperscript{21}, an exercise circuit\textsuperscript{18,24} and treadmill training\textsuperscript{22,23,25}. In four trials, the intervention covered both PTA with, or without selective stent placement\textsuperscript{19–23,25}; the other trials referred to PTA alone.

**Complications**

Two trials did not report complications of PTA\textsuperscript{18,24}, and one did not report complications at all\textsuperscript{15,16}. One trial reported ‘few’ complications\textsuperscript{19,20} and the other four trials three, four, six and seven complications respectively\textsuperscript{13,21–23,25}. These complications consisted primarily of haematomas, but bleeding, artery dissections and artery rupture also occurred. For (S)ET either no complications were reported, or no complications occurred. Compliance with (S)ET was mentioned occasionally, and reported as a percentage\textsuperscript{21}, frequency per week\textsuperscript{13} or mean total sessions attended\textsuperscript{25}. Treatment failure, loss to follow-up or crossover to another intervention had multiple causes.

**Secondary prevention (co-interventions)**

Effective secondary prevention for cardiovascular events was outlined in recent guidelines\textsuperscript{6,30}. Secondary prevention with an antiplatelet drug and a statin can reduce the risk of cardiovascular events in this specific high-risk population\textsuperscript{31}. Secondary prevention as given in the included RCTs reflected changing insights over a long time, and varied widely. In one RCT, patients allocated to PTA and already on an antiplatelet drug could continue their medication, but it was unclear whether the other patients were prescribed an antiplatelet drug\textsuperscript{13}. Two RCTs prescribed an antiplatelet drug alone\textsuperscript{15,16,21}, and one trial acted in accordance with the management of PAD in primary care, which was not specified\textsuperscript{18}. One RCT advised an antiplatelet drug and a statin\textsuperscript{24}, one recommended an antiplatelet drug, a statin and treatment of hypertension on indication\textsuperscript{19,20}, and another advised an antiplatelet drug, a statin and regular check-up by an internist of risk profile, diabetes, lipids and hypertension\textsuperscript{22,23}. The same holds for the remaining RCT, which also included lifestyle advice given according to the Dutch guidelines for cardiovascular risk management, and advice on smoking cessation\textsuperscript{25}. As statins have been shown to increase walking distance in randomized trials\textsuperscript{32,33}, an attempt was made to determine the effect of statins on walking distance in the individual studies. Unfortunately, none of the papers described in detail how many patients were taking a statin (Table 4).
<table>
<thead>
<tr>
<th>Trial</th>
<th>Freq/ wk</th>
<th>Minutes</th>
<th>Duration</th>
<th>Sort</th>
<th>By whom and/or where and/or how</th>
<th>Extra</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creasy 18</td>
<td>2</td>
<td>30</td>
<td>First 6 months</td>
<td>Dynamic leg exercises* at home</td>
<td>Department of physiotherapy</td>
<td>As exercise tolerance and walking ability improved the intensity was increased. Patients were encouraged to perform some of the exercises at home on a daily basis, and to take daily walks exercising beyond the onset of symptoms of intermittent claudication. Attendance records were kept, and patients attending more than once a week were classified as good attendees. After the first 6 months patients were invited on a regular basis according to progress thereafter.</td>
</tr>
<tr>
<td>Whyman 15,25</td>
<td></td>
<td></td>
<td></td>
<td>Exercise therapy advice</td>
<td></td>
<td>Patients were advised to continue to walk as far as possible and as frequently as possible within the limits imposed by pain.</td>
</tr>
<tr>
<td>Hobbs 16</td>
<td>2</td>
<td>60</td>
<td></td>
<td>Exercise circuit + at home</td>
<td>Group and individual</td>
<td>Circuit sequence of exercise, 3 minutes per station and 2 minutes rest. On days when not attending; advice to perform the exercises unsupervised at home. Training logs were kept to detail number of repetitions performed and maximal heart rate.</td>
</tr>
<tr>
<td>Nylaende 15,20</td>
<td></td>
<td></td>
<td></td>
<td>Exercise therapy advice</td>
<td></td>
<td>Information was provided about the importance of walking. The patients were advised how to organize their own exercise programme by walking along the same path twice daily and trying to steadily increase the K/WD.</td>
</tr>
<tr>
<td>Greenhalgh 21</td>
<td>Minimal 1 (1-2)</td>
<td>30</td>
<td>6 months</td>
<td>Walking circuit</td>
<td>By physiotherapist or nurse in classes</td>
<td>Continuous walking until maximum pain threshold. Increase daily exercise levels.</td>
</tr>
<tr>
<td>Spronk 12,23</td>
<td>2</td>
<td>30</td>
<td>6 months</td>
<td>Start treadmill with 3.5 km/h without incline, workload (speed or incline) was increased until severe level of claudication pain was reached** at home</td>
<td>By vascular technologist, hospital based</td>
<td>* Workload was lowered to 3 km/hour until the pain abated, to avoid patients were walking with an ischemic leg the whole time. After the pain had been abated, the patient resumed walking at higher workload. Also instruction for at home, 3 times weekly for 30 min, evaluation and feedback of this home based exercise hours were also reported. After the 6 months period, patients were asked to continue exercise at home.</td>
</tr>
<tr>
<td>Mazari 14</td>
<td></td>
<td>12 weeks</td>
<td></td>
<td>Exercise circuit</td>
<td>By physiotherapist or physicians</td>
<td>For the first 6 weeks, patients completed 1 full circuit, then after the circuit was increased by one station per week, by the end of the program; patients were completing 12 stations per session.</td>
</tr>
<tr>
<td>Kruidenier 25</td>
<td>2-3</td>
<td>30</td>
<td>6 months</td>
<td>Increase walking distance by interval training with short (3-5 minutes) walking intervals up to sub maximal pain</td>
<td>By physiotherapist in community based setting</td>
<td>Frequency of sessions; phased down according to progress. Secondary goals: increase endurance and strength, and improving walking patterns. Patients were encouraged to walk on a daily basis beside the physiotherapy sessions.</td>
</tr>
</tbody>
</table>
### Table 6. Treadmill test, QoL questionnaires

<table>
<thead>
<tr>
<th>Trial</th>
<th>Speed (km/h)</th>
<th>Incline (%)</th>
<th>Duration</th>
<th>QoL questionnaires</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creasy</td>
<td>3</td>
<td>10</td>
<td>Max. 15 min (750 m)</td>
<td></td>
</tr>
<tr>
<td>Whyman</td>
<td>4</td>
<td>10</td>
<td>Max. 10 min (667 m)</td>
<td>NHP</td>
</tr>
<tr>
<td>Hobbs</td>
<td>3</td>
<td>10</td>
<td>Max. 12 min (600 m)</td>
<td>VAS, SF-36, CLAU-S</td>
</tr>
<tr>
<td>Nylaende</td>
<td>3</td>
<td>10</td>
<td>Max. 12 min (600 m)</td>
<td>VAS, SF-36, CLAU-S</td>
</tr>
<tr>
<td>Greenhalgh</td>
<td>4</td>
<td>10</td>
<td>Max. 15 min (1000 m)</td>
<td>SF-36</td>
</tr>
<tr>
<td>Spronk</td>
<td>3.5</td>
<td>-</td>
<td></td>
<td>SF-36, VascuQoL, EQ-5D</td>
</tr>
<tr>
<td>Mazari</td>
<td>2.5</td>
<td>10</td>
<td>Max. 5 min (207 m)</td>
<td>SF-36, VascuQoL</td>
</tr>
<tr>
<td>Kruidenier</td>
<td>3.2</td>
<td>Graded (starting 0%, increased by 2% every 2 minutes, max 10%)</td>
<td>Max. 30 min (1600 m)</td>
<td>SF-36, WIQ, EQ-5D</td>
</tr>
</tbody>
</table>

NHP=Nottingham Health Profile VAS= Visual Analog Scale score for pain SF-36=Short Form 36 CLAU-S= Claudication Scale VascuQoL=Vascular Quality of life questionnaire EQ-5D= EQ-5D WIQ=Walking Impairment Questionnaire
**Assessment of outcome**

Table 6 shows the diversity in speed and duration for the treadmill tests. All but two RCTs used a treadmill test with a 10 per cent incline. These two trials used either a graded treadmill test or treadmill testing without an incline. Table 6 also shows the various instruments used for measuring QoL. Generic questionnaires used were the Short Form 36 (SF-36; QualityMetric, Lincoln, Rhode Island, USA) in five RCTs, the Nottingham Health Profile and the EuroQol 5D (EQ-5D; EuroQol Group, Rotterdam, The Netherlands). Three RCTs used the disease-specific Vascular Quality of life questionnaire (VascuQol) and the Claudication Scale (CLAU-S). Other applied questionnaires were the Walking Impairment Questionnaire (WIQ) and a visual analogue scale score for pain.

**Study outcomes**

All outcomes (MWD, ICD, ABPI) of the trials are shown in Figs 2–4 and Tables 7-9. These results are presented by anatomical region: aorto-iliac, femoro-popliteal, and mixed aorto-iliac and femoro-popliteal artery disease. For clarity, it was decided not to list all details of the QoL assessments. Because the interventions and outcome assessments were very heterogeneous, the data could not be pooled. Therefore, the results of the individual trials are reported in brief in the following sections.

**Aorto-iliac artery disease**

The Mild to Moderate Intermittent Claudication (MIMIC trial) compared SET versus SET plus PTA for the aorto-iliac and femoro-popliteal regions separately. For the aorto-iliac region the mean MWD increased in both groups at 6 months’ follow-up compared with baseline, but significantly more in the group with additional PTA (P = 0.04). Clinical improvement, defined as walking 200 m without claudication, was attained significantly more often in the additional PTA group at 6, 12 and 24 months (Fig. 2; table 7). Patients with additional PTA scored better on the SF-36 physical domain at 24 months.

**Femoro-popliteal artery disease**

Three trials included patients with femoro-popliteal arterial disease (Fig. 3; Table 8). One trial comparing SET and PTA reported significantly better improvements in MWD, ICD and ABPI after PTA at 6 month follow-up. No data on QoL were reported in this trial. The MIMIC trial found that patients with PTA in addition to SET had a significantly longer MWD after 24 months, but not at 6- and 12-month follow-up. The largest clinical improvement (defined as walking 200 m without claudication) observed in the SET alone group was 25 per cent at 12
months’ follow-up; in the group with additional PTA the clinical improvement ranged from 32 per cent at 6 months to 63 per cent at 24 months, which was significantly better. The APBI was also significantly higher in the additional PTA group at 24 months. Qol assessed with the SF-36 was similar for all domains for both groups at 24 months. The last trial compared three interventions: SET, PTA and SET combined with PTA. Follow-up was recorded after 3 months. The MWD, ICD and ABPI increased in all three groups compared with baseline, with the best improvement in patients allocated to SET plus PTA. Improvements in MWD, ICD and ABPI between the SET and PTA groups were similar. Changes in Qol measured with SF-36 and VascuQol were also similar for the three groups. In summary, SET with additional PTA gave the best improvement in MWD, ICD and ABPI. Changes in MWD, ICD and ABPI between PTA and SET were equivocal, either comparable or in favour of PTA. Qol improved significantly during follow-up compared with baseline for all treatments, without differences between the groups.

Mixed aorto-iliac and femoro-popliteal artery disease
The results for MWD, ICD and ABPI are presented in Fig. 4 and Table 7-9. Five trials did not specify the level of arterial obstruction. One trial included patients with both iliac artery, superficial femoral artery (SFA) and combination disease. This trial compared SET with PTA. SET conferred a significantly greater improvement in MWD and ICD than PTA at 6, 9, 12 and 15 months. The ABPI improved only in the PTA group in the first 3 months, and this was sustained at 6 and 9 months. Two RCTs compared optimal medical treatment (OMT) versus OMT with additional PTA. In the first trial OMT consisted of daily aspirin, and advice on smoking and exercise. MWD was not different between groups after 6 and 24 months. The ICD and ABPI improved in favour of the PTA group after 6 months, but at 24 months only the OMT group had improved further. In the second trial OMT consisted of medication, and advice on smoking, nutrition and exercise. The MWD and ICD were significantly increased at 3, 12 and 24 months compared with baseline. Only in the group with OMT and additional PTA did the ABPI improve significantly compared with baseline at all time points. All improvements were significantly better in the OMT plus PTA group compared with OMT alone at the different follow-up intervals. In another RCT, patients were allocated to SET or PTA for both iliac and femoral lesions. Approximately 70 per cent of the patients had iliac artery disease. After 6 and 12 months of follow-up MWD, ICD and ABPI were improved compared with baseline in both groups, without significant differences between them, except for ICD at 6 months in favour of SET. The last trial compared PTA versus PTA plus SET in a majority of patients with iliac artery lesions (85 per cent). The MWD increased in both
Table 7. Results for MWD, ICD and ABI in patients with aorto-iliac artery disease

<table>
<thead>
<tr>
<th>Outcome measures</th>
<th>Trial</th>
<th>Baseline</th>
<th>FU 6months</th>
<th>FU 12months</th>
<th>FU 24months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Intervention</td>
<td>Intervention</td>
<td>Intervention</td>
<td>Intervention</td>
</tr>
<tr>
<td></td>
<td></td>
<td>E</td>
<td>E+P</td>
<td>E</td>
<td>E+P</td>
</tr>
<tr>
<td>MWD</td>
<td>Greenhalgh</td>
<td>126</td>
<td>114</td>
<td>178</td>
<td>316*</td>
</tr>
<tr>
<td>ICD†</td>
<td>Greenhalgh</td>
<td>64</td>
<td>49</td>
<td>0%</td>
<td>60%*</td>
</tr>
<tr>
<td>ABI</td>
<td>Greenhalgh</td>
<td>0.66</td>
<td>0.68</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

MWD= Maximum Walking Distance, ICD= Initial Claudication Distance, ABI= Ankle Brachial Index
E= SET (Supervised Exercise Therapy), P= PTA (Percutaneous Transluminal Angioplasty), E+P= PTA+SET
* Significantly compared to the E group.
† Improvement, expressed as percentage of patients attaining 200 meters without claudication.
groups at 3 and 6 months compared with baseline, but significantly more in the PTA group. The ABPI at 6 months was similarly improved in both groups compared with baseline. In summary, for mixed iliac and femoro-popliteal artery disease, PTA plus SET compared with PTA alone demonstrated an improvement in MWD. The two trials evaluating SET versus PTA had inconsistent results: one showed a benefit in terms of MWD and ICD after SET and in ABPI after PTA; the other trial demonstrated equal benefit in both groups, without significant differences. Results on MWD, ICD, ABPI and Qol from the two trials comparing OMT plus PTA versus OMT were ambivalent. For some outcomes both trials showed results in favour of OMT plus PTA. In all these trials, however, PTA was performed additionally in patients undergoing OMT (advice on smoking, nutrition and exercise plus medical therapy). Data on Qol in these five trials were assessed by seven different instruments with equivocal results.

**DISCUSSION**

The aim of this systematic review was to obtain the best available evidence on the relative effectiveness of PTA, (S)ET or their combination to provide recommendations for treatment of patients with IC. Owing to the heterogeneity of the interventions, especially of ET, and the assessment of outcomes, it was not possible to draw definitive conclusions. Comparing SET alone with PTA alone did not demonstrate the superiority of one treatment over the other. It seems that patients benefit most from the combination of PTA and SET, although this was not observed for all outcomes. It might be that PTA gives patients a head start for effective SET, reflected by a better increase in walking distance; however, this did not improve Qol more than SET or PTA alone. The evidence base for treatment of IC with either SET or PTA is not solid. The interpretation of the present findings is limited not only by the heterogeneity of interventions, and the heterogeneity of assessment and reporting of outcome measures, but also by shortcomings in design of individual studies.

Studies were generally of mediocre methodological quality, of small sample size and underpowered, or even conducted without a power calculation. In addition, some trials were terminated prematurely. The patients were heterogeneous with regard to baseline walking distance and mixed location of arterial lesions. Although most included studies showed that ET can improve walking distance, the most effective exercise regimen (intensity, frequency, duration) remains unknown. This was reflected in the variation in exercise programmes in the trials. Furthermore, co-interventions such as secondary prevention with antiplatelet agents or statins, which might influence the study outcomes, were different within and among trials.
Table 8. Results for MWD, ICD and ABI in patients with femoro-popliteal artery disease

<table>
<thead>
<tr>
<th>Outcome measures</th>
<th>Trial</th>
<th>Baseline</th>
<th>FU 3months</th>
<th>FU 6months</th>
<th>FU 12months</th>
<th>FU 24months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Intervention</td>
<td>Intervention</td>
<td>Intervention</td>
<td>Intervention</td>
<td>Intervention</td>
</tr>
<tr>
<td></td>
<td></td>
<td>E</td>
<td>P</td>
<td>E+P</td>
<td>M</td>
<td>E</td>
</tr>
<tr>
<td>MWD</td>
<td>Hobbs</td>
<td>111</td>
<td>185</td>
<td>84</td>
<td></td>
<td>124</td>
</tr>
<tr>
<td></td>
<td>Greenhalgh</td>
<td>126</td>
<td>133</td>
<td></td>
<td></td>
<td>167</td>
</tr>
<tr>
<td></td>
<td>Mazari</td>
<td>46.2</td>
<td>51.8</td>
<td>63.1</td>
<td>92.8</td>
<td>87.0</td>
</tr>
<tr>
<td>ICD</td>
<td>Hobbs</td>
<td>59</td>
<td>84</td>
<td>47</td>
<td></td>
<td>92</td>
</tr>
<tr>
<td></td>
<td>Greenhalgh†</td>
<td>63</td>
<td>71</td>
<td></td>
<td></td>
<td>23%</td>
</tr>
<tr>
<td></td>
<td>Mazari</td>
<td>33.5</td>
<td>27.4</td>
<td>40.0</td>
<td>61.2</td>
<td>59</td>
</tr>
<tr>
<td>ABI</td>
<td>Hobbs</td>
<td>0.65</td>
<td>0.69</td>
<td>0.74</td>
<td></td>
<td>0.70</td>
</tr>
<tr>
<td></td>
<td>Greenhalgh</td>
<td>0.63</td>
<td>0.66</td>
<td></td>
<td></td>
<td>0.8</td>
</tr>
<tr>
<td></td>
<td>Mazari</td>
<td>0.65</td>
<td>0.70</td>
<td>0.65</td>
<td>0.8</td>
<td>0.84</td>
</tr>
</tbody>
</table>

E= SET (Supervised Exercise Therapy); P= PTA (Percutaneous Transluminal Angioplasty); E+P= PTA+SET; M= (Best Medical Therapy)
MWD= Maximum Walking Distance; ICD= Initial Claudication Distance; ABI= Ankle Brachial Index
* Significant difference compared to other group(s), † Improvement, expressed as percentage of patients attaining 200 meters without claudication
Table 9. Results for MWD, ICD and ABI on mixed aorto-iliac and femoro-popliteal artery disease

<table>
<thead>
<tr>
<th>Trial</th>
<th>Baseline</th>
<th>FU 3months</th>
<th>FU 6months</th>
<th>FU 12months</th>
<th>FU 24months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intervention</td>
<td>Intervention</td>
<td>Intervention</td>
<td>Intervention</td>
<td>Intervention</td>
</tr>
<tr>
<td></td>
<td>E</td>
<td>P</td>
<td>E+P</td>
<td>E</td>
<td>P</td>
</tr>
<tr>
<td>Creasy†</td>
<td>120</td>
<td>127</td>
<td>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whyman‡</td>
<td>183</td>
<td>228</td>
<td>519.5</td>
<td>667</td>
<td></td>
</tr>
<tr>
<td>Nylaende</td>
<td>265.4</td>
<td>323.9</td>
<td>303.4</td>
<td>427.3*</td>
<td>298</td>
</tr>
<tr>
<td>Spronk§</td>
<td>186</td>
<td>174</td>
<td>1138</td>
<td>755</td>
<td>1034</td>
</tr>
<tr>
<td>Kruidenier</td>
<td>343.3</td>
<td>293.4</td>
<td>782.9</td>
<td>974*</td>
<td>685.0</td>
</tr>
<tr>
<td>Creasy</td>
<td>77</td>
<td>91</td>
<td>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whyman‡</td>
<td>78</td>
<td>56</td>
<td>172</td>
<td>667*</td>
<td></td>
</tr>
<tr>
<td>Nylaende</td>
<td>69.6</td>
<td>93.5</td>
<td>96.6</td>
<td>316.5*</td>
<td>123</td>
</tr>
<tr>
<td>Spronk§</td>
<td>104</td>
<td>82</td>
<td>899</td>
<td>679*</td>
<td>943</td>
</tr>
<tr>
<td>Creasy</td>
<td>0.66</td>
<td>0.63</td>
<td>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whyman‡</td>
<td>0.71</td>
<td>0.74</td>
<td>0.74</td>
<td>0.88*</td>
<td></td>
</tr>
<tr>
<td>Nylaende</td>
<td>0.65</td>
<td>0.63</td>
<td>0.68</td>
<td>0.92*</td>
<td></td>
</tr>
<tr>
<td>Spronk§</td>
<td>0.63</td>
<td>0.62</td>
<td>0.03</td>
<td>0.14</td>
<td>0.04</td>
</tr>
<tr>
<td>Kruidenier</td>
<td>0.71</td>
<td>0.69</td>
<td>0.93</td>
<td>0.88</td>
<td></td>
</tr>
</tbody>
</table>

E = SET (Supervised Exercise Therapy); P = PTA (Percutaneous Transluminal Angioplasty); E+P = PTA+SET, except Whyman and Nylaende, where exercise was advised
MWD= Maximum Walking Distance; ICD= Initial Claudication Distance; ABI= Ankle Brachial Index
* Significant difference compared to other group(s)
† Data were discussed in text and shown in figures, no raw data were available.
‡ medians reported
§ Mean score improvement compared to baseline
Finally, in only one study was the outcome assessor blinded to the allocated treatment to minimize the risk of bias.\textsuperscript{22,23}

An important finding of the present review is that there is no consensus on how to evaluate the success of an intervention in patients with claudication. The aim of treating such patients is to improve pain-free walking distance and presumably Qol. Although standard treadmill testing is not representative of daily life\textsuperscript{39}, it seems attractive for comparison within and between studies. Despite the publication of the Trans-Atlantic Inter-Society Consensus Document on Management of Peripheral Arterial Disease (TASC), which proposed a standard treadmill test of 2 m.p.h. (3.2 km/h) and 10–12\% incline\textsuperscript{6}, few investigators adhered to these recommendations. Uniformity in assessment of walking distance is desirable in future research to facilitate comparison of study outcomes. Yet, the ideal treadmill test in this respect is unknown. The graded Gardner protocol might be preferred because of its better reproducibility compared with non-graded tests.\textsuperscript{40} Alternatively, corridor walking might better reflect the functional capacity of claudicants than the somewhat artificial assessment of a treadmill test.\textsuperscript{41}

There is no consensus on the assessment of Qol in claudicants, given that seven different instruments were used in the included studies. Based on current knowledge, the ideal Qol questionnaire is not yet known, but a suggestion for future research is to choose one generic (for example SF-36) and one disease-specific (such as WIQ or VascuQol) Qol instrument, if only to facilitate the interpretation of individual study results. Like any other systematic review, this review was subject to potential publication bias. No attempt was made to identify grey literature (unpublished studies); Hopewell and colleagues\textsuperscript{42} pointed out that published trials tend to be larger and show an overall greater treatment effect than unpublished trials.

It has been stated that SET is an underutilized tool for the management of IC.\textsuperscript{43} The superiority or inferiority of SET over PTA has not yet been demonstrated, leaving both treatments suitable options for improving walking distance, irrespective of the level of arterial obstruction. Although complications of PTA were few in the trials, it is known from other studies that invasive treatments are associated with risks\textsuperscript{7} This should be taken into account when deciding on a specific treatment. On the other hand, the effectiveness of SET may be limited by poor patient compliance. It might be that a combination of PTA and exercise (SET or exercise advice) is superior to exercise or PTA alone, but this needs to be
confirmed. In addition, optimization of SET and technical developments in percutaneous techniques, such as the use of drug-eluting balloons and stents, might improve the effectiveness of interventions. However, at the moment the results of these developments are awaited. Finally, more studies are needed to address the cost-effectiveness of each treatment strategy.

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REFERENCES


