Drug therapy for improving walking distance in intermittent claudication: a systematic review and meta-analysis of robust randomised controlled studies

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CRD summary
This review concluded that several drugs were shown to improve walking distance in people with intermittent claudication, but with limited benefits. Overall the authors’ conclusions were supported by the results, but they should be interpreted with some caution due to the possibility of publication bias, a lack of information on study quality and differences between studies.

Authors’ objectives
To evaluate the efficacy of pharmacological interventions in improving walking capacity and health-related quality of life for people with intermittent claudication.

Searching
MEDLINE, EMBASE and The Cochrane Library were searched from inception to February 2009. Reference lists from relevant reviews published in the previous five years were screened. Four relevant websites were searched. The review was restricted to published peer-reviewed studies. No language restrictions were applied.

Study selection
Robust double-blind randomised controlled trials (RCT) that compared pharmacological agents with placebo in patients with moderate intermittent claudication (Fontaine stage II) and an ankle-brachial pressure index (ABI) of less than 0.9 that reported data for the outcomes maximal walking distance or pain-free walking distance were eligible for inclusion. Robust studies were defined based on sample size: those with fewer than 56 patients were excluded.

Treadmill tests were used to evaluate walking with protocols that involved either constant or graded loads (most were 3km/h). Specific interventions assessed by the included studies were: anti-platelet agents (ticlopidine, cloricromene, mesoglycan, indobufen, defibrotide); lipid lowering agents (atorvastatin, simvastatin, policosanol,avasimibe); phosphodiesterase inhibitors (cilostazol, pentoxifylline, phosphodiesterase inhibitor); prostaglandins (prostaglandin, iloprost); proteoglycans (heparan sulfate,calcium-heparin, sulodexide, L-arginine); vasodilators (naftidrofuryl, inositol nicotinate); calcium chelators (EDTA); CNS-stimulators (hydroxytryptamine); propionul-L-carnitine; and prostacyclin. Duration of follow-up ranged from 0 to 18 months.

Two reviewers independently assessed studies for inclusion.

Assessment of study quality
One reviewer assessed blinding procedures at treatment and outcome assessment, quality of randomisation, allocation concealment, description of drop-outs and withdrawals, intention-to-treat (ITT) analysis, presence of power calculation and adequate description of statistical methods. Results were double checked by a second reviewer.

Data extraction
One reviewer extracted data as means and standard deviations (SD) for maximal walking distance, where possible. Data were extracted on an ITT basis.

Methods of synthesis
Weighted mean differences (WMD) together with 95% confidence intervals (CI) were estimated for maximal walking distance using random-effects models. Results were stratified on intervention grouping. Studies had to report mean and standard deviation for maximal walking distance to be included in the meta-analysis. Heterogeneity was assessed using the X² test.

Results of the review
Forty three RCTs were included (n=11,686) in the review; 26 provided sufficient information for inclusion in the meta-analysis.

Significant beneficial effects on maximal walking distance were reported for: anti-platelet agents (WMD 59m, 95% CI 37m to 81m; five RCTs); lipid-lowering agents (WMD 163m, 95% CI 83m to 242m; five RCTs); phosphodiesterase inhibitors (WMD 49m, 95% CI 37m to 61m; 12 RCTs); prostaglandins (WMD 66m, 95% CI 5m to 128m; four RCTs); and prosteoglycans (WMD 57m, 95% CI 16m to 97m; three RCTs).

There was no difference in WMD for maximal walking distance for vasodilators (five RCTS) as a whole compared to placebo. However, the four studies that evaluated naftidrofuryl reported significant beneficial effects (WMD 90, 95% CI 14m to 167m).

There was strong evidence of statistical heterogeneity for all meta-analyses except that of antiplatelet agents.

**Authors' conclusions**

Several drugs have been shown to improve maximal walking distance, but with limited benefits. Statins seem to be the most efficient drug available at the time of the review.

**CRD commentary**

The review addressed a focused question supported by clearly defined inclusion criteria. An appropriate literature search was conducted for published studies, but restriction of the review to published peer-reviewed studies raised the possibility of publication bias. Appropriate steps were taken to minimise bias and errors in the selection of studies with some attempts for quality assessment, but data extraction was carried out only by a single reviewer. Study quality was assessed with appropriate criteria, but the results were not presented. Methods used to pool studies were appropriate, but there was substantial heterogeneity between studies and this was not investigated further. Overall the authors’ conclusions were supported by the results, but they should be interpreted with some caution due to the possibility of publication bias, a lack of information on study quality and differences between studies.

**Implications of the review for practice and research**

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that there was a need for strict trials on exercise therapy for intermittent claudication that should also examine issues of cost and QoL. There was also a question of whether particular drugs had synergistic interactions with exercise and smoking cessation and how to educate patients to take responsibility in their own smoking cessation and rehabilitation with exercise.

**Funding**

Regional Hospital Herning and Regional Hospital Viborg; Aase and Ejnar Danielsen's Fund; Ringkobing Council Health research; A.P. Moeller's Fund; Jacob Madsen and Wife's Fund; Snedkermester Sophus Jacobsen and wife Astrid Jacobsen's Fund; Region Midjylland's Health Research Fund.

**Bibliographic details**


**PubMedID**

19586783

**DOI**

10.1016/j.ejvs.2009.06.002

**Original Paper URL**

Database of Abstracts of Reviews of Effects (DARE)
Indexing Status
Subject indexing assigned by NLM

MeSH
Cardiovascular Agents /therapeutic use; Double-Blind Method; Exercise Test; Humans; Hydroxymethylglutaryl-CoA Reductase Inhibitors /therapeutic use; Intermittent Claudication /drug therapy /etiology /physiopathology; Peripheral Vascular Diseases /complications /drug therapy /physiopathology; Phosphodiesterase Inhibitors /therapeutic use; Platelet Aggregation Inhibitors /therapeutic use; Quality of Life; Randomized Controlled Trials as Topic; Recovery of Function; Treatment Outcome; Vasodilator Agents /therapeutic use; Walking

AccessionNumber
12009108561

Date bibliographic record published
16/12/2009

Date abstract record published
03/03/2010

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.