Antithrombotic drugs in the primary medical management of intermittent claudication: a meta-analysis


Authors' objectives
To assess the efficacy of antithrombotic drugs for patients with intermittent claudication.

Searching
The authors searched the MEDLINE database (1976 to June 1998) using the search terms: 'atherosclerosis', 'intermittent claudication', and 'peripheral vascular diseases'. The authors also searched pertinent reviews and articles for additional relevant studies. The search was limited to English language studies.

Study selection
Study designs of evaluations included in the review
Prospective controlled studies. Double reports or trials without clinical outcomes were excluded. Duration of studies ranged from 20 days to 7 years.

Specific interventions included in the review
Antithrombotic drugs as a primary treatment including antiplatelet drugs (aspirin 330-1200 mg daily and dipyridamole 225 mg daily, ticlopidine 500-1000 mg daily, suloctidil 300 mg daily, picotamide 900 mg daily, indobufen 400 mg daily, cilostazol 200 mg daily, and trifluysus 600 mg daily) and anticoagulant drugs (low molecular weight heparin 8,000 or 15,000 IU aXa, sulodexide 600, 1000 or 1200 LU im/600 LU os, vitamin K inhibitors 2 to 4.5 mg daily and defibrotide 200, 400 or 800 mg daily). Studies evaluating merely analgesic treatment were excluded. Control groups received placebo, no treatment, or another active drug treatment.

Participants included in the review
Patients with stage II intermittent claudication (defined by Fontaine, see Other Publications of Related Interest no.1). Studies regarding selected populations (hypertensive, dislipidaemic, diabetic patients) were excluded.

Outcomes assessed in the review
The primary outcomes were: mortality, cerebro- or cardiovascular events (stroke, myocardial infarction), amputations, number of lower limb arterial occlusions or number of revascularisation procedures performed in the lower limbs (angioplasty, bypass graft, endarterectomy, thromboendarterectomy), pain-free and total walking distance, and ankle brachial index and calf blood flow. Studies which did not assess at least one of the outcome measures were excluded from the review.

How were decisions on the relevance of primary studies made?
Two authors independently graded the included trials. Any disagreement was resolved by a third author. The quality of the assessment process was evaluated using a sample of 100 articles analysed by three independent operators. The Kappa statistic was calculated giving a score ranging from 0.90 to 0.95.

Assessment of study quality
Included studies were graded either level 1 (randomised and double- or assessor-blind), level 2 (open randomised) or level 3 (non-randomised comparative). Two authors independently reviewed the validity of the trials. Any disagreement was resolved by a third reviewer.

Data extraction
Two authors independently performed the data extraction using a standardised form. Any disagreement was resolved by
a third author. Data were extracted for the categories of study identification, level of study design, sample size, any run-in before the trial, dosage of the active drug, and duration of the study.

**Methods of synthesis**

How were the studies combined?
Pooled odds ratios (ORs) and mean differences were calculated with 95% confidence intervals (CIs).

How were differences between studies investigated?
The authors state that they tested for heterogeneity and if positive, pooling was not performed. However, the data for these tests are not given.

**Results of the review**

Fifty-four studies were included in the review. Forty-four studies (7,590 participants, 2 studies (247 participants) did not specify how participants were assigned to groups) assessed the efficacy of an active drug in comparison with placebo or no treatment (4,273 in the intervention groups and 3,564 in the control groups). Three of the 44 studies as well as ten further studies compared two active drugs (7,201 participants (3,562 active/3,639 control).

Active treatment versus controls studies:

Total walking distance was assessed with aspirin, ticlopidine, sulocotidil, indobufen, and defibrotide, and results were similar to those observed for pain-free walking distance, but did not reach statistical significance, except for indobufen and defibrotide, which increased total walking distance for a (common) difference of the means of 98.3 m (95% CI: 49.2, 147), and to 88.8 m (95% CI: 45, 132.6), respectively.

Mortality was significantly decreased by ticlopidine compared to placebo (OR 0.68, 95% CI: 0.49, 0.95) and clopidogrel decreased vascular events in comparison to aspirin (OR 0.76, 95% CI: 0.63, 0.92) in level 1 studies.

Lower-limb arterial occlusions were statistically significantly decreased by aspirin (OR 0.46, 95% CI: 0.27, 0.77) and the number of revascularisation procedures performed were statistically significantly decreased by ticlopidine (OR 0.62, 95% CI: 0.41, 0.93). At least one haemodynamic measure (ankle brachial index or calf blood flow, at rest or after exercise) was assessed with all drugs. In general, no differences in favour of actively treated patients were detected compared to control, except for patients receiving aspirin (after exercise calf blood flow; common difference of the means, in ml/100 ml/min, 2.6, 95% CI: 0.28, 4.91), vitamin K inhibitors (ankle brachial index at rest or after exercise; difference of the means 0.1, 95% CI: 0.01, 0.19, and 0.09, 95% CI: 0.02, 0.2, respectively), defibrotide (ankle brachial index at rest; difference of the means 0.04, 95% CI: 0.01, 0.07; calf blood flow at rest; difference of the means 1.1 ml/100 ml/units, 95% CI: 0.76, 1.4).

A small but statistically significant improvement in pain-free walking distance was determined by picotamide, indobufen, low molecular weight heparins, sulodexide and defibrotide, in small studies.

Comparative studies:

Main comparisons regarded ticlopidine, aspirin, clopidogrel (13 studies). Clopidogrel compared to aspirin (1 study) reported superiority for clopidogrel in rate of vascular events (any vascular death, stroke, myocardial infarction) with OR 0.76, 95% CI: 0.63, 0.92; p = 0.004). The OR for vascular death at the end of treatment period was 0.77, 95% CI: 0.58, 1.03; p = 0.075, which was not statistically significant.

With regard to the results observed with indobufen on walking distance, the heterogeneity test was positive and results were not pooled.

**Authors’ conclusions**

The authors state that clopidogrel and ticlopidine do reduce clinically important events in patients with intermittent claudication and could be added to the primary medical treatment of these patients. The use of aspirin in these patients
cannot be based on direct evidence, but only on analogy with coronary and cerebral atherosclerosis, where it has documented efficacy. Other antithrombotic drugs were not properly evaluated in patients with intermittent claudication.

CRD commentary
The authors have stated their research question and some inclusion and exclusion criteria. The literature search is limited. There is no mention of a search for unpublished data and only English language studies were included, although the authors do state that the risk of publication bias from only including English language articles is low. The authors do report who, and how many of the authors, performed the selection of studies and the data extraction from the included studies. There is also some assessment of validity for the included studies by grouping of the studies into levels of study design but this is not used to subgroup the analyses of the included studies.

The analysis was performed by pooling odds ratios and although the authors state that there were tests for heterogeneity, the calculation is not actually stated in the review.

The authors conclusions appear to follow from the results but these should be viewed with caution because of the stated methodological limitations in the process of the review.

Implications of the review for practice and research
Practice: The authors state that patients with peripheral arterial disease should be advised to practice physical training and firmly discouraged to smoke. The use of vasoactive drugs is associated with a statistically significant but small improvement in pain-free walking distance and therefore their clinical usefulness is questionable. In particular, the effects of pentoxifylline and naftidrofuryl on mortality and vascular events, as well as quality of life, were not assessed so the prescription of these vasoactive drugs to patients at Fontaine II of disease is clinically questionable.

The authors further state that the review suggests that the antiplatelet drugs clopidogrel and ticlopidine do modify the natural course of the disease with a lower incidence of adverse events. These observations would lead to the suggestion to add clopidogrel, 75mg once daily, to the primary medical management of patients with intermittent claudication. Alternatively ticlopidine could be given, with appropriate measures for the timely detection of neutropenia or of the recently described ticlopidine-induced thrombotic thrombocytopenic purpura. In current clinical practice, aspirin is the first choice option for these patients, although direct evidence of its efficacy is lacking. However, it could be argued that aspirin is a reasonable choice for these patients, less expensive and less effective, compared to clopidogrel.

Research: The authors state that data on the effectiveness of aspirin in intermittent claudication is poor (evidence based on a single study of artery segments rather than patients) and more good quality studies are required in this area.

Bibliographic details

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Other publications of related interest

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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.