A meta-analysis of randomized placebo control trials in Fontaine stage-III and stage-IV peripheral occlusive arterial disease
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Authors' objectives
The authors appear to examine the effectiveness of iloprost and other pharmacotherapeutic agents in patients with Fontaine Stage III and IV peripheral occlusive arterial disease (POAD).

Searching
MEDLINE was searched, and reference lists of published trials and reviews were examined. Relevant pharmaceutical companies were contacted for additional material.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were included.

Specific interventions included in the review
Pharmacotherapeutic agents versus placebo in patients with Fontaine Stage III and IV POAD. The agents studied were: iloprost, ancred, naftidrofuryl, prostaglandin E1, prostavasin (PGE1) and epoprostenol (PGI2).

Participants included in the review
Patients with Fontaine Stage III and IV POAD. The trials examining iloprost included only patients with ischaemia secondary to atherosclerosis, in whom reconstructive surgery had either failed or was technically not possible. Patients with inflammatory arteriopathy, thromboangiitis obliterans (Buerger's disease), acute ischaemia, purely neuropathic ulceration or gangrene necessitating an immediate amputation and attempted reconstruction, and/or sympathectomy within the preceding 3 months, were excluded.

Outcomes assessed in the review
Iloprost trials: partial ulcer healing in Stage IV patients, complete pain relief in Stage III patients, major amputation and death. Other trials: amputation, death, ulcer healing response and pain relief. Treatment response is defined as ulcer healing or complete relief of pain.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the authors performed the selection.

Assessment of study quality
The authors do not appear to state how the quality of the studies was assessed.

Data extraction
The authors do not state how data were extracted, or how may of the authors performed the extraction. However, for the iloprost trials, the data were extracted for analysis on the bases of intention to treat and treatment received and measured.

Methods of synthesis
How were the studies combined?
A meta-analysis was performed to estimate overall rate difference using the DerSimonian and Laird modification of the
Cochran method (see Other Publications of Related Interest).

How were differences between studies investigated?
The authors do not state how differences between the studies were investigated.

Results of the review
Iloprost trials: 6 RCTs with 705 patients.

Other trials: 11 RCTs with 421 patients.

Iloprost trials: at the end of the treatment almost twice as many patients in the iloprost group were defined as responders (evidence of ulcer healing or complete pain relief), compared to the placebo group; rate difference 0.22 (95% confidence interval, CI: 0.12, 0.33, P<0.001).

Three iloprost studies reported data on major amputations at up to 6 months follow-up. The difference in the rates of amputation on intention to treat basis were -0.12 (95% CI: -0.21,-0.03, P<0.05), indicating that patients receiving iloprost were significantly less likely to undergo a major amputation.

The number of deaths, with or without prior major amputation, in the 2 iloprost studies for which mortality data were available, were too few to achieve statistical significance. In total, there were 11% deaths in the iloprost group (12 out of 106), compared to 34% in the placebo group (24 out of 71). The combined major amputation or mortality for patients in these 2 trials indicated that patients receiving iloprost had a significantly greater probability of completing the follow-up period of up to 6 months with both legs, than those who received placebo; rate difference -0.20 (95% CI: -0.32, -0.08, P<0.05).

Other RCTs: data on ulcer healing were available for 4 of the 11 RCTs. When all 4 studies were analysed together there was no statistically-significant difference between the study drug and placebo, although slightly more patients showed a response to placebo than the study drug; rate difference -0.03(95% CI: -0.17, 0.10, P=0.15).

Seven of the papers assessed pain relief; of these, in only 2 was complete pain relief necessary for a patient to be regarded as a responder. The rate difference in pain relief for the 7 trials was 0.14 (95%CI: -0.15, 0.43, P=0.07).

There was no significant difference in major amputation rates in any of the 7 RCTs for which data were extractable; rate difference 0.04 (95% CI:-0.04, 0.12, P=0.37). Duration of follow-up varied from 4 weeks to 6 months.

Three trials reported mortality data but there was no significant benefit for the treatment groups when analysed individually or together. Death was recorded between 2 and 6 months after treatment. The results were identical when trials using non-prostanoids were excluded from the meta-analysis.

Authors' conclusions
These data suggest that for both symptomatic and objective criteria, iloprost has a beneficial effect in patients with Fontaine Stages III and IV POAD who have already had a failed attempt at arterial reconstruction and/or further reopening procedures are impossible. Other agents in patients with Fontaine Stage III and IV POAD showed no significant benefit over the placebo for any of the end points reported. Further studies are necessary to (1) investigate the possible benefit of repeated courses of treatment with iloprost in patients with non-reconstructible Fontaine Stage III and IV POAD, and (2) look at patients who may only be suitable for relatively high-risk reconstructions.

CRD commentary
A well-conducted review is presented. The authors highlight that the validity of the meta-analysis depends on the underlying quality of the primary studies, although there appears to be no mention of how the quality of the included RCTs was assessed. There were slight discrepancies between data in the tables and text.
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Other publications of related interest

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