CRD summary
This review concluded that patients with peripheral arterial disease, particularly those with critical ischaemia, showed improvement of their symptoms with therapeutic angiogenesis, with acceptable tolerability. Methodological limitations, particularly the lack of reporting and small sample sizes of the included trials, make it difficult to verify the conclusions, which may not be reliable.

Authors’ objectives
To determine the safety and efficacy of gene and cell angiogenic therapies in the treatment of peripheral arterial disease.

Searching
Published trials were identified through a search of MEDLINE and EMBASE to March 2008. Search terms were not reported.

Study selection
Parallel-group randomised controlled trials (RCTs) of therapeutic angiogenesis by any gene, recombinant protein, or cell therapy modality compared to placebo, in patients with peripheral arterial disease, were eligible for inclusion. Peripheral arterial disease had to be Fontaine stage II, III or IV (intermittent claudication, ischaemic rest pain, or ulcer). A diagnosis of peripheral arterial disease was required to be verified by a clinical expert on assessment. Patients with inflammatory arteriopathies, diabetic neuropathy, no absolute indication for immediate amputation, cancer or active proliferative diabetic retinopathy were excluded.

Included trials were required to address one of the following outcomes: walking distance, ankle brachial pressure index rest pain relief, ulcer healing, (loss of) patency, amputation, mortality, cardiovascular or cerebrovascular events and/or side effects.

Of the included trials, over half reported patients with intermittent claudication; the rest reported patients with critical limb ischaemia. Primary efficacy endpoints were peak walking time in the majority of trials, ulcer healing and/or pain relief in one trial, and the outcomes for one trial were not reported. Primary safety end-points were death from any cause, malignancy, retinopathy by ocular neovascularisation, oedema, hypotension and proteinuria events.

The authors did not state how the studies were selected for the review.

Assessment of study quality
The authors stated that two independent reviewers evaluated validity, but details of the validity assessment were not reported.

Data extraction
Two independent reviewers used data on the number of events in each group to derive odds ratios (OR) and 95% confidence intervals (CI) for the end-point response and adverse events in each trial. Patients were regarded as responding at the end of treatment if they had complete or partial healing in stage IV patients, and pain relief or improvement in stage III patients. Patients who were randomly assigned to treatment or placebo, but who did not undergo a procedure, were not included in the analysis.

The authors did not state how many reviewers performed the data extraction.
Methods of synthesis
Pooled odds ratios and corresponding 95% confidence intervals (CI) were calculated using a fixed-effect analysis. Heterogeneity was assessed using a $\chi^2$ test. Subgroup analysis investigated effects in patients with different clinical grades of peripheral arterial disease.

Results of the review
Six trials ($n=543$ patients) were included in the review. Of the 543 patients, 344 received therapeutic angiogenesis and 199 received placebo. Follow-up time ranged from six to 24 months.

Therapeutic angiogenesis significantly improved peripheral arterial disease in the treatment group compared with placebo group (OR 1.437, 95% CI 1.03 to 2.01), but tolerability was significantly poorer (OR 1.685, 95% CI 1.01 to 2.81).

Subgroup analysis by peripheral arterial disease severity showed significantly improved results among critical patients in the treatment group (OR 2.20, 95% CI: 1.01 to 4.79).

The adverse events rates show a higher risk of potential non-serious adverse events (oedema, hypotension, proteinuria) in the treatment group (OR 1.81, 95% CI 1.01 to 3.38; $P = 0.045$) compared with the placebo group.

Authors' conclusions
Patients with peripheral arterial disease, particularly those with critical ischaemia, showed improvement of their symptoms with therapeutic angiogenesis, with acceptable tolerability.

CRD commentary
This review addressed a clear question in terms of participants and interventions, but studies were required to report one of several outcomes, which were combined to provide an overall estimate of efficacy. A limited number of relevant databases were searched, language restrictions were unclear and search terms were not reported. Only published studies were eligible for inclusion, so publication bias may be present. The authors did not report what efforts were used to reduce the risk of reviewer bias for study selection and data extraction, so the risk of bias was unclear.

Two authors assessed validity, but the details were not reported, so the reliability of the data was unclear. Results were pooled using meta-analysis, despite the use of different end-points. Statistical heterogeneity was assessed and subgroup analyses performed.

Methodological limitations, particularly the lack of reporting and small sample sizes of included trials make it difficult to verify the conclusions, which may not be reliable.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice

Research: The authors stated that trials assessing the synergistic effects of the combination of several growth factor genes, as well as the combination of gene and cell therapy, are required.

Funding
Not stated.

Bibliographic details

PubMedID
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.