Beta-adrenergic blocking agents and intermittent claudication: systematic review
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CRD summary
This review assessed the use of beta-blockers in patients with intermittent claudication (IC). The authors concluded there was no evidence to suggest that clinicians should be cautious in prescribing beta-blockers to patients with IC. Limitations in the conduct of the review and methods of analysis mean that the results of the meta-analyses are unreliable. However, the authors' overall conclusions are suitably cautious.

Authors' objectives
To assess the effects of beta-adrenergic blocking agents (beta-blockers) in patients with intermittent claudication (IC).

Searching
MEDLINE (1966 to October 2003), the Cochrane Library (Issue 3 2003) and Igaku-Chuo-Zasshi (1983 to October 2003) were searched for studies; the search terms were reported. The authors also reported conducting a manual search but provided no details of the sources searched. Only studies reported in English or Japanese were included.

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

Specific interventions included in the review
Studies were eligible if they compared beta-blockers with placebo or no treatment and had treatment and washout periods of at least 2 weeks. The drugs had to be approved for use in Japan or the USA. The included studies used atenolol, labetolol, pindolol, acebutolol, metoprolol and propranolol for between 2 and 10 weeks.

Participants included in the review
Studies of patients with IC were eligible for inclusion.

Outcomes assessed in the review
Studies that assessed walking distance and walking time (primary review outcomes) and ankle-brachial index (ABI) and calf blood flow (secondary review outcomes) were eligible for inclusion. The review assessment of walking distance was based on maximal walking distance and initial claudication distance (pain-free walking distance); assessment of walking time was based on maximal walking time and onset time of claudication (pain-free walking time); and calf blood flow was assessed at rest and after exercise.

How were decisions on the relevance of primary studies made?
Three reviewers agreed on the selection of studies.

Assessment of study quality
Validity was assessed and scored using the Jadad scale, which considers the reporting and handling of randomisation, blinding and withdrawals. The maximum possible score was 5 points. Studies scoring 3 or more points were considered to be high-quality studies. The authors did not state who performed the validity assessment.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.
Standardised mean differences (SMDs) with 95% confidence intervals (CIs) were calculated for each study. Data from crossover studies were treated as unpaired data from a parallel-group study. Where studies used more than one active treatment arms, SMDs were calculated separately for each treatment arm versus control.

**Methods of synthesis**

How were the studies combined?

Pooled SMDs with 95% CIs were calculated using a fixed-effect model (inverse variance method) in the absence of significant heterogeneity and a random-effects model (DerSimonian and Laird) when significant heterogeneity was found.

How were differences between studies investigated?

Statistical heterogeneity was tested using a chi-squared test (significance level of P<0.1). High- and low-quality studies were analysed separately; where results differed, the results from the high-quality studies were presented. Studies using beta-blockers with intrinsic sympathomimetic activity (ISA) were analysed separately.

**Results of the review**

Nine crossover RCTs (n approximately 123) were included.

Six RCTs were considered to be of a high quality (scoring 3 or more on the Jadad scale).

Walking distance: the maximal walking distance was significantly worse in patients receiving beta-blockers compared with control (SMD -0.31, 95% CI: -0.58, -0.04, P=0.03; based on 3 RCTs), as was the initial claudication distance (SMD -0.39, 95% CI: -0.73, -0.06, P=0.02; based on 1 high-quality RCT). No statistically significant heterogeneity was found (P=0.44 and P=0.76, respectively). Maximum walking distance also appeared to be worse for patients receiving beta-blockers with ISA, although this was not statistically significant.

Walking time: there was no significant difference between beta-blockers and control for maximal walking time (SMD 0.07, 95% CI: -0.24, 0.37, P=0.67; based on 4 RCTs) or initial claudication time (SMD 0.12, 95% CI: -0.23, 0.47, P=0.51; based on 3 RCTs). All these studies were rated as high quality. The results were similar for beta-blockers with ISA.

ABI: there was no significant difference between beta-blockers and control for ABI (SMD 0.24, 95% CI: -0.30, 0.78, P=0.39; based on 1 low-quality RCT with 14 patients).

Calf blood flow: there was no significant difference between beta-blockers and control for calf blood flow at rest (SMD 0.00, 95% CI: -0.26, 0.25, P=0.97; based on 3 RCTs) or after exercise (SMD -0.23, 95% CI: -0.69, 0.22, P=0.31; based on 1 high-quality RCT).

**Authors’ conclusions**

There was no evidence to suggest a cautious approach in prescribing beta-blockers to patients with IC, or that the safety precautions included in package inserts in Japan are inappropriate.

**CRD commentary**

The review addressed a clear question that was defined in terms of the participants, interventions, outcomes and study design. Three databases were searched. Manual searches were also undertaken, but no details of these were reported. The inclusion of only English and Japanese articles means that relevant studies published in other languages might have been missed. Methods were used to minimise errors and bias in the selection of studies, but it was unclear whether similar steps were taken for the validity assessment and data extraction. Only RCTs with pre-specified minimal treatment and washout periods were included. Validity was assessed using an established checklist, although only the composite score was presented; this makes it difficult for the reader to judge the validity of the studies for themselves.

No details of the participants in the primary studies were provided, therefore it is not possible to assess the
generalisability of the results. Statistical heterogeneity was assessed and the studies were combined in a meta-analysis. However, studies assessing two or more beta-blocker treatments were included more than once in each analysis. This means that the results of the meta-analyses are unreliable. In addition, the included studies were very small (23 patients or fewer) and were of short-term treatment (longest lasted 10 weeks); these factors should also be considered when interpreting the results. The results of the individual studies presented in this review seem reliable, but the results of the meta-analyses should be treated with caution. The authors’ cautious conclusions about the lack of evidence in this area appear appropriate, but this review was not sufficiently robust to make any claims about precautions in drug packaging, particularly as none of the included studies were conducted in Japan and the review did not assess adverse events.

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

**Practice:** The authors stated that reluctance to prescribe beta-blockers to patients with IC may not be appropriate, but these patients should be monitored when beta-blockers are administered.

**Research:** The authors stated that research to examine the effect of race and alpha-sensitivity on beta-blockers in patients with IC is required.

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