Aspirin for the prevention of cardiovascular events in patients with peripheral artery disease: a meta-analysis of randomized trials

CRD summary
This review found that aspirin treatment in patients with peripheral artery disease provided a statistically significant reduction in nonfatal stroke but not in cardiovascular events. The authors also concluded that given the limited statistical power of their analysis, further randomised controlled trials are required. These cautious conclusions are likely to be reliable.

Authors' objectives
To assess the effect of aspirin on cardiovascular event rates in patients with peripheral artery disease.

Searching
MEDLINE, Cochrane Central Register of Controlled Trials, EMBASE, Science Citation Index, Web of Science and Social Science Citation Index databases were searched from 1966 to December 2008. Search terms were reported. References of retrieved articles were checked, experts were contacted and proceedings of major scientific meetings were monitored for ongoing trials. The search was cross-referenced to include relevant studies noted in the most recent meta-analysis of the Antithrombotic Trialists' Collaboration.

Study selection
Randomised controlled trials (RCTs) that compared aspirin with placebo or other control in patients with peripheral arterial disease were eligible for inclusion. Trials were required to report all-cause mortality, cardiovascular mortality, myocardial infarction, stroke or major bleeding. Trials which reported no events in any trial arm were excluded from the review.

Included studies used aspirin monotherapy or aspirin combined with dipyridamole. Most used a placebo comparison group. Aspirin doses ranged from 100 mg/day to 1,500 mg/day for monotherapy and from 25 mg three times daily to 500 mg three times daily for combination therapy. Patients were asymptomatic with an ankle brachial index of 0.99 or less, or were undergoing percutaneous intervention or bypass surgery. Some trials enrolled only patients who also had diabetes. Mean patient ages ranged from 57 to 67 years where reported.

Two reviewers independently assessed the studies for inclusion in the review and disagreements were resolved through discussion.

Assessment of study quality
The studies were assessed for validity using the Jadad scale, which awards up to 5 points for the criteria of randomisation, blinding and treatment of withdrawals and dropouts. The authors did not state how many reviewers performed the validity assessment.

Data extraction
Relative risks (RR) with 95% confidence intervals (CI) were calculated using intention-to-treat data for the primary composite outcome of nonfatal myocardial infarction, nonfatal stroke and cardiovascular death. RRs were also calculated for all cause-mortality, components of the primary outcome and major bleeding. Authors' definitions of major bleeding were accepted. The authors did not state how many reviewers performed the data extraction.

Methods of synthesis
The RCTs were combined in a Mantel-Haenszel random effects meta-analysis. Sensitivity analyses were used to assess the impact of including studies with no events in one treatment arm (using a 0.5 correction). Statistical heterogeneity between studies was assessed using the Q and I² statistics.
Subgroup analyses were employed to investigate the effects of the following factors: aspirin monotherapy compared with placebo or control; use of aspirin at currently recommended doses (75 mg/day to 325 mg/day); studies with follow up of over one year; studies designed to assess cardiovascular events; exclusive enrollment of patients with peripheral arterial disease and diabetes; and Jadad score of 4 or 5.

Sensitivity analyses were also used to assess the impact of each individual study and of employing a fixed-effect analysis. Publication bias was assessed through analysis of funnel plots. A power calculation for the meta-analysis was performed.

**Results of the review**

Eighteen RCTs (n=5,269) were included in the review. Where reported, Jadad scores ranged from 2 to 5 points with six RCTs scoring 4 or 5 points. Six RCTs could not be assessed for quality. Duration of follow-up ranged from 10 days to 6.7 years.

There was no overall statistically significant difference in the composite outcome of nonfatal myocardial infarction, nonfatal stroke and cardiovascular death between the aspirin and placebo or control groups (RR 0.88, 95% CI: 0.76, 1.04, 18 RCTs). There was a significantly lower incidence of nonfatal stroke in the aspirin groups (RR 0.66, 95% CI: 0.47, 0.94, 18 RCTs), but there were no statistically significant differences between the groups for any other secondary efficacy outcome. There was no statistically significant difference between the groups in incidence of major bleeding, but this was not formally assessed in many included RCTs.

Results of subgroup and sensitivity analyses were also reported. No evidence of significant publication bias was detected.

**Authors' conclusions**

Treatment with aspirin alone or with dipyridamole provided a statistically nonsignificant reduction in the primary endpoint of cardiovascular events and a statistically significant reduction in nonfatal stroke in patients with peripheral arterial disease. The lack of statistical significance for the primary endpoint may have reflected the limited power of the meta-analysis to detect a difference. Additional RCTs of aspirin therapy in these patients would be required to establish the net benefit and risks of treatment.

**CRD commentary**

The review question and the inclusion criteria were clear. The authors searched a number of relevant databases and made systematic attempts to identify unpublished studies. This reduced the chances of relevant studies being omitted from the review and reduced the chances of publication bias. Publication bias was assessed and no evidence for it found. The authors reported using methods designed to reduce reviewer bias and error in the selection of studies, but not in the extraction of data and the assessment of validity. A validity assessment was conducted using an appropriate tool and was used to inform the synthesis. Despite clinical heterogeneity, the decision to use meta-analysis appeared appropriate. The cautious conclusions accurately reflected the results of the review and are likely to 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 additional appropriately powered RCTs of aspirin therapy in patients with peripheral arterial disease and assessing cardiovascular and bleeding events were required. They noted that a large RCT (Aspirin in Asymptomatic Atherosclerosis, n = 3,350) was underway.

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