Aspirin for the secondary prophylaxis of vascular disease in primary care
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Authors' objectives
To provide evidence linked recommendations for general practitioners on the use of aspirin for the secondary prophylaxis of nonfatal and fatal cardiovascular disease and stroke, in the management of adult patients at raised vascular risk.

Searching
MEDLINE and the Cochrane Controlled Trials Register were searched. In addition, the authors searched high-quality review articles and bibliographies, and contacted experts in the field. The search strategy was also informed by the expert knowledge and experience of the reviewers.

Study selection
Study designs of evaluations included in the review
The studies considered were systematic reviews, meta-analyses, randomised trials, quality of life studies and economic studies with follow-up ranging from 2 to 4 years.

Specific interventions included in the review
Aspirin (75 to 150 mg/day) and other antiplatelet therapies.

Participants included in the review
Patients at risk of cardiovascular disease or stroke including actual and suspected acute myocardial infarction (MI), previous MI, stable angina, unstable angina, past history of stroke or transient ischaemic attack, and intermittent claudication and diabetes.

Outcomes assessed in the review
The incidence of vascular events (nonfatal stroke or MI) and vascular death (fatal stroke or MI) was assessed.

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 quality of the studies was assessed on the basis of the internal validity, external validity, and construct validity. The papers were categorised according to study design, using a scale of categories of evidence adapted from the US Agency for Health Care Policy and Research Classification (see Other Publications of Related Interest no.1). A single reviewer categorised the papers.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the authors performed the data extraction.

Methods of synthesis
How were the studies combined?
The data were combined using the methods of Whitehead and Whitehead (see Other Publications of Related Interest no.2) and DerSimonian and Laird (see Other Publications of Related Interest no.3).
The risk ratios and risk differences, along with 95% confidence intervals (CIs), were calculated for each clinical group using a random-effects model.

How were differences between studies investigated?
Heterogeneity was tested using the Q statistic.

The subgroups were also analysed to investigate the effects of clinical grouping on the overall relative risk (RR) results.

**Results of the review**
Eighty-three randomised controlled trials were included in the review. Thirty-one trials used aspirin as the active treatment (3,093 antiplatelet events out of 23,333 antiplatelet total), 47 trials used an alternative antiplatelet agent (661 antiplatelet events out of 6,050 antiplatelet total), and 5 trials used a combination of aspirin and an alternative antiplatelet agent (the number of events was not stated). The breakdown by clinical subgroup was as follows: 9 trials of acute MI; 11 trials of prior MI; 6 trials of stable angina; 7 trials of unstable angina; 19 trials of prior stroke or transient ischaemic attack; 23 trials of intermittent claudication; and 8 trials of diabetes. The number of participants was not stated.

The overall RR (83 trials) of MI, stroke or vascular death was 0.79 (95% CI: 0.76, 0.82) in favour of antiplatelet therapy (aspirin) versus placebo. The test for heterogeneity showed evidence of homogeneity between the included trials (Q=74.81, d.f.=82, p=0.70).

When the trials were grouped according to whether aspirin or alternative antiplatelet therapy was used, and the confounded trials that use an alternative antiplatelet agent in conjunction with aspirin were excluded, the resulting analysis provided no evidence of systematic differences in the effect between aspirin and other antiplatelet agents: the RR was 0.79 (95% CI: 0.76, 0.83) and 0.80 (95% CI: 0.73, 0.87) for aspirin and the alternative antiplatelets, respectively. Heterogeneity was found in the subgroup of aspirin trials, but not in the subgroup of alternative antiplatelet trials, but neither of these results were statistically significant.

For the individual clinical groups, statistically-significant results in favour of antiplatelet therapy were achieved for the clinical subgroups of acute MI (RR 0.74, 95% CI: 0.68, 0.80), prior MI (RR 0.79, 95% CI: 0.73, 0.85), stable angina (RR 0.71, 95% CI: 0.58, 0.87), unstable angina (RR 0.61, 95% CI: 0.51, 0.74), and prior stroke or transient ischaemic attack (RR 0.82, 95% CI: 0.76, 0.88). The results were not statistically significant for the intermittent claudication or diabetes groups.

**Cost information**
The cost of aspirin itself was negligible. Non-proprietary aspirin, in 75 mg dispersible tablets, costs approximately £1 per year to prescribe, although proprietary brands may cost 10 to 20 times more.

**Authors' conclusions**
There was strong evidence of a common underlying treatment effect from the use of aspirin, or other antiplatelet agents, in reducing the risk of death or vascular event in patients at raised vascular risk. The attributable benefits of prophylactic use of aspirin in the secondary prophylaxis of vascular disease outweigh the related risks.

**CRD commentary**
The authors clearly stated their research question and the inclusion and exclusion criteria. Although two databases were searched, the literature search was limited in that it may have missed studies published outside of the USA. The authors did not mention searching for unpublished data, but they did contact experts in the field.

The authors did not report who selected the articles for inclusion. The quality assessment of the included studies was limited and the scoring was not reported for the individual studies, although it was summarised for the overall recommendations. Details of the individual studies and the data extracted were only reported for the major studies. However, the number of antiplatelet events, the total participation or antiplatelets, and the results were reported for the individual trials in an appendix to the review. The data synthesis was appropriate and was reported in detail. The authors
tested for heterogeneity between the included studies, and also analysed clinical subgroups and subgroups of different
antiplatelet treatments.

The results of the review follow from the data presented.

Implications of the review for practice and research
The authors state that additional research is needed. This is because many of the included trials were conducted before
the use of other therapies, and the potential interaction between relevant drugs has not been explored. They further state
that research is needed in the following areas: the appropriate duration of therapy; the effect of a 75 mg daily dose of
aspirin in patients with intermittent claudication; diabetes as sole risk factor for vascular disease. A formal evaluation of
the cost-effectiveness of aspirin and other antiplatelets is also required.

The authors made several recommendations for practice of which the strongest are listed below.

The use of aspirin in the secondary prophylaxis of vascular disease is cost-effective.

Patients with suspected acute MI should be treated with 150 mg aspirin daily, and treatment continued for one month.

After one month, patients should be treated according to the ‘previous MI’ section.

Patients who have previously had an MI should be treated with 75 mg aspirin daily, for 3 years.

Patients who have stable angina should be treated with 75 mg aspirin daily, for 4 years.

Patients with suspected unstable angina should subsequently be treated with 75 mg aspirin daily, for 18 months.

After 18 months, patients with a history of unstable angina should be treated in accordance with the ‘stable angina’
section.

Patients with a past history of a stroke or transient ischaemic attack should be treated with 75 mg aspirin daily, for 4
years.

There is insufficient evidence to support the use of aspirin for the secondary prophylaxis of vascular events in patients
who have intermittent claudication or diabetes, but no additional vascular risk factors.

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Bibliographic details
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Other publications of related interest
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pain management: operative or medical procedures and trauma. Rockville (MD): Agency for Health Care Policy and
North of England evidence based guideline development project: guideline on the use of aspirin as secondary
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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.