Evaluation of the benefits and risks of low-dose aspirin in the secondary prevention of cardiovascular and cerebrovascular events
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Authors' objectives
To compare the benefit and gastrointestinal risk of low-dose aspirin for the secondary prevention of thromboembolic events.

Searching
MEDLINE, EMBASE, and Excerpta Medica were searched for reports published after 1970 on aspirin for secondary prevention indications, which have been approved by the U.S. Food and Drug Administration (FDA). These indications are summarised in the FDA’s 1998 rule and updated professional labelling for aspirin.

Study selection
Study designs of evaluations included in the review
Randomised, placebo-controlled trials were eligible for inclusion in the review.

Specific interventions included in the review
Studies evaluating the use of low-dose aspirin (50 to 325 mg/day) against placebo in the secondary prevention of myocardial infarction (MI) and stroke, regardless of precipitating event, were eligible for inclusion in the review. Interventions where aspirin was administered for less than 3 months, or was prescribed short term for thromboprophylaxis in procedures such as angioplasty or coronary artery bypass grafts, were excluded. Also excluded was the use of aspirin for non-prevention indications (e.g. pain, headache or arthritis, aspirin co-administered with another agent, or the use of aspirin to prevent cardiovascular events in otherwise healthy individuals (primary prevention).

Participants included in the review
Participants who had previously experienced a stroke, transient ischaemic attack or MI, or who had a history of angina, were eligible for inclusion in the review. The weighted mean age of the participants across the included studies was 59.5 years. The weighted mean percentage of male participants was 83.8%.

Outcomes assessed in the review
Efficacy and safety outcomes, including all fatal and nonfatal vascular events, were assessed in the review. These included MI, stroke, vascular death, vascular event (i.e., any stroke, MI, or other vascular event defined as possibly or definitely of cardiac, cerebral, embolic, haemorrhagic, or unknown cause), and all-cause mortality. In addition, data on serious adverse events related to bleeding, particularly gastrointestinal (GI) bleeding, were assessed. Subjective tolerability was not evaluated.

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 reviewers performed the selection.

Assessment of study quality
The authors do not report the method used to assess validity, or how the validity assessment was performed.

Data extraction
Data from each published study were abstracted by the same two individuals, then re-abstracted by a third for quality control.
Data were extracted on the inclusion and exclusion criteria, health status on entry, and outcomes using specially developed forms. The data were then transferred to a database and checked against hard copy entries. To facilitate comparison across studies with differing end points, the summary measure ‘vascular events’ was used. This was defined as MI, stroke or other vascular event (including vascular death). The relative risks (RRs), absolute risk reductions (ARRs) and 95% confidence interval (CIs) were estimated for each outcome variable in each study.

**Methods of synthesis**

How were the studies combined?

The outcome data were reported differently across the studies. Thus, the results for categories were only pooled if they were reported in the same way. A Peto fixed-effect model was not used for statistical pooling because of differences in the length of follow-up across the studies. Therefore, the RR for each outcome was calculated assuming a constant follow-up time. The pooled RR and the 95% CI were calculated using all studies with reported outcomes. The ARRs were not aggregated because of differences in the follow-up periods across the studies, and were therefore grouped narratively. The numbers-needed-to-treat for GI bleeding events and all-cause mortality were calculated using the pooled risk ratio and the pooled placebo event rates.

How were differences between studies investigated?

Homogeneity of risk across all studies was calculated using the method described by Breslow and Day (see Other Publications of Related Interest).

**Results of the review**

Six randomised controlled trials (n=6,300) were included in the review.

For all-cause mortality, the RRs for each of the individual studies ranged from 0.5 (95% CI: 0.2, 1.1, p=0.08) to 1.0 (95% CI: 0.3, 3.0, p>0.99), suggesting that the numbers were too small in the individual studies to determine an impact.

The results of the homogeneity test (p=0.7) indicated that the results were homogeneous across the studies.

The pooled RR was 0.82 (95% CI: 0.7, 0.99, p=0.03). The data suggested that aspirin reduces the risk of death by approximately 20% in the studied population. The ARRs ranged from 2.0% (plus or minus 3.1%) at the 12-month follow-up, to 8.7% (plus or minus 6.3%) at the 20-month follow-up.

Across all outcomes, the ARRs ranged from 0.9% (plus or minus 3.7%) at the 52-month follow-up, to 18.6% (plus or minus 7.7%) at the 3-month follow-up.

The pooled RR was 0.7 (95% CI: 0.6, 0.8) for vascular events and 0.7 (95% CI: 0.6, 0.8) for MI. Significant heterogeneity was found in both of these results (p<0.001).

Five of the 6 studies reported GI bleeding, which was a rare find: only 58 cases were reported, approximately half of which were severe enough to require withdrawal. There were no reported deaths related to GI bleeding, and GI bleeding led to almost no permanent morbidity. Only one study demonstrated a statistically-significant increased risk of GI bleeding as a result of aspirin intake. The analysis of GI bleeding across all studies suggested a pooled risk ratio of 2.5% (95% CI: 1.4, 4.7, p=0.001). No significant heterogeneity was found (P=0.5).

Only 2 of the 6 included studies reported cases of haemorrhagic stroke; the results were therefore not conclusive, although the pooled RR from the 2 homogeneous (P>0.99) studies was 0.8 (95% CI: 0.7, 1.0). Based on the number-needed-to-treat with aspirin to either prevent one death or cause one GI bleeding event, it was determined that 1.5 deaths could be prevented for every nonfatal GI bleeding attributed to the use of aspirin.

**Authors’ conclusions**

Aspirin use for the secondary prevention of thromboembolic events has a favourable benefit-to-risk profile and should be encouraged in those at high risk.
CRD commentary
The review question and the study selection criteria were clearly stated. The literature search was reasonably comprehensive, but it was unclear whether any language restrictions were applied and there were no details of efforts to identify additional material. Thus, it is possible that some material may have been missed. The authors provided no information on the literature selection or validity assessment procedures, although the data extraction procedures were rigorous. However, no tests for publication bias were reported. The statistical tests employed seem appropriate given the problem of diverse follow-up periods, which the authors acknowledge.

There was adequate presentation and discussion of the study findings. The conclusions seem appropriate given the data presented.

Implications of the review for practice and research
Practice: The authors state that aspirin use for the secondary prevention of thromboembolic events has a favourable benefit-to-risk profile and should be encouraged in those at high risk. The study findings should assist physicians and patients in understanding the role and safety profile of aspirin in the secondary prevention of cardiovascular and cerebrovascular events. The authors state that their overview analysis clearly supports the broader use of aspirin.

Research: The authors state that further studies are needed on the adverse interactions between aspirin and Helicobacter pylori infection.

Reviewer's comment: There is scope for further research on the benefits of aspirin in the prevention of cerebrovascular events.

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