Aspirin prophylaxis in patients at low risk for cardiovascular disease: a systematic review of all-cause mortality

Boltri J M, Akerson M R, Vogel R L

Authors' objectives
To assess whether aspirin reduces all-cause mortality in low-risk patients.

Searching
MEDLINE and the Cochrane Library were searched using the terms 'aspirin' or 'antiplatelet therapy' and 'primary prevention' or 'prevention' and 'primary' and 'mortality'. Additional searches were made with 'primary prevention' and 'myocardial infarction' or 'stroke'. No search dates were reported. The Internet was also searched using the same search terms. The authors did not state whether any language restrictions were applied.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs), non-randomised clinical trials, cohort studies and case-control studies were eligible for inclusion. The review included two RCTs and one cohort study. Follow-up time was between 5 and 6 years.

Specific interventions included in the review
The intervention of interest was aspirin. This was administered at a variety of different doses: one study assessed 325 mg of aspirin taken every other day against placebo, another assessed 500 mg aspirin daily versus no aspirin, and a third assessed between 1 and 15 aspirin tablets per week (the exact dosage was not specified) versus no aspirin.

Participants included in the review
Participants at low risk of cardiovascular disease were eligible for inclusion. Low risk was defined as having no more than one of the following risk factors: hypertension, low high-density lipoprotein cholesterol, high low-density lipoprotein cholesterol, family history of premature coronary heart disease, smoking, diabetes or advancing age (men greater than 45 years and women greater than 55 years). Patients with past cerebrovascular events, myocardial infarction (MI) or angina were classified as high risk.

The review actually included both high- and low-risk patients as these were not distinguished within the primary studies. In one study the mean age of the participants was 53.2 years, 50% were current or past smokers and 9% had hypertension. In another study more than half of the participants were at least 60 years old, 6% had a history of heart disease other than MI, 10% had hypertension and 75% were current or former smokers. In a third study the mean age of the participants was 46 years, 29% were smokers and 15% had hypertension.

Outcomes assessed in the review
The primary outcomes were MI, stroke and mortality. Morbidity associated with aspirin use was also reviewed as a secondary outcome.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The validity of the RCTs was assessed using the Jadad scale, which considers the methods of randomisation, blinding, and the reporting of withdrawals and drop-outs. The validity of the cohort study was not assessed. Two independent reviewers undertook 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. Data on the study population, study design, number of participants, the follow-up time, and the treatment and control were extracted. The odds ratio (OR) was recalculated for each study along with the associated 95% confidence interval (95% CI).

**Methods of synthesis**

**How were the studies combined?**
The results of the two RCTs were combined in a meta-analysis using the Mantel-Haenszel method. The authors did not report whether any factors were taken into account when weighting the studies, or whether publication bias was assessed.

**How were differences between studies investigated?**
The authors did not report any formal statistical method to investigate differences between the studies.

**Results of the review**

Three studies (n=114,888) were included: two RCTs (n=27,210) and one cohort study (n=87,678).

The first RCT showed a lower rate of MI for the aspirin group relative to the controls (OR 0.58, 95% CI: 0.47, 0.71). No differences were observed between the groups for the outcome measures of stroke, total cardiovascular mortality or total mortality. More side-effects, including gastric ulcers, gastrointestinal bleeding, haemorrhagic stroke and other bleeding disorders, were observed in the aspirin-treated group relative to the controls. The second RCT showed no significant differences between the aspirin-treated group and untreated controls on rates of MI, stroke, total cardiovascular mortality or total mortality. By the end of the study, 44% of the aspirin group had discontinued aspirin secondary to side-effects, the most common being dyspepsia.

The results of the cohort showed that mortality from aspirin use was dose dependent. Mortality was 0.84% (OR 1.51, 95% CI: 1.26, 1.82) for study participants taking 1 to 6 aspirin tablets each week, 0.99% (OR 1.80, 95% CI: 1.39, 2.33) for those taking 7 to 14 aspirin tablets, and 1.82% (OR 3.32, 95% CI: 2.64, 4.21) for those taking 15 or more aspirin tablets. The rates of MI, stroke, total cardiovascular mortality and total mortality were also significantly higher in all the groups taking aspirin.

When combined, the two RCTs showed no significant differences in mortality between the aspirin and placebo groups, whereas the cohort study showed increased mortality associated with aspirin use.

**Authors’ conclusions**

There is currently no evidence for or against the recommendation of using aspirin in low-risk individuals to decrease mortality.

**CRD commentary**
The review question was clearly defined in terms of the intervention, participants, outcome measures and study designs. However, no studies were identified that assessed the primary prevention in only low-risk participants. Therefore, studies that included both low- and high-risk participants were included, making the interpretation of the results somewhat difficult. Several sources were searched for potentially relevant studies, but no attempt was made to identify unpublished studies. The authors did not report the methods used to assess the studies for inclusion or to extract the data, thus it is unclear whether any efforts were made to minimise bias and errors. The quality of the included RCTs was adequately assessed, whereas a quality assessment of the cohort study was not undertaken.

Information on the primary studies was both tabulated and presented in the text, and was appropriately combined in a narrative discussion. Differences between the studies were also explored. Overall, the authors’ conclusions that there is currently no evidence to recommend for or against the use of aspirin in low-risk individuals, in order to decrease
mortality, is consistent with the evidence presented.

**Implications of the review for practice and research**
The authors did not state any implications for practice or further research.

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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.