Aspirin for the primary prevention of cardiovascular events in women and men: a sex-specific meta-analysis of randomized controlled trials


CRD summary
This review concluded that aspirin reduces the risk of stroke in women and of myocardial infarction in men, but increases the risk of major bleeding for both groups. The conclusion appears to follow from evidence presented, although the search for studies could have been more extensive and the inadequate description of the review methods makes it difficult to verify the findings.

Authors' objectives
To determine the effect of aspirin in the primary prevention of cardiovascular disease in women and men.

Searching
MEDLINE was searched from 1966 to March 2005 for studies in English; the search terms were reported. The bibliographies of the retrieved citations were checked and major scientific meetings were monitored for additional studies.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion. The follow-up period was between 3.6 and 10.1 years.

Specific interventions included in the review
Studies of aspirin administered for the primary prevention of cardiovascular disease were eligible for inclusion. The aspirin dosage ranged from 100 mg every other day to 500 mg daily. The comparator was placebo.

Participants included in the review
Males and females without cardiovascular disease were eligible for inclusion. The participants were described as apparently healthy or having one or more risk factors for cardiovascular disease. The proportion of participants who smoked or had hypertension, high cholesterol or diabetes varied between the studies. The mean age of the participants ranged from 54.6 to 64.7 years.

Outcomes assessed in the review
Studies reporting data on major cardiovascular events, including myocardial infarction (MI), stroke and cardiovascular mortality, were eligible for inclusion. The outcomes of interest in the review were a composite measure of cardiovascular mortality, nonfatal MI or stroke (any cardiovascular event), each of these three outcomes alone, all-cause mortality and major bleeding. Stroke sub-types (ischaemic and haemorrhagic) were also investigated.

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

Assessment of study quality
The authors stated that they assessed the validity of the trials on the basis of adequacy of blinding of randomisation, completeness of follow-up and objectivity of outcome assessments. The authors did not state how the papers were assessed for validity, or how many reviewers performed the validity assessment.
**Data extraction**
The total number of events for each of the outcomes of interest were extracted for men and women. The data were extracted in an intention-to-treat format. The authors did not state how many reviewers performed the data extraction.

**Methods of synthesis**
How were the studies combined?
The authors stated that a Mantel-Haenszel model and a random-effect model were used to calculate and compare the summary odds ratios (ORs), with 95% confidence intervals (CIs), in males and females. The authors appear to have reported the pooled data from the Mantel-Haenszel model. A funnel plot was used to assess publication bias.

How were differences between studies investigated?
In addition to pooling the data on males and females separately, the Cochran Q statistic was used to assess heterogeneity.

**Results of the review**
Six RCTs (n=95,456) were included. Three studies included only males, one included only females and two included both sexes.

Aspirin was associated with a statistically significant decrease in cardiovascular events in women (OR 0.88, 95% CI: 0.79, 0.99, P=0.03) and men (OR 0.86, 95% CI: 0.78, 0.94, P=0.01) compared with placebo.

In women, aspirin was associated with a statistically significant reduction in the occurrence of stroke (OR 0.83, 95% CI: 0.70, 0.97, P=0.02). When stroke sub-type was investigated, aspirin was associated with a reduction in ischaemic stroke but not haemorrhagic stroke. There was no statistically significant effect on MI, cardiovascular and all-cause mortality for women.

In men, aspirin was associated with a statistically significant reduction in the occurrence of MI (OR 0.68, 95% CI: 0.54, 0.86, P<0.001), but had no statistically significant effect on stroke overall (though there was a statistically significant increase in haemorrhagic stroke) and no effect on cardiovascular and all-cause mortality.

Aspirin therapy increased the risk of bleeding in both men and women.

No evidence of publication bias or statistically significant heterogeneity was found.

**Authors’ conclusions**
For women and men, low-dose aspirin therapy decreased the risk of cardiovascular events and increased the risk of major bleeding. For women, aspirin decreased the risk of ischaemic stroke, while for men, aspirin decreased the risk of MI.

**CRD commentary**
The review question, inclusion criteria and criteria for the quality assessment were clear, but the authors did not adequately describe how they performed the study selection, data extraction and quality assessment processes. Although major scientific meetings were monitored for unpublished papers, the electronic search was restricted to MEDLINE and to English language papers, so relevant studies might have been missed. Study quality was assessed, but only some components of the quality assessment were reported. In addition, since the authors did not consider the impact of study quality on the findings of the review, the possibility of bias cannot be ruled out.

The authors did not detect any statistical heterogeneity, although they did discuss possible reasons for variations in the results. As the authors pointed out, they were unable to assess the effect of aspirin therapy on subgroups of participants, so the findings of the review may not be generalisable to all subgroups, particularly the elderly. Overall, the authors’ conclusion appears to be supported by the evidence presented, although it was not possible to verify this given the lack of detail concerning the methods used and the quality of the studies.
Implications of the review for practice and research

Practice: The authors stated that aspirin is associated with a significant decrease in the risk of cardiovascular events and a significant increase in the risk of major bleeding, so both its beneficial and harmful effects should be considered when used.

Research: The authors stated that because of the relatively small number of MI among women and stroke among men, further studies with larger sample size are needed to determine if the effect of aspirin on cardiovascular events differs between women and men.

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Other publications of related interest
This additional published commentary may also be of interest. Thompson DR. Review: aspirin was effective for primary prevention of stroke in women and MI in men but increased major bleeding. Evid Based Nurs 2006;9:76.

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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.