Aspirin for the prevention of cardiovascular events in patients without clinical cardiovascular disease: a meta-analysis of randomized trials

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CRD summary
The review concluded that aspirin reduced major cardiovascular events by about 10% but increased the incidence of major bleeding in individuals without clinical cardiovascular disease. A limited search, no quality assessment and insufficient reporting of review processes and control treatments mean that the authors’ conclusions may not be reliable.

Authors’ objectives
To evaluate the impact of aspirin treatment on major cardiovascular events and major bleeding in patients without clinical cardiovascular disease.

Searching
MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL) and EMBASE were searched for relevant papers from 2005 onwards. The search was restricted to articles published in English. Search terms were not reported. It appeared that eligible studies published from 1966 to 2005 were identified from a previous meta-analysis.

Study selection
Randomised controlled trials (RCTs) that involved a comparison of aspirin for the primary prevention of cardiovascular disease versus open control or placebo alone were eligible for inclusion. Outcome data had to be available on myocardial infarction, stroke and cardiovascular death.

Mean patient age ranged from 53 to 78 years. The percentage of females ranged from zero to 100%. The percentage of participants with diabetes ranged from 2% to 100%. The percentage of smokers ranged from 11% to 65%. Aspirin dose ranged from 100mg every other day to 500mg daily. The primary outcome was a major cardiovascular event composite of non-fatal myocardial infarction, non-fatal stroke or cardiovascular death.

The authors did not state how many reviewers selected studies for inclusion.

Assessment of study quality
The authors did not state that they assessed study quality.

Data extraction
Data were extracted from each study to calculate relative risk (RR), absolute risk reduction (ARR), number needed to treat (NNT) and number needed to harm (NNH); these were estimated with 95% confidence intervals (CIs).

The authors did not state how many reviewers extracted data.

Methods of synthesis
The studies were synthesised via meta-analysis using a random-effects model. Heterogeneity was assessed using the Q test and I² statistic. Additionally, data were analysed using a fixed-effect model. Sensitivity analyses removed each study from the analysis one at a time. Subgroup analyses excluded studies that recruited only participants with diabetes, studies that recruited participants with subclinical atherosclerosis and studies that used extended or controlled release aspirin. A linear meta-regression of the log-transformed relative risk estimates was used to evaluate potential covariates (year of publication, baseline cardiovascular risk, mean age, sex and dose of aspirin) of the calculated effects. Publication bias was assessed using a funnel plot.

Results of the review
Nine RCTs were included in this review (102,621 participants). Sample sizes ranged from 1,276 to 39,876. Follow-up ranged from 4.4 to 10.1 years.
A significant difference favoured aspirin for major cardiovascular events (RR 0.90, 95% CI 0.85 to 0.96; nine studies). Over a mean follow-up period of 6.9 years this related to an ARR of 0.39% (95% CI 0.18% to 0.61%) and corresponded to a NNT of 253 (95% CI 163 to 568) to prevent one major cardiovascular event.

A significant difference favoured control treatment for haemorrhagic stroke (RR 1.35, 95% CI 1.01 to 1.81; nine studies). Over a mean follow-up period of 6.9 years this related to an absolute risk increase of 0.06% (95% CI 0.003% to 0.126%) and corresponded to a NNH of 1,560 (95% CI 764 to 33,333) to cause one haemorrhagic stroke.

A significant difference favoured control treatment for major bleeding (RR 1.62, 95% CI 1.31 to 2.00; nine studies). Over a mean follow-up period of 6.9 years this related to an absolute risk increase of 0.38% (95% CI 0.21% to 0.55%) and corresponded to a NNH of 261 (95% CI 182 to 476) to cause one major bleeding event.

There was no significant difference in the rate of fatal and nonfatal myocardial infarction, nonfatal myocardial infarction, fatal and nonfatal stroke, nonfatal stroke (eight studies), death, ischaemic stroke and cardiovascular death. For myocardial infarction there was significant heterogeneity of 63%. No significant heterogeneity was found for any other analysis. Meta-regression did not reveal relationships between any of the investigated covariates and the effect of aspirin on major cardiovascular events and major bleeding.

No dose or formulation effects of aspirin on major cardiovascular events were found.

The relative risk of major cardiovascular events was similar across all sensitivity and subgroup analyses.

**Authors' conclusions**
Aspirin reduced major cardiovascular events by about 10% but increased the incidence of major bleeding in individuals without clinical cardiovascular disease. Therefore, the initiation of preventive aspirin therapy requires careful consideration of risks and benefits by physicians.

**CRD commentary**
The review question and inclusion criteria were clear. No details were reported for the search for trials published prior to 2005. Relevant databases were searched from 2005 onward. Search terms were not reported, so it was unclear how comprehensive the search strategy was. The search was restricted to trials published in English and no searching for unpublished data was reported, so language bias may have been introduced and some relevant studies may have been missed. It was unclear whether appropriate methods such as independent duplicate processes were used to minimise the possibility of reviewer error and bias during study selection and data extraction.

No formal quality assessment of the included trials was reported, so the reliability of the trials could not be assessed. Appropriate trial details were reported. Control treatment details for individual studies were not provided and it appeared that open-label trials were eligible. Data were synthesised appropriately. Differences between trials in participant characteristics and aspirin dose, preparation and frequency of administration were addressed in subgroup analyses. Suitable measures were used to assess heterogeneity.

A limited search, no quality assessment and a lack of reporting of control treatment and review process details mean that the authors' conclusions may not be reliable.

**Implications of the review for practice and research**
**Practice:** The authors recommended that clinicians consider their findings when making decisions about primary preventive therapies (relative to drugs with unequivocal benefit such as statins and blood pressure medications).

**Research:** The authors did not state any implications for research.

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**Bibliographic details**
Record Status
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.