Aspirin and risk of hemorrhagic stroke: a meta-analysis of randomized controlled trials
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Authors' objectives
To estimate the risk of haemorrhagic stroke associated with aspirin treatment.

Searching
MEDLINE was searched from 1966 through June 1997 for articles published in the English language using the keywords 'aspirin' and 'cerebrovascular disorders', as well as 'stroke'. Articles retrieved were those identified in the database as clinical trials on human subjects. A manual search was preformed using the authors' reference files and reference lists from original communications and review articles.

Study selection

Study designs of evaluations included in the review
Studies were included if they fulfilled the following criteria: random allocation to aspirin or concurrent control group; and information available regarding the occurrence of stroke subtypes during follow-up. Study duration ranged from 1 week (though this appears to contradict the inclusion criteria) to 72 weeks. The major reasons for exclusion are stated.

Specific interventions included in the review
The administration of oral aspirin in doses ranging from 75 mg to 1500 mg per day for at least one month was studied. Interventions other than the use of aspirin were excluded.

Participants included in the review
Participants included healthy patients and those with the following pre-existing diseases: transient ischaemic attacks; myocardial infarction; cerebral ischaemia; atrial fibrillation; stable angina; minor ischaemic stroke; and carotid stenosis. Other characteristics of patients in trials included: mean age range 53 years to 75 years; % male range 47% to 100%; % white from 75% to 100%; % hypertensive from 10% to 64%; % hyperlipidaemia from 2% to 50% (included several trials where the incidence was not stated); and % smoking from 11% to 73%.

Outcomes assessed in the review
The primary outcome was the incidence of stroke sub-type. Other outcomes included the incidence of total stroke and myocardial infarction, cardiovascular disease mortality, and all-cause mortality during treatment.

How were decisions on the relevance of primary studies made?
Two authors independently reviewed identified studies with disagreements being resolved by the other authors.

Assessment of study quality
Validity criteria included degree of blinding, sample size and study duration. Data on validity criteria was extracted using a standardised protocol and reporting form with disagreements being resolved by consensus.

Data extraction
The following data were extracted in duplicate using a standardised protocol and reporting form with disagreements being resolved by consensus: first author; year of publication; country of origin; sample size; mean age, age range, race and sex distribution of subjects; presence of pre-existing disease and prevalence of hypertension, hyperlipidaemia, and cigarette smoking; design details including degree of blinding (open, single or double) and type of control treatment (placebo or no treatment); dosage of aspirin; and study duration. Absolute risk (AR) and relative risk (RR) with 95% confidence limits were calculated for each study.
Methods of synthesis
How were the studies combined?
A pooled AR was estimated with each study being weighted by its sample size. A pooled RR was estimated from the log transformed RR of the individual studies with weighting by the reciprocal of the variance of the logarithmic RR using a fixed-effect model.

How were differences between studies investigated?
Heterogeneity across AR was tested using the Woolf chi-squared statistic. Where heterogeneity was detected, a random-effects model was used to calculate the pooled estimates. Pre-stated subgroup analysis were conducted to explore the influence of the following covariables on the results: health status of subject (pre-existing disease vs no pre-existing disease); age (64 years vs equal to or greater than 64 years); sample size (<1120 subjects vs equal to or greater than 1120 subjects); dosage of aspirin (< 413 mg/day vs equal to or greater than 413 mg/day); study duration (< 28 days vs equal to or greater than 28 days); and date of publication (< 1988 vs equal to or greater than 1989).

Results of the review
Sixteen trials were included (55,462 participants).

Assessment of publication bias: Kendall's tau correlation coefficient between sample size and standardised AR = 0.03 (P = 0.90). Kendall's tau correlation between sample size and standardised logarithmic RR = 0.37 (P = 0.05). Plot of sample size vs In (RR) showed significant correlation was due to 2 trials with large sample size and moderately large RR. AR per 10,000 persons associated with aspirin treatment: No significant heterogeneity among studies (P = 0.99).

All cause mortality: -120 (95% CI: -77, -162: P < 0.001). Cardiovascular mortality: -97 (95% CI: -59, -135: P < 0.001).

Total myocardial infarction: -137 (95% CI: -107, -167: P < 0.001).

Fatal myocardial infarction: -36 (95% CI: -16, -55: P < 0.001).

Total stroke: -31 (95% CI: -5, -57: P = 0.02).

Fatal stroke: 4 (95% CI: -8, 16: P < 0.5).

Haemorrhagic stroke: 12 (95% CI: 5, 20: P < 0.001).

Ischaemic stroke: -39 (95% CI: -17, -61: P < 0.001).

AR of haemorrhagic stroke in sub-groups with P value from Woolf's chi-squared test: Pre-existing disease (14 trials) AR = 16 (95% CI: 5, 26) vs no pre-existing disease (2 trials) AR = 9 (95% CI: -2, 19). P = 0.36. Age (8 trials): < 64 years AR = 9 (95% CI: 2, 16) vs age equal to or greater than 64 years AR = 34 (95% CI: 1, 66), P = 0.15. Sample size (8 trials): < 1120 subjects AR = 12 (95% CI: -37, 62) vs equal to or greater than 1120 subjects 12 (95% CI: 5, 20), P = 0.98. Dosage of aspirin (8 trials) < 413 mg/day AR = 11 (95% CI: 4, 18) vs equal to or greater than 413 mg/day AR = 19 (95% CI: -8, 46), P = 0.59.

Study duration (8 trials): < 28 days AR = 6 (95% CI: -2, 14) vs equal to or greater than 28 days AR = 16 (95% CI: 5, 28), P = 0.14.

RR of aspirin use: No significant heterogeneity among studies (P = 0.99)

All cause mortality: 0.85 (95% CI: 0.80, 0.90: P < 0.001).

Cardiovascular mortality: 0.84 (95% CI: 0.79, 0.90: P < 0.001).

Total myocardial infarction: 0.68 (95% CI: 0.62, 0.74: P < 0.001).
Fatal myocardial infarction: 0.78 (95% CI: 0.68, 0.90; P < 0.001).

Total stroke: 0.88 (95% CI: 0.76, 1.02; P = 0.08). Fatal stroke: 1.07 (95% CI: 0.85, 1.35; P = 0.60). Date of publication (8 trials): < 1988 RR = 1.37 (95% CI: 0.72, 2.61) vs equal to or greater than 1989 AR = 2.21 (95% CI: 1.33, 3.66).

Authors’ conclusions
Aspirin therapy increases the risks of haemorrhagic stroke. However, the overall benefit of aspirin use on myocardial infarction and ischaemic stroke may outweigh its adverse effects on risk of haemorrhagic stroke in most populations.

CRD commentary
The aims and inclusion criteria were clearly stated. Details were given of methods used to select primary studies and extract data with reasons given for the exclusion of identified studies. Some aspects of validity were assessed. Heterogeneity was assessed and investigation of the influence of various factors determined a priori was investigated. Results were clearly presented. The authors acknowledge the possibility of publication bias resulting from limiting identified studies to those published in the English language.

The authors conclusions are supported by the evidence.

Implications of the review for practice and research
Practice: The authors consider that aspirin treatment may not be recommended for reducing the incidence of myocardial infarction in those aged under 50 years of age who are at high risk of this event since the benefits have not been well documented.

Research: The authors consider that subsequent studies should investigate the risk-benefit ratio of aspirin treatment for prevention of cardiovascular disease in populations with varying risks of haemorrhagic stroke, ischaemic stroke, and myocardial infarction.

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Other publications of related interest
These additional published commentaries may also be of interest. Gubitz G. Benefits of aspirin on myocardial infarction and ischemic stroke outweigh its adverse effects on risk of hemorrhagic stoke. Evidence-baed healthcare 1999:3;72-73. Aspirin and risk of hemorrhagic stroke. [series of letters].JAMA 1999:282(8);731-733.

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