Risk of gastrointestinal haemorrhage with long term use of aspirin: meta-analysis

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Authors' objectives

To assess the incidence of gastrointestinal haemorrhage associated with long-term aspirin therapy, and to determine the effect of dose reduction and formulation on the incidence of such haemorrhage.

Searching

Two authors independently searched MEDLINE and EMBASE from 1990 to 1999 using the free text terms: 'aspirin' or 'acetylsalicylic*', or 'salicylic*'. The authors also selected trials from a list of 200 antiplatelet studies identified in a previous systematic review (see Other Publications of Related Interest), and manually checked the reference lists of retrieved studies. No language restrictions were reported.

Study selection

Study designs of evaluations included in the review

Randomised controlled trials (RCTs) with a duration of at least one year and a minimum of 50 participants in each study arm. Abstracts, review articles, case reports, clinical observations and unpublished data were not included.

Specific interventions included in the review

Comparisons of long-term aspirin therapy (modified release or standard formulations) with placebo or no treatment.

Participants included in the review

Patients taking aspirin for the prevention of cardiovascular disease, either as prophylaxis in healthy persons or secondary prevention. Studies assessing the effects of aspirin in special group, such as pregnant women, children and patients with pre-existing platelet disorders, were excluded. All trials included in the review had excluded patients with a history of peptic ulcer, gastrointestinal haemorrhage, or other contraindication to aspirin.

Outcomes assessed in the review

The incidence of gastrointestinal haemorrhage was assessed.

How were decisions on the relevance of primary studies made?

Two authors independently reviewed the papers for inclusion.

Assessment of study quality

The authors evaluated the studies for participants, blinding, type of control, assessment of compliance, and duration of treatment and follow-up. Validity was not assessed, but the inclusion criteria specifically excluded quasi-randomised studies and reviewed a minimum of 50 patients per treatment group. Two authors independently quality assessed the included papers.

Data extraction

Two authors independently performed the data extraction.

Data were extracted for the categories of: study identification, year of publication, aspirin formulation, dose, duration of treatment and indication, age of participants (mean or range), percentage male (%), definition of haemorrhage used, loss to follow-up (%), and concealment of allocation.

Data from the original studies and additional tables, graphs and references, are available on the BMJ website. See Web Address at end of abstract.

Methods of synthesis

How were the studies combined?

The studies were pooled using the Peto odds ratios (ORs) with 95% confidence intervals (CIs). The authors also calculated the number-needed-to-harm (NNH). Both fixed-effect and random-effects models were calculated; results are reported using the fixed-effect model.

How were differences between studies investigated?

Heterogeneity was assessed using the chi-squared statistic.

Meta-regression was also performed using a random-effects model to assess whether there was a linear relationship between daily dose of aspirin and risk of gastrointestinal haemorrhage. A sensitivity analysis was also performed to investigate whether the two largest trials included in the review unduly influenced the results.

Results of the review

Twenty-four RCTs with 65,987 participants were included.

All 24 trials were double-blind and placebo-controlled. Fourteen trials had sufficient data to suggest that adequate concealment had taken place; in the other trials this was unclear. The number of patients lost to follow-up was reported in 16 trials, only one of which failed to achieve over 90% follow-up.

Gastrointestinal haemorrhage occurred in 2.47% of patients taking aspirin compared with 1.42% taking placebo (OR 1.68, 95% CI: 1.51, 1.88, p<0.0001), which was statistically significant. The NNH was 106 (95% CI: 82, 140), based on an average of 28 months therapy.

At doses below 163 mg/day, gastrointestinal haemorrhage occurred in 2.30% of patients taking aspirin, compared with 1.45% taking placebo (OR 1.59, 95% CI: 1.40, 1.81), which was statistically significant. Meta-regression showed no relation between gastrointestinal haemorrhage and dose (OR 1.015, 95% CI: 0.984, 1.047, p=0.3, per 100 mg reduction of dose).

For modified release formulations of aspirin (5 trials with 4,298 participants), the OR was 1.93 (95% CI: 1.15, 3.23).

Omitting the two largest trials did not significantly change the results.

The funnel plot indicated that additional negative studies were not found.

Authors' conclusions

The authors state the long-term therapy with aspirin is associated with a statistically-significant increase in the incidence of gastrointestinal haemorrhage. There is no evidence to suggest that reducing the dose or using modified release formulations would reduce the incidence of gastrointestinal haemorrhage.

CRD commentary

This is a good review. The authors have clearly stated the research question and inclusion and exclusion criteria. The literature search appears to be thorough, although the authors omitted unpublished literature. A funnel plot was performed which may indicate that additional negative studies were not found. All processes of the review were performed independently by two reviewers.

Most of the data extraction is reported in tables which are stored on the journal's website. The studies are also discussed in the text of the review. The studies were combined in a statistical meta-analysis using both fixed-effect and random-effects models. There were tests for heterogeneity, and further subgroup analyses and meta-regression were performed to investigate the robustness of the results. The authors' conclusions appear to follow from the results.

Implications of the review for practice and research

Practice: The authors state that they believe their findings are relevant to everyday practice.

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

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Other publications of related interest
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