Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials

Antithrombotic Trialists’ (ATT) Collaboration

CRD summary
This review concluded that the use of aspirin for the prevention of cardiac events needed to be weighed against an increase in major bleeds. There was no justification in advocating the routine use of aspirin. Despite some concerns, the analyses contained a large number of people and the results seemed consistent. The conservative conclusions were likely to be reliable.

Authors’ objectives
To evaluate the prevention of cardiovascular events and incidence of major bleeding associated with the use of low-dose aspirin in patients with or without a prior history of vascular disease.

Searching
MEDLINE, EMBASE, Derwent, SciSearch and BIOSIS Previews were searched; search terms and dates were not reported. Relevant journals, abstracts and conference proceedings were handsearched. The reference lists of included studies and reviews were scanned and colleagues contacted, including representatives from pharmaceutical companies. (This information was supplied on request by the lead author.)

Study selection
Randomised trials comparing aspirin with no aspirin where no other antiplatelet drug was administered were eligible for inclusion. Primary prevention trials had to recruit at least 1,000 non-diabetic patients without a history of occlusive disease and provide at least two years scheduled treatment. Secondary prevention trials had to include patients with previous myocardial infarction, stroke or trans-ischaemic attacks. The primary outcomes were myocardial infarction, stroke, trans-ischaemic attacks, all-cause and cardiovascular death, and major extracranial bleeding. Where reported, participants were mostly men. Mean age ranged from 53 to 68 years. The proportion with diabetes ranged from two per cent to 23 per cent, hypertension 10 per cent to 100 per cent and vascular disease less than one per cent to eight per cent in primary prevention trials and 100 per cent in secondary prevention trials. Aspirin dose ranged from 100 mg on alternate days to 500 mg daily. The authors did not state how many reviewers performed the study selection.

Assessment of study quality
The authors did not report any validation or checking of the data used in the analyses.

Data extraction
Individual patient data were obtained for the incidence of the outcomes of interest; rate ratios of yearly events for aspirin/no aspirin and 99% confidence intervals (CI) were calculated for each study. For trials with unequal randomisation, the control group was multiplied to be comparable in size to the intervention group and control totals were adjusted.

Methods of synthesis
Pooled rate ratios with 95% CI were calculated (the method used was not reported). The X² test was used to test heterogeneity. Poisson regression stratified by trial was used to identify risk factors for cardiovascular outcomes and major bleeding, and to predict five-year absolute effects of aspirin in patients with different risks of coronary heart disease.

Results of the review
Twenty two trials met the inclusion criteria (n=112,485; range 60 to 39,876): six primary prevention trials (n=95,456) and 16 secondary prevention trials (n=17,029).

In the six primary prevention trials, the rate of serious vascular events was 0.51 per cent per year with aspirin and 0.57 per cent per year without aspirin, representing a statistically significant 12 per cent proportional reduction in occurrence
with aspirin (rate ratio 0.88, 95% CI 0.82, 0.94). There was an 18 per cent proportional decrease in the incidence of major coronary events (rate ratio 0.82, 95% CI 0.75, 0.90), but no significant difference in the overall incidence of stroke (rate ratio 0.95, 95% CI 0.85, 1.06). There was no significant effect of aspirin on mortality.

Extracranial bleeding was significantly increased with aspirin (rate ratio 1.54, 95% CI 1.30, 1.82). No statistically significant heterogeneity was observed. The secondary prevention trials showed very similar rate ratios for patients with a history of vascular disease to those found in the primary prevention trials.

Results for a large number of subgroup analyses, including separate analyses for different types of coronary events and stroke, and differences in baseline characteristics, were presented. Hypothetical calculations for five-year predictive effects of aspirin were also presented.

**Authors' conclusions**

In primary prevention without previous disease, aspirin is of uncertain net value as the reduction in occlusive events needs to be weighed against any increase in major bleeds.

**CRD commentary**

The authors addressed a clear research question supported by appropriate inclusion criteria. The authors acknowledged that some primary prevention trials contained patients with a history of coronary events and, therefore, did not meet the inclusion criteria. The authors searched several relevant databases and made an attempt to locate unpublished data. It was unclear whether language restrictions were applied, so language bias may be present. The authors did not state whether study selection was conducted in duplicate, or whether the accuracy and integrity of the data used in the individual patient data analyses were checked or validated in any way. Therefore, error and bias can not be ruled out. Despite these concerns regarding the conduct of the review, the analyses contained a large number of people, the results were seemingly consistent and the conservative conclusions were likely to be reliable.

**Implications of the review for practice and research**

Practice: The authors stated that the results do not justify general guidelines advocating the routine use of aspirin to all apparently healthy individuals above a moderate level of risk of coronary heart disease.

Research: The authors did not state implications for research.

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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.