Effect of aspirin on vascular and nonvascular outcomes: meta-analysis of randomized controlled trials

CRD summary
The authors concluded that aspirin as primary prevention reduced risk of non-fatal myocardial infarction, but not the risk of cardiovascular or cancer mortality; bleeding increased with aspirin. Further research was needed and guidelines should be reappraised. The authors’ conclusions reflect the evidence, but the limitations of the review should be borne in mind. Recommendations for further research seem appropriate.

Authors' objectives
To assess the effects of aspirin for the primary prevention of vascular and non-vascular outcomes.

Searching
PubMed and the Cochrane Library were searched from inception to June 2011 without language restrictions; search terms were reported. Reference lists of retrieved articles were searched manually.

Study selection
Randomised placebo-controlled trials (RCTs) that assessed the effects of aspirin were eligible for inclusion if they reported vascular and non-vascular outcomes for at least one year follow-up. Eligible trials were required to include at least 1,000 patients from primary prevention settings. Patients with a history of peripheral arterial disease were eligible for inclusion if they had been asymptomatic and had no history of coronary vascular disease.

Primary outcomes were total coronary heart disease and total cancer mortality, and bleeding events (including ‘non-trivial’ bleeding events, as defined in the review). Secondary outcomes were vascular disease, total coronary vascular disease, cause-specific death, and all-cause mortality. Non-vascular outcomes were obtained from secondary data.

Included trials were conducted in the USA, UK, Italy, and Japan from 1988 to 2010. The mean age of included patients was 57.3 years (53.8 to 64.5 years). The mean proportion of men was 46%. Eight percent of patients had diabetes (range 2 to 100%) and 16% smoked. Aspirin doses ranged from 75 to 500mg daily or 100 to 325mg on alternative days. Some trials allowed concomitant treatment (agents other than anti-platelets).

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

Assessment of study quality
The authors assessed trial quality according to the Delphi system, which included criteria on randomisation, allocation concealment, similarity of randomised groups at baseline, a priori reporting of inclusion criteria, blinding, use of intention-to-treat analyses, and reporting of main outcome data.

The authors did not state how many reviewers performed the quality assessment.

Data extraction
Three reviewers extracted the number of vascular and non-vascular outcome events to calculate unadjusted odds ratios (ORs) and associated 95% confidence intervals (CIs). Where no events were observed, 0.5 was added to treatment arms. Where trials reported combined clinical end points and at least one additional endpoint (such as the total coronary heart disease and either non-fatal myocardial infarction or fatal coronary heart disease, but not both), the number of events for the missing end points were calculated, if these events did not overlap. Crude event rates were calculated using data on number of events and mean (or median) follow-up time. Discrepancies were resolved through discussion with additional reviewers.

Methods of synthesis
Odds ratios and 95% confidence intervals were combined using a random-effects model. The number needed to treat
(NNT) and number needed to harm (NNH) were calculated to represent the number of patients needing to be treated with aspirin for six years to avoid one event.

Heterogeneity was assessed using $I^2$. Heterogeneity was explored by subgroup analyses (period of publication, number of patients per trial, number of events per trial, average daily dose of aspirin, aspirin regimen, concomitant treatment) and meta-regression. Sensitivity analyses were also performed to exclude non-Western populations, exclude trials that recruited people with diabetes only or peripheral arterial disease only, excluded cohorts of healthcare professionals, and use fixed-effect meta-analysis instead of random-effects meta-analysis).

Publication bias was assessed using funnel plots and the Egger test.

**Results of the review**

Nine RCTs (n=102,621 patients) were included in the review. Five trials met all quality assessment criteria, two did not use intention-to-treat analyses, and two were not blind to care providers and participants. The mean follow-up duration was six years (range 3.8 to 10.1 years).

Aspirin significantly reduced the risk of total cardiovascular events (OR 0.90, 95% CI 0.85 to 0.96; nine RCTs; $I^2=0$%), mainly resulting from a significant reduction in the risk of nonfatal myocardial infarction (OR 0.80, 95% CI 0.67 to 0.96; nine RCTs; $I^2=62.1$%). No other events were significantly different between aspirin and control groups.

There was an increased risk of total bleeding events (OR 1.70, 95% CI 1.17 to 2.46; nine RCTs; $I^2=98$%) and non-trivial bleeding events (OR 1.31, 95% CI 1.14 to 1.50; nine RCTs, $I^2=65.7$%) in patients who received aspirin. The greatest risk of non-trivial bleed was for patients who received daily aspirin (OR 1.48, 95% CI 1.17 to 1.86).

The number of patients needed to treat to avoid one nonfatal myocardial infarction event was 162. The number needed to treat was 120 to avoid one coronary vascular disease event. The number needed to treat for non-vascular mortality was 292. At least one non-trivial bleeding event was caused for every 73 patients treated with aspirin.

Findings from subgroup and sensitivity analyses were reported in the review.

There was no evidence of significant publication bias for the main outcomes.

**Authors’ conclusions**

Despite significant reductions in nonfatal myocardial infarction, use of aspirin in primary prevention in patients without prior coronary vascular disease did not result in reductions in cardiovascular death or cancer mortality. Clinically important bleeding events were increased with aspirin, suggesting that further research was needed and guidelines should be reappraised.

**CRD commentary**

The review question and supporting inclusion criteria were clearly stated. The literature search reduced the potential for language bias, but did not appear to include a search for unpublished data on the primary outcomes. Publication bias was formally assessed and no evidence of significant bias was found. However, less than 10 trials were included, which meant that the findings should be interpreted with some caution. It was unclear whether quality assessment and study screening were performed in duplicate. [A: The authors reported that study selection was performed in duplicate, but only one reviewer performed the quality assessment, which meant that reviewer error and bias could not be ruled out.]

Appropriate criteria were used to assess trial quality; trials appeared to be of generally high quality. There was significant statistical heterogeneity for some outcomes and attempts were made to explore this further. The authors acknowledged certain limitations with the review, such as heterogeneity, use of secondary data to assess certain outcomes, and the uncertain generalisability of the findings to non-Western populations.

The authors’ conclusions reflect the evidence. Given the methodological issues highlighted in the review, the authors’ recommendations for further research and reassessment of guidelines seem appropriate.

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

**Practice:** The authors stated that patients and health professionals should carefully consider the benefits and harms of
daily aspirin treatment in primary prevention. They also stated that it may be time to reassess existing guidelines for aspirin use in primary prevention.

**Research:** The authors stated that future research should assess the impact of low dose, alternate-day aspirin treatment on both vascular and non-vascular outcomes, particularly in patients with favourable risk to benefit ratio for aspirin use and/or involving more high-risk patients. Longer term studies are also needed to assess the effect of aspirin in cancer prevention.

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