Low-dose aspirin in patients with stable cardiovascular disease: a meta-analysis
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CRD summary
The authors concluded that low-dose aspirin therapy reduced the incidence of adverse cardiovascular events and all-cause mortality in patients with stable cardiovascular disease, but increased the risk of severe bleeding. The authors' conclusion reflected the evidence presented, but poor reporting of the review methods and potential for language bias made the reliability of the authors' conclusion unclear.

Authors' objectives
To evaluate the benefit and risk of low-dose aspirin in patients with stable cardiovascular disease.

Searching
MEDLINE was searched from 1966 to March 2006. Search terms were reported. Reference lists of review articles were searched and major scientific meetings were monitored for additional studies.

Study selection
Randomised controlled trials (RCTs) that compared aspirin treatment to a control group in patients with stable cardiovascular disease who had been blindly assigned to treatment were eligible for inclusion. Studies that included patients during the acute presentation of a myocardial infarction, stroke/transient ischaemic attack or unstable angina were excluded. Outcomes included cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, all cardiovascular events and mortality.

Most of the included studies included patients following cerebrovascular events. Studies with patients who enrolled following a myocardial infarction and chronic stable angina were included. All studies were undertaken between 1974 and 1996 in Europe. Aspirin dose in the included studies ranged from 50mg/day to 300mg/day; all control groups were placebo. Mean age ranged from 55 to 67 years of age. The proportion of females ranged from zero to 48%. The proportion of smokers ranged from 16% to 76%. The proportion of patients with hyperlipidaemia ranged from 23% to 37%. The proportion of patients with diabetes ranged from 4% to 15%. The proportion of patients with claudication ranged from 8% to 22%. The proportion of patients with hypertension ranged from 36% to 61%.

The authors did not state how many reviewers performed the study selection.

Assessment of study quality
Study quality was assessed using the criteria: adequate blinding of randomisation; completeness of follow-up; and objectivity of outcome assessments.

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

Data extraction
Odds ratios (OR) and 95% confidence intervals (CI) were extracted.

The authors did not state how many reviewers performed data extraction.

Methods of synthesis
Studies were combined to calculate pooled odds ratios and 95% CI using a random-effects model. Numbers-needed-to-treat (NNT) or numbers-needed-to-harm (NNH) were calculated. Heterogeneity was assessed using the Q statistic. Subgroup analysis investigated outcomes by: aspirin dosage (lower dose 50 to 100mg versus higher dose 300mg); studies in which patients were enrolled for cerebrovascular events versus prior myocardial infarction or stable angina; and length of follow-up (up to two years versus at least two years). Intention-to-treat data were used. Publication bias...
was assessed through funnel plots.

Results of the review
Six RCTs (n=9,853) were included. All studies generated randomised treatment allocation sequences. Five trials used a fixed aspirin dose. Four trials had a blinded outcome assessment. Five trials reported more than 99% follow-up. Four trials were completely or partially funded by pharmaceutical companies. Duration of follow-up ranged from 13 to 50 months. There was no evidence of publication bias.

Aspirin therapy resulted in significant reductions for: all cardiovascular events combined (OR 0.79, 95% CI 0.72 to 0.88, NNT=30), risk of nonfatal myocardial infarction (OR 0.74, 95% CI 0.60 to 0.91, NNT=83), risk of stroke (OR 0.75, 95% CI 0.65 to 0.87, NNT=40) and risk of all-cause mortality (OR 0.87, 95% CI, 0.76 to 0.98, NNT=71). Patients treated with aspirin were significantly more likely to experience severe bleeding (OR 2.2, 95% CI 1.4 to 3.4, NNH=111).

Neither aspirin dose nor length of follow-up affected any clinical outcome. Patients with ischaemic heart disease showed significant reductions in risk of major cardiovascular events, all-cause mortality and myocardial infarction (two studies). Studies in which patients were enrolled following cerebrovascular events exhibited a significant reduction in risk of major cardiovascular events (four studies).

There was no evidence of statistical heterogeneity for any comparisons.

Authors’ conclusions
In patients with stable cardiovascular disease, low-dose aspirin therapy reduced the incidence of adverse cardiovascular events and all-cause mortality; it increased the risk of severe bleeding.

CRD commentary
The review question and the inclusion criteria were clear. The authors undertook a limited search for published and unpublished studies. It was unclear whether language restrictions were applied and language bias may have been present. Publication bias was considered to be absent; with so few studies this was unsurprising. The authors did not report whether attempts to minimise error and bias were undertaken for study selection, data extraction and quality assessment. An appropriate quality assessment was reported; all studies were of high quality. Results were pooled using meta-analysis. Heterogeneity was assessed. Subgroup analyses were undertaken. As acknowledged by the authors, there were issues about generalising the findings to present-day patients with cardiovascular disease and to settings outside of Europe or in younger age groups; all studies in the review were over 10 years old.

The authors’ conclusion reflected the evidence presented, but poor reporting of the review methods and potential for language bias made the reliability of the authors’ conclusion unclear.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that research should focus upon the optimal dose of aspirin for each clinical setting for long-term reduction in cardiovascular disease and mortality; additional consideration should be given to appropriate patient selection and management options to reduce the bleeding risk.

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