Low doses of acetylsalicylic acid increase risk of gastrointestinal bleeding in a meta-analysis

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CRD summary
This review found that treatment with aspirin increased the risk of gastrointestinal bleeding and this risk increased with the accompanying use of clopidogrel and anti-coagulant therapies. The lack of information on risk of bias in individual studies means the reliability of authors' conclusions is uncertain.

Authors' objectives
To evaluate the risk of all-cause mortality and gastrointestinal bleeding events in patients treated with low-dose aspirin alone or in combination with clopidogrel, anticoagulants or proton pump inhibitors.

Searching
PubMed, EMBASE, AMED, CINAHL, TOXNET, the Cochrane Central Register of Controlled Trials (CENTRAL; gastrointestinal disease group), PsyCINFO, the Web of Science, Science Direct and IngentaConnect were searched from inception to October 2010; search terms were reported. The references of published systematic reviews were searched for additional studies. There were no language restrictions.

Study selection
Randomised controlled trials (RCTs) that evaluated the therapeutic role or safety of low-dose aspirin in patients who were administered this treatment on a daily basis for at least one month either alone or in combination with clopidogrel, the anticoagulants warfarin or coumadins, or proton pump inhibitors were eligible for inclusion. An additional criterion for inclusion was that the comparators were either no low-dose aspirin or placebo. Active controlled trials pharmacokinetic studies and studies that reported on surrogate markers for safety were excluded from the review.

Although there was some variation across the patient populations, approximately half of the studies were of patients with cardiovascular disease. The mean ages of the patients ranged from 54-79 years, and in most studies, the majority of patients were males. Low doses of aspirin were defined as doses ranging from 75-325mg/day, and were administered alone, or in combination with clopidogrel, anticoagulants or proton-pump inhibitors. Some studies used concomitant medications in both groups which were nutritional supplements, anticoagulants, felodipine, fluindione, heparin, simvastatin and sotalol. The outcomes evaluated were all-cause mortality, bleeding events including gastrointestinal bleeding and fatal bleeding and dyspepsia.

Two reviewers independently performed the study selection.

Assessment of study quality
Methodological quality was assessed in terms of evaluating sequence generation, allocation concealment, blinding status, use of intention-to-treat analyses and losses to follow-up. Losses to follow-up of more than 20% were considered important by the reviewers.

Two reviewers independently assessed methodological quality, any differences between the reviewers were resolved by consensus.

Data extraction
Intention-to-treat data were extracted to calculate odds ratios (OR) or relative risks (RR) and 95% confidence intervals (CI) for the outcomes.

Two reviewers independently extracted data, any discrepancies between the reviewers were resolved by consensus.

Methods of synthesis
Pooled odds ratios or relative risks with 95% confidence intervals were calculated using a DerSimonian and Laird random-effects model. Statistical heterogeneity was evaluated using $I^2$. The incidence rate difference (IRD) per person years for the outcomes was also calculated. Numbers-needed-to-harm for each study drug combination were also
calculated. Random effects regression analyses were undertaken to assess the impact of co-administered drug, type of control (placebo compared to standard care), loss to follow-up evaluation and the duration of the trial. Subgroup analyses of specific at-risk populations were conducted for the outcome of major bleeding. Adjusted indirect comparisons for any bleeds and major gastrointestinal bleeding between clopidogrel plus low-dose aspirin and warfarin plus low-dose aspirin were applied.

**Results of the review**

Sixty-one RCTs (203,355 participants) were included in the review.

**Low-dose aspirin-alone (35 trials, 87,581 participants, 338,735 person years of follow-up):** Twenty-one studies reported adequate sequence generation, allocation concealment was reported in 18 RCTs and all RCTs used intention-to-treat analyses. Blinding was not described in 13 RCTs and there were inadequately reported losses to follow-up in two trials.

A protective effect for all-cause mortality was observed with low-dose aspirin treatment (RR 0.93, 95% CI 0.87 to 0.99; I²=11%; 32 RCTs) largely because of effects in secondary prevention populations. Treatment with low-dose aspirin was associated with increased incidence of: major gastrointestinal bleeding, (OR 1.55, 95% CI 1.27 to 1.90; I²=14%; 28 RCTs), numbers-needed-to-harm 500 (95% CI 334 to 1,000), IRD 1.1 (95% CI 0.4 to 1.7 per 1,000 person-years); any gastrointestinal bleeding (OR 1.31, 95% CI 1.21 to 1.42; I²=48%), numbers-needed-to-harm 166 (95% CI 125 to 250), IRD 2.1,(95% CI 0 to 4.7 per 1,000 person years); any bleeding (OR 1.54, 95% CI 1.36 to 1.74; I²=62%), numbers-needed-to-harm 71 (95% CI 63 to 90), IRD 8.1 (95% CI 4.0 to 12.2 per 1,000 person years).

There were no differences between low-dose aspirin groups and no low-dose aspirin/placebo groups for fatal bleeding or dyspepsia. Meta-regression analyses showed that the risks of major gastrointestinal bleeding and any gastrointestinal bleeding were higher for patients with histories of gastrointestinal bleeds and in studies of longer duration of follow-up.

**Low-dose aspirin and clopidogrel (five trials, 81,765 participants):** The reviewers stated that all studies reported methodologic issues. There were significant increases in major gastrointestinal bleeding (OR 1.86, 95% CI 1.49 to 2.31, IRD 8.9 95% CI 0 to 10 per 1,000 person-years) associated with dual therapy and in any bleeding (OR 1.46, 95% CI 1.15 to 1.86; I²=95%), IRD 22 (95% CI 2 to 43 per 1,000 person-years) compared to low-dose aspirin. There were no differences between groups for fatal bleeding, mortality, and fatal haemorrhagic strokes.

**Low-dose aspirin and anticoagulants (18 RCTs, 9,875 participants, 64,481.5 person years of follow-up):** Randomisation was reported in nine RCTs, allocation concealment was described in seven RCTs, and five trials reported blinding measures. Seventeen RCTs reported losses to follow-up and all trials used intention-to-treat analyses. There were significantly increased risks in: major gastrointestinal bleeding observed (OR 1.93, 95% CI 1.42 to 2.61; I²= 24%), approximate numbers-needed-to-harm 125 (95% CI 91 to 250), IRD 2.1 (95% CI 0 to 5 per 1,000 person-years); any gastrointestinal bleeding (OR 1.81, 95% CI 1.32 to 2.49; I²=76%) IRD 2.8 (95% CI 0 to 9.3 per 1,000 person-years); any bleeding (OR2.28, 95% CI 1.81 to 2.87, I²=80% IRD 44 (95% CI 30 to 59 per 1,000 person-years); and haemorrhagic stroke (OR 1.86, 95% CI 1.08 to 3.22; I²=0%). There were no significant differences in all-cause mortality and fatal bleeding, and no data were available for dyspepsia.

**Low-dose aspirin and proton pump inhibitors (three RCTs, 4,134 participants, 2,090 person years of follow-up):** One RCT reported all quality items adequately, but the other RCT only reported losses to follow-up and the use of intention-to-treat analyses. The combination of adverse event rates from all the trials showed the use of proton pump inhibitors reduced the risk of adverse gastrointestinal events in patients given low doses of aspirin (OR 0.34, 95% CI 0.21 to 0.57).

The indirect comparisons found that the risk of major bleeding was increased with clopidogrel plus low-dose aspirin compared to no treatment (OR 2.75, 95% CI 1.83 to 4.12) and anti-coagulant therapy plus low-dose aspirin, but there were no differences between clopidogrel and anticoagulants plus aspirin. For the outcome of any bleeding clopidogrel plus aspirin, and anti-coagulant therapy plus low-dose aspirin, were both associated with higher risks of any bleeds compared to no treatment.

**Authors’ conclusions**

Treatment with low-dose aspirin increased the risk of gastrointestinal bleeding and this risk increased with the accompanying use of clopidogrel and anti-coagulant therapies. The risk decreased with the concomitant use of proton
pump inhibitors.

**CRD commentary**
The review addressed a clear question and criteria for the inclusion of studies were defined and replicable. Appropriate databases were searched without language restrictions for relevant studies. Steps were taken to minimise errors and bias at each stage of the review process. Although some aspects of the reporting of study quality were assessed, the risk of bias was not evaluated. In addition, the results were not presented for individual studies. This made it difficult to evaluate the reliability of the individual meta-analyses. The authors pooled appropriate groups of studies together and conducted regression analyses and subgroup comparisons to explore potential sources of heterogeneity. One of the review authors was an employee of AstraZeneca (manufacturer of omeprazole) which represented a potential conflict of interest. The lack of information on risk of bias in the included studies means that the reliability of the authors' conclusions is uncertain.

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

**Practice:** The authors stated that given the prevalence of low-dose aspirin use in combination with other preventive strategies for cardiovascular disease and unrelated therapies, the risk of bleeding-related harm should be considered when balancing risks and benefits of treatment.

**Research:** The authors stated that it was necessary for all new low-dose aspirin studies to report more precise information on the incidence of bleeding, particularly gastrointestinal bleeding episodes to enable improved estimation of the balance of risks and benefits when using aspirin therapies.

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