Aspirin effect on the incidence of major adverse cardiovascular events in patients with diabetes mellitus: a systematic review and meta-analysis

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CRD summary

The authors concluded that the results suggested aspirin reduced the risk of major adverse cardiovascular events in patients with diabetes without cardiovascular disease, but that there also appeared to be higher rates of bleeding and gastrointestinal complications. The authors' conclusions reflect the evidence presented and are likely to be reliable.

Authors' objectives

To evaluate the benefits and harms of aspirin for the prevention of major adverse cardiovascular events in patients with diabetes.

Searching

PubMed, EMBASE, The Cochrane Library and BIOSIS Previews were searched up to February 2011 with no language restrictions. The full search strategy was available as a web appendix. Bibliographies of retrieved studies, recent meta-analyses and clinical trial registries were handsearched for additional articles.

Study selection

Randomised controlled trials (RCTs) that compared aspirin therapy with a cardiac-neutral comparator (for example placebo or vitamins) in adults (18 years or over) with diabetes mellitus but without a previous history or clinical evidence of cardiovascular disease were eligible for inclusion. Trials were excluded if they lasted less than 12 months or if it was not possible to extract data for diabetes-specific outcomes.

The primary outcome of interest was major adverse cardiovascular events (defined as a composite of non-fatal myocardial infarction, non-fatal ischaemic stroke and cardiovascular death resulting from myocardial infarction and ischaemic stroke), and all cause mortality. Other outcomes of interest were haemorrhage, gastrointestinal bleeding and other gastrointestinal events not resulting in bleeding.

In included trials, aspirin dose ranged from 75mg to 650mg either daily or every other day. Half the trials exclusively enrolled patients with diabetes mellitus. Participants had diabetes (either type 1 or type 2) for over six years. Mean glycated haemoglobin levels ranged from 7% to over 10%. The duration of trials ranged from 3.6 to 10.1 years.

Two reviewers independently selected studies for inclusion. Disagreements were resolved by consensus.

Assessment of study quality

Trial quality was assessed using the Jadad Score with additional assessment of placebo control, intention-to-treat analysis and potential baseline difference. The maximum Jadad score was 5 points.

Two reviewers independently assessed the quality of the studies.

Data extraction

Data for all outcomes were extracted on an intention-to-treat basis and used to calculate risk ratios (RR) and 95% confidence intervals (CIs).

Two reviewers independently extracted data. Discrepancies were resolved through discussion.

Methods of synthesis

Results for major adverse cardiovascular events were combined using the Mantel-Haenszel fixed-effect model. The remaining outcomes were combined using the DerSimonian and Laird random-effects model due to the presence of statistical heterogeneity. Heterogeneity was assessed using Cochran's Q and I^2. Summary absolute risk reduction and the number needed to treat were also calculated. To balance risk and benefit, 'the likelihood of being helped versus harmed metric' was estimated.

Subgroup analysis was conducted to explore the effects of dosage, trial quality and whether a trial exclusively enrolled patients with diabetes.

Publication bias was assessed using Egger's test.

Results of the review

Seven RCTs (11,618 patient) were included in the review. Two trials scored a maximum of 5 points for quality. Allocation concealment, placebo or active comparator control, and blinding of participants and outcome-assessors was reported in five RCTs. Loss to follow-up was reported in six RCTs. Intention-to-treat analysis was reported in four RCTs. No trials reported on potential baseline differences.

There were suggestions of the beneficial effect of aspirin, but the results did not reach statistical significance for major adverse cardiovascular events (RR 0.91, 95% CI 0.82 to 1.00; six RCTs), myocardial infarction (RR 0.85, 95% CI 0.66 to 1.10; seven RCTs), stroke (RR 0.84, 95% CI 0.63 to 1.11; six RCTs), cardiovascular death (RR 0.95, 95% CI 0.71 to 1.27; five RCTs) or all-cause mortality (RR 0.95, 95% CI 0.85 to 1.06; five RCTs). There was evidence of heterogeneity for the analyses of myocardial infarction (I^2=53.1%), stroke (I^2=47.4%) and cardiovascular death (I^2=41.1%). Subgroup analysis did not substantially change the results.

In the aspirin groups, there were higher rates of hemorrhagic complications (RR 2.50, 95% CI 0.77 to 8.10), gastrointestinal bleeding (RR 2.13, 95% CI 0.63 to 7.25), or gastrointestinal events not resulting in bleeding (RR 2.92, 95% CI 0.17 to 50.23) compared with control but these did not reach statistical significance.

Ninety-two people would need to be treated to prevent one major cardiovascular event. The estimate of the 'the likelihood of being helped versus harmed metric' was 6 (range 2 to 8).

There was no significant evidence of publication bias.

Authors' conclusions

The results suggested that aspirin reduced the risk of major adverse cardiovascular events in patients with diabetes without cardiovascular disease. However, there also appeared to be higher rates of bleeding and gastrointestinal complications.

CRD commentary

The review question was clearly defined with appropriate inclusion criteria. Several relevant sources were searched with no language restrictions; attempts were made to locate unpublished studies. Formal assessment of publication bias found no evidence, although there were only a small number of included trials, so the analysis may not be reliable. Appropriate methods were used to reduce reviewer error and bias at all stages of the review.

Trial quality was assessed using appropriate criteria and results of the assessment were reported. Some study details were reported. There were differences between trials in patient populations and reporting of outcomes. The methods of analyses appeared appropriate. The reasons for heterogeneity were explored.

The authors' conclusions reflect the evidence presented and are likely to be reliable.

Implications of the review for practice and research

Practice: The authors stated that the findings suggested that people with diabetes but without cardiovascular disease lay between primary and secondary prevention patients on the spectrum of benefit and risk. Therefore, it was important to consider individual risk in clinical decision making about aspirin for those with diabetes.

Research: The authors stated there were two ongoing trials evaluating the role of aspirin in patients with diabetes without prior cardiovascular events.

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