Aspirin in diabetic retinopathy: a systematic review

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Authors' objectives
To assess the impact of aspirin alone and in combination with other antiplatelet agents on the progression of diabetic retinopathy.

Searching
The Cochrane Library (including the Cochrane Controlled Trials Register) and MEDLINE were searched up to 2001.

Study selection
Study designs of evaluations included in the review
Only randomised controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Studies of aspirin alone versus placebo, or aspirin in combination with dipyridamole versus placebo, were eligible for inclusion. Aspirin alone was used in two of the included studies, while in one study aspirin alone was compared with aspirin-dipyridamole. The aspirin dosage ranged from 650 to 990 mg/day; the dipyridamole dosage was 225 mg/day. All of the included studies used placebo comparisons. The duration of the trials was 3 to 5 years, except for one study which lasted 8 weeks.

Participants included in the review
Men and women in the age range 17 to 70 years with a clinical diagnosis of diabetes mellitus, with or without diabetic retinopathy, were eligible for inclusion. The exclusion criteria were confirmed arterial hypertension that required long-term anti-aggregating or anticoagulant treatment, and the evidence of a contraindication to aspirin. The participants in the included studies were aged from 17 to 70 years.

Outcomes assessed in the review
Studies using outcome measures of progression of diabetic retinopathy, mortality and quality of life were eligible for inclusion. The outcomes assessed included the effect of therapy on reducing the development of diabetic retinopathy, the occurrence of vitreous or pre-retinal haemorrhage, the development of microaneurysms, and the efficacy of aspirin on the blood flow rate in a major temporal retinal artery.

How were decisions on the relevance of primary studies made?
Two reviewers independently assessed the identified articles.

Assessment of study quality
The studies were assessed for randomisation, allocation concealment, blinding, description of withdrawals and dropouts, and intention-to-treat analysis. They were categorised as follows: all quality criteria met with low risk of bias (A); one or more criteria only partly met with moderate risk of bias (B); or one or more criteria not met with high risk of bias (C).

One reviewer carried out the validity assessment.

Data extraction
Two reviewers independently extracted the data using a standard data extraction form.

Methods of synthesis
How were the studies combined?
A narrative synthesis of the studies was undertaken.

How were differences between studies investigated?
Differences between the studies were reported in the tables.

Results of the review
Six publications, referring to 3 RCTs (n=4,194), met the inclusion criteria. The authors also referred to 4 and 5 studies though, presumably, they meant publications.

Most of the studies were categorised as A or B for methodological quality. All of the studies checked medication compliance. The number of study participants ranged from 8 to 3,711.

Aspirin alone neither prevented the development of high-risk proliferative retinopathy (relative risk, RR=0.97, 95% confidence interval, CI: 0.85, 1.11), nor increased the risk of vitreous haemorrhage (RR 1.0, 95% CI: 0.8, 1.3) (1 large study).

The authors stated that there was no significant difference in the severity of vitreous or pre-retinal haemorrhage for aspirin versus placebo or aspirin-dipyridamole versus placebo (1 study; data not reported). There was no statistically significant difference in the 5-year vitrectomy rates in the aspirin group compared with the placebo group (5.4% and 5.2%, respectively), although the authors reported that the CI (which was not reported) includes important benefit and harm. There was no significant difference in the aspirin alone group and the aspirin-dipyridamole group in the development of microaneurysms. The mean annual increase in microaneurysms was significantly higher (P=0.02) in the treated group than the placebo group.

In a two-period crossover study of 8 patients there was a mean aspirin-placebo treatment difference of 21% (95% CI: 4, 38, P=0.03).

Authors' conclusions
The risk of the development or progression of diabetic retinopathy is not increased or decreased when using 650 mg/day of aspirin.

CRD commentary
This was a clearly stated review question. Two relevant electronic databases were searched, details of the search strategy were provided, and language restrictions do not appear to have been imposed. However, attempts could have been made to identify unpublished studies and studies may have been missed. The study selection and data extraction processes were carried out in duplicate, which helps to reduce errors and any bias; however, one reviewer conducted the quality assessment. Adequate information on the individual studies was provided, and it was appropriate that the authors carried out a narrative synthesis. A quality assessment was reported but the discussion of the studies, in the context of quality, was limited. The authors' conclusions appear to follow from the information presented.

Implications of the review for practice and research
Practice: The authors stated that there are no ocular contraindications for patients with diabetes in relation to the use of aspirin for cardiovascular disease or other medical conditions.

Research: The authors stated that further large studies on the potential preventive effects of aspirin in diabetic retinopathy, in particular early retinopathy, are required.

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