Primary prevention of major cardiovascular and cerebrovascular events with statins in diabetic patients: a meta-analysis

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CRD summary
This review concluded that statins reduced the incidence of a first major cardiovascular or cerebrovascular event, fatal or non-fatal stroke, and fatal or non-fatal myocardial infarction, but not deaths, for patients with diabetes. The authors' conclusions reflect the evidence presented, but the very limited reporting of possible trial biases, makes it difficult to evaluate their reliability.

Authors' objectives
To assess the efficacy of statins for the primary prevention of a first major cardiovascular or cerebrovascular event, in patients with diabetes.

Searching
EMBASE, PubMed, The Cochrane Library, and ClinicalTrials.gov were searched for studies published in English from 1966 to November 2011; search terms were reported. Reference lists of reviews and meta-analyses were searched.

Study selection
Double-blind randomised controlled trials (RCTs), comparing a statin with placebo, with at least 500 patients with diabetes, were eligible for inclusion if they reported the incidence of major cardiovascular or cerebrovascular events over at least two years of follow-up. Trials of patients with various disorders were included if the results for patients with diabetes were reported separately. The primary outcome was the composite of major cardiovascular or cerebrovascular events; secondary outcomes were major cardiovascular and cerebrovascular events separately.

In the included trials, the statins were either 40mg simvastatin or 10mg atorvastatin. Across the trials, 70% of participants were male, and the mean age of participants was 62 years; all trials were restricted to patients who were at least 40 years old. Where reported, between 52% and 100% of participants had hypertension, their mean body mass index was 29 or 30, their baseline total cholesterol ranged from 5.0 to 5.4 millimoles per litre (mmol/L), their low-density lipoprotein cholesterol ranged from 2.9 to 3.3 mmol/L, and their high-density lipoprotein cholesterol ranged from 1.2 to 1.4 mmol/L. All trials excluded patients who had experienced myocardial infarction; other selection criteria varied across trials.

The authors did not state how many reviewers selected trials for the review.

Assessment of study quality
Three reviewers assessed the quality of the RCTs using the Jadad scale (maximum score 5); it was unclear they assessed all items independently and how any disagreements were resolved.

Data extraction
Three reviewers extracted the first-time incidence, or overall incidence, of each event type. Relative risks and the absolute risk reduction, with 95% confidence intervals, were calculated. It was unclear if the data were extracted independently, and if so, how any disagreements were resolved.

Methods of synthesis
Pooled relative risks, with 95% confidence intervals, were calculated using fixed-effect or random-effects models, based on $\chi^2$ (cut-off not reported) and the number of trials (fixed-effect was used if only two RCTs were available). The number needed to treat, with 95% confidence interval, was calculated. $X^2$ and $I^2$ were used to assess heterogeneity. Publication bias was investigated in funnel plots.

Results of the review
Four trials met the inclusion criteria (10,187 patients). All them were of good quality, with Jadad scores of 4 or 5; two
trials excluded patients who were 80% compliant or less. Follow-up ranged from 2.4 to 4.8 years.

Treatment with a statin significantly reduced the first-time incidence of a major cardiovascular or cerebrovascular event (RR 0.75, 95% CI 0.67 to 0.85; NNT 35; four RCTs; I²=46%), the incidence of fatal or non-fatal stroke (RR 0.69, 95% CI 0.51 to 0.92; NNT 101; three RCTs; I²=7%), and the incidence of fatal or non-fatal myocardial infarction (RR 0.70, 95% CI 0.54 to 0.90; NNT 86; three RCTs; I²=25%), but not all-cause mortality (two RCTs). There was no evidence of publication bias.

Authors' conclusions

Statins for diabetic patients significantly reduced the rates of a first major cardiovascular or cerebrovascular event, fatal or non-fatal stroke, and fatal or non-fatal myocardial infarction, and reduced all-cause mortality, but not significantly.

CRD commentary

The review addressed a clear question supported by appropriate inclusion criteria. Relevant sources were searched, but publication and language bias might be present. Publication bias was investigated, but four trials is too few for the assessment to be reliable. It was unclear whether the three reviewers who extracted the data and assessed trial quality did so independently; it was unclear whether similar methods to reduce error and bias were used for study selection.

Appropriate criteria were used to assess trial quality, but the results were not reported in full, and allocation concealment was not assessed. All the RCTs were considered to be of high quality. The model used to meta-analyse the trials was chosen based on I² and the number of trials; a fixed-effect model was used if there were only two RCTs, but it is questionable whether four RCTs were sufficient to inform the distribution of effects for a random-effects model. Two trials excluded patients whose compliance was below a specified threshold, so their results might not reflect clinical practice, where compliance is often lower than in trials.

The authors' conclusions reflect the evidence presented, but the very limited reporting of possible trial biases makes it difficult to evaluate the reliability of the data, so the conclusions may be overly strong.

Implications of the review for practice and research

Practice: The authors did not state any implications for practice.

Research: The authors stated that the results of observational studies, that take into account the effects of non-adherence, could be important for economic evaluations and decision making.

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