Effect of HMGCoA reductase inhibitors on stroke: a meta-analysis of randomized controlled trials

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Authors' objectives
To assess the efficacy of hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, compared with other cholesterol-lowering interventions, for reducing the incidence of stroke.

Searching
MEDLINE, EMBASE and published meta-analyses were searched for relevant studies. The authors also searched the reference lists of retrieved papers for citations to additional articles, and identified all RCTs that met the study inclusion criteria until October 1996.

Study selection
Study designs of evaluations included in the review
Randomised control trials (RCTs) comparing dietary or pharmaceutical cholesterol-lowering interventions with placebo or usual diet were included in the review. Trials were eligible if they randomly assigned participants to active treatment or placebo, and reported the incidence of nonfatal and fatal strokes. Studies were included regardless of whether they focused on primary or secondary prevention of coronary heart disease, and whether they used unifactorial or multifactorial interventions.

Specific interventions included in the review
The specific interventions included: HMG-CoA reductase inhibitors (pravastatin, lovastatin, simvastatin) and placebos; dietary interventions such as soya bean oil, diets and usual diets; fibrates (clofibrate, gemfibrozil) and placebos; resins (colestipol, cholestyramine), placebos and usual diet; and various other interventions, e.g. oestrogen, thyroxine, niacin, clofibrate plus niacin, ileum bypass surgery, fish oil and olive oil, and placebos.

Participants included in the review
The study participants had an average age ranging from 45 to 66 years. In addition, they had not previously had a stroke, and were being treated to reduce baseline cholesterol levels. Patients who had received a heart transplant were excluded.

Outcomes assessed in the review
The incidences of nonfatal and fatal stroke were assessed.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the authors performed the selection.

Assessment of study quality
The authors assessed the methodologic quality of included trials with respect to the following variables: the proportion of participants with complete follow-up; concealment of randomisation; blinding of patients and caregivers; and blinding for outcome assessment.

The authors created a dichotomous variable for each of the four quality variables. They then added the scores to yield a summary scale ranging from 0 to 4, where 0 was the lowest and 4 was the highest quality score. The authors combined fatal and nonfatal strokes into a single category since too few studies reported data on death from stroke.

The quality results for the included studies were reported in tabular format. The authors do not state how the papers were assessed for quality, or how many of the authors performed the quality assessment.
Data extraction
The trials were reviewed for methods, inclusion and exclusion criteria, and outcomes.

Methods of synthesis
How were the studies combined?
The trials were grouped according to the following categories: HMG-CoA reductase inhibitors (8 studies), fibrates (5 studies), resins (3 studies), dietary interventions (10 studies), and other interventions (5 studies).

To pool the treatment effects across studies, the authors calculated a weighted average risk ratio of all outcomes in the treatment and control groups using a random-effects model.

How were differences between studies investigated?
The Breslow-Day test was used to assess heterogeneity (see Other Publications of Related Interest no.1). The authors examined the effects of major drug classes separately because a previous meta-analysis suggested that HMG-CoA reductase inhibitors had a greater beneficial effect than other antilipidaemic interventions on major morbidity and mortality. However, the authors reported the overall estimates and results of overall tests for heterogeneity.

The authors tested the difference between combined estimates of intervention type using the z-score, by dividing the difference in the subgroup summary log relative risk by the standard error of the difference.

Results of the review
Twenty-eight trials, with a total of 49,477 participants in the intervention group and 56,636 participants in the control group, were included.

The risk ratio for nonfatal and fatal stroke with HMG-CoA reductase inhibitors was 0.76 (95% confidence interval: 0.62, 0.92; test of heterogeneity, P>0.2). The risk ratios for nonfatal and fatal stroke with fibrates, resins and dietary interventions were all close to 1.0, whilst the difference between the HMG-CoA reductase inhibitor effect and the pooled estimate for all other interventions would, under the null hypothesis, be unlikely to occur by chance (P=0.01). Trials with HMG-CoA reductase inhibitors also showed reductions in the rates of death from coronary heart disease and overall mortality.

Authors' conclusions
This meta-analysis of RCTs suggests that in hyperlipidaemic patients who have not previously experienced stroke, HMG-CoA reductase inhibitors reduce the incidence of stroke. Other, less potent antilipidaemic drugs and dietary interventions are not efficacious for stroke prevention.

CRD commentary
The authors did not state which terms they used to search the databases and other literature, nor the date they started their search. They also did not search for non-English language studies or unpublished data. [A: The authors do, however, note that this review was informed by a previous literature search which did include unpublished reports (see Other Publications of Related Interest no.2)]. The authors did rate each of the included studies for quality, but did not include any information as to whether the studies were analysed as intention to treat. In addition, there were no figures for any participants who did not complete the studies.

The results of this review indicate a benefit of HMG-CoA reductase inhibitors over other cholesterol-lowering interventions, although the authors acknowledge that their results should be treated with caution. This is because the results may be influenced by various study design effects, and a lack of data concerning the relationship between elevated cholesterol levels and nonfatal and fatal stroke. In this meta-analysis, the authors compared the results between studies rather than within. Hence, they are not making direct comparisons, and their conclusion that clinicians should use HMG-CoA reductase inhibitors should be backed by more direct studies of these inhibitors versus the other
cholesterol-lowering interventions.

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