Stroke, statins, and cholesterol: a meta-analysis of randomized, placebo-controlled, double-blind trials with HMG-CoA reductase inhibitors

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**Authors' objectives**
To estimate the effect of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (‘statins’) on stroke risk.

**Searching**
MEDLINE was searched from 1980 to 1996, and Current Contents (Life Sciences) from January through May 1996. The search strategy used the terms 'HMG-CoA reductase inhibitor', 'lovastatin', 'simvastatin', 'pravastatin', 'fluvastatin', 'atorvastatin', 'randomized controlled trial' (RCT), and 'double-blind method', both as MeSH and textwords. Reviews and preliminary reports were searched for further references.

**Study selection**

*Study designs of evaluations included in the review*
Randomised controlled trials (RCTs), which were double-blind, placebo-controlled monotherapy trials. Only trials in which strokes were observed were included in the analysis. If this information was incomplete or not reported, the study investigators were contacted. The length of follow-up of the included studies ranged from 0.23 to 5.4 years.

*Specific interventions included in the review*
Statin drugs (HMG-CoA reductase inhibitors) versus placebo. The statins included lovastatin (3 trials), simvastatin (2 trials) and pravastatin (8 trials). There was no information on the dosages.

*Participants included in the review*
The reported mean age of the participants ranged from 55 to 68 years. Within each trial:

- 8 to 100% of the patients had suffered a previous myocardial infarction;
- 12 to 80% were smokers;
- 16 to 49% had hypertension;
- 5 to 99% had angina; and
- 0.1 to 15% had diabetes mellitus (having diabetes was the exclusion criteria for 5 studies).

*Outcomes assessed in the review*
The number of fatal or nonfatal strokes was measured.

**How were decisions on the relevance of primary studies made?**
Two assessors independently evaluated whether the studies were randomised, placebo-controlled double-blind trials.

**Assessment of study quality**
The authors did not report the method used to assess validity, or how the validity assessment was performed.

**Data extraction**
The authors do not state how the data were extracted for the review, or how many of the authors performed the data extraction.
Methods of synthesis
How were the studies combined?
For each trial, the number of strokes in the treatment arm was compared with the number of strokes expected on all observations, assuming that the drug treatment had no effect. The pooled odds ratio (OR), along with the 95% confidence interval (CI), was approximated from the difference between the observed and expected number of strokes summed over all trials.

How were differences between studies investigated?
Heterogeneity between the studies was evaluated using the chi-squared test. Heterogeneity was also tested after pooling the data from the small trials.

Results of the review
Thirteen trials (20,438 patients) were included.

Total strokes: treatment with the HMG-CoA reductase inhibitor led to an overall stroke risk reduction of 31% (OR 0.69, 95% CI: 0.57, 0.83). The risk reduction in the 10 smaller trials was 72% (OR 0.28, 95% CI: 0.14, 0.56). The 3 larger studies showed a significant reduction of 30, 31 and 11% in the risk of stroke. When the 3 large trials were analysed with the combined data in the 10 small trials, the test statistic became significant (chi-squared 8.3, p<0.05) due to heterogeneity between the larger trials.

Fatal strokes: the total number of fatal strokes was considerably smaller, but did not differ between the active- and placebo-treated groups (30 and 27 patients, respectively; OR 1.09, 95% CI: 0.65, 1.84). When the data were analysed after the exclusion of transient ischaemic attacks in 4 studies, the risk reduction was 30% (OR 0.70, 95% CI: 0.57, 0.85).

Authors' conclusions
The combined data suggested that treatment with HMG-CoA reductase inhibitors prevents stroke in middle-aged persons. Since stroke is especially common in old age, these data reinforce the need for clinical trials to evaluate the effect of HMG-CoA reductase inhibitors in preventing stroke in the elderly.

CRD commentary
This was a thorough and well-presented review. However, the search strategy could have been more expansive, by including other databases, such as EMBASE, as well as investigating the availability of unpublished research within the field. More specific information about the methodology used is also required. For example, there were no inclusion or exclusion criteria specified, in terms of the type of participants and the disease investigated. In addition, the authors did not mention how they assessed the validity of the individual trials included in the review.

The three larger trials, included in the review, had a longer follow-up period (4.9 to 5 years) than the 10 smaller trials (0.23 to 4 years). They also differed in their aims: the larger trials were investigating clinical intervention and the smaller trials were looking at atherosclerotic regression. For all three larger trials, the number of fatal strokes within the treatment group was greater than that in the control group. Furthermore, the largest trial included in the review, which had the least number of patients with angina problems, found only an 11% reduction in the risk of stroke. However, it was noted in the discussion section of the review that, unlike the other two large studies, the participants were selected on the basis of having risk factors rather than the clinical end point of atherosclerosis.

Further large trials looking specifically at the effect of statins on stroke, with at least a 5-year follow-up period, are required. In addition, trials that only include patients with signs and symptoms of atherosclerosis are needed. The authors' conclusions follow from their results, but they do not mention that the findings for fatal stroke are not so conclusive. However, they do go on to recommend further research to evaluate the effect of HMG-CoA reductase inhibitors in preventing stroke in older patients, as the included trials only looked at middle-aged patients. As noted by the authors, the lack of trials including older patients will limit the generalisability of the review, as age is a powerful
risk factor of both atherosclerosis and ischaemic stroke.

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