Differential effects of lipid-lowering therapies on stroke prevention: a meta-analysis of randomized trials


CRD summary
This review assessed the effectiveness of lipid-lowering therapies in reducing the incidence of stroke. The authors concluded that such treatments do reduce stroke incidence in patients with a history of heart disease. This review involved a large number of patients and the conclusions are likely to be broadly accurate.

Authors' objectives
To examine the effectiveness of lipid-lowering therapy in stroke prevention.

Searching
PubMed was searched from 1966 to 2001. In addition, the reference lists of relevant published trials and reviews were checked. Only studies published in English were eligible for inclusion.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) that compared lipid-lowering therapy with placebo were eligible for inclusion in the review; both primary prevention and secondary prevention trials were eligible. Crossover trials and short-term efficacy trials using serum cholesterol as the primary end point were excluded from the review. The mean follow-up in the included studies was 4.7 years (range: 0.5 to 7.4).

Specific interventions included in the review
All lipid-lowering therapies, including statins, were eligible for inclusion in the review. Trials that employed other interventions in addition to lipid-lowering therapy were also eligible for inclusion. The interventions in the review included statins, non-statin drugs, diets, multifactorial advice and ileal bypass.

Participants included in the review
Both participants free of heart disease at baseline and those with a history of heart disease were eligible for inclusion.

Outcomes assessed in the review
The outcome assessed was the incidence of strokes, either fatal or nonfatal, including ischaemic and haemorrhagic strokes. Transient ischaemic attacks were excluded from the review, as were trials in which serum cholesterol levels were the primary outcome. The incidence of myocardial infarctions, both fatal and nonfatal, was also included in the review.

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

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the extraction.

Baseline cholesterol was defined as the average total plasma cholesterol level in the control and treatment groups before treatment. The percentage of cholesterol reduction for each trial was calculated as the percentage of total cholesterol.
reduction during the study between the treated and control groups. Relative risks (RRs) were calculated for each outcome for each trial.

Methods of synthesis
How were the studies combined?
The trials were combined in a fixed-effect meta-analysis. A pooled estimate of overall RR was calculated using the inverse variance. An effect model analysis, using a weighted regression model, was also performed. A weighted linear regression model was used to assess the relationship between cholesterol reduction and reduction in stroke incidence.

How were differences between studies investigated?
A chi-squared test for heterogeneity was carried out on the overall pooled analysis. Subgroups were identified on the basis of treatment type, and chi-squared tests for heterogeneity were also conducted for each subgroup.

Results of the review
Thirty-eight RCTs with 83,161 patients were included in the review. Ten trials were of primary prevention and 28 were of secondary coronary prevention.

The pooled estimate of the 31 trials (n=70,396) included in the meta-analysis showed that stroke incidence in the lipid-lowering therapy groups was lower than in the placebo groups (RR 0.828, P<0.001). No statistically significant heterogeneity was found between the trials or between the types of treatment.

There was no difference between the lipid-lowering therapy and placebo groups in the incidence of fatal strokes (RR 1.09, 95% CI confidence interval: 0.86, 1.38).

Ten trials (n=30,766) reported the incidence of haemorrhagic stroke. There was no significant difference between the groups (RR 1.16, 95% CI: 0.75, 1.80).

Eight of the 10 primary prevention trials were included in the meta-analysis (n=28,553). Stroke incidence was not significantly different in the two groups (RR 0.95, P=0.67).

Twenty-three of the 28 secondary prevention trials were included in the meta-analysis (n=41,843). Stroke incidence in the lipid-lowering therapy groups was lower than in the placebo groups (RR 0.74, 95% CI: 0.64, 0.86).

Statin treatment reduced stroke incidence by the greatest amount in comparison with placebo (RR 0.76, 95% CI: 0.66, 0.87).

The pooled estimate showed that the incidence of myocardial infarction was significantly lower in lipid-lowering therapy groups than in placebo groups: (RR reduction 22%, P<0.001).

The weighted regression showed a significant correlation between the reduction in RR of stroke and total cholesterol levels. The final cholesterol levels showed a clear separation between benefit and no benefit of lipid-lowering therapy on stroke incidence, with a cut-off for benefit of 232 mg/dL.

Authors’ conclusions
Lipid-lowering therapy reduces stroke incidence in coronary patients. This is particularly the case when the total cholesterol level is lowered to less than 232 mg/dL.

CRD commentary
The review question and the inclusion criteria were clear. The search involved only one electronic database, making it possible that some relevant studies were missed. In addition, since the review included only studies published in English, it is possible that both publication bias and language bias might have occurred in the inclusion of studies. The authors did not report assessing validity. This may mean that poorly conducted studies with, for example, high rates of
withdrawals, were given equal weight with well-conducted studies. The authors also did not report using methods to minimise bias and error in the study selection and data extraction processes. However, given the large number of patients included in the review, the authors' conclusions are likely to be broadly accurate.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors identified the need for further research investigating lipid-lowering therapy in populations at high risk of stroke.

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