Authors' objectives
To determine if 3-hydroxy-3-methylglutaryl co-enzyme A (HMG-CoA) reductase inhibitors (statins) are effective in preventing fatal and nonfatal stroke in patients at increased risk of coronary artery disease.

Searching
MEDLINE was searched from 1983 to June 1996 using single word combinations: 'pravastatin' and 'trial'; 'simvastatin' and 'trial'; 'lovastatin' and 'trial'; and 'fluvastatin' and 'trial'. Two pharmaceutical companies (Merck and Bristol-Meyers) were contacted to obtain their lists of references on HMG-CoA reductase inhibitor trials of any studies relevant to stroke reduction. Bibliographies of identified studies were reviewed until all possible references were obtained.

Study selection
Study designs of evaluations included in the review
Randomised placebo controlled trials (RCTs) that used HMG-CoA reductase inhibitors to lower serum cholesterol were included. All included studies were double-blind. Trial duration ranged from 6 months to 5.4 years with a weighted total mean duration of 4.3 years.

Specific interventions included in the review
The following HMG-CoA reductase inhibitors in primary and secondary coronary prevention were compared to placebo: lovastatin (10 to 80 mg); pravastatin (10 to 40 mg); and simvastatin (10 to 40 mg). Multi-intervention therapies in which the effect from statins could not be separated out were excluded.

Participants included in the review
Primary prevention trials included the following groups of patients: low density lipoprotein (LDL) above 155 mg/dL with no prior history of myocardial infarction (MI) and no serious electrocardiographic abnormalities or concurrent illness; hypercholesterolemic patients with early carotid artery disease; patients free of symptoms or signs of coronary artery disease; and patients with prior history of MI. Secondary prevention trials included the following groups of patients: hypercholesterolemic patients with angiographically documented coronary atherosclerosis, or prior history of MI (with or without one carotid artery lesion) or angina pectoris or patients who had undergone coronary angioplasty or those with two or more additional risk factors for coronary artery disease; and patients with total cholesterol < 240 mg/dL and prior MI.

Weighted overall mean age was 57.2 years. Percentage male ranged from 51% to 100%. Mean baseline cholesterol included: close to desirable (203 and 209 mg/dL); mild to moderately elevated (range 231 to 236 mg/dL); and severely elevated (250 to 272 mg/dL).

Outcomes assessed in the review
Total stroke, non-fatal stroke, fatal stroke and cardiovascular end points were assessed. Cardiovascular outcomes included coronary events defined as the number of non-fatal myocardial infarctions plus the number of deaths from coronary heart disease.

How were decisions on the relevance of primary studies made?
Each identified abstract was independently reviewed and assessed by three authors for measures of total mortality or cardiovascular end points. A full report was obtained of each reference designated as relevant by at least one author. Two authors independently reviewed bibliographies of retrieved studies. Predetermined inclusion criteria were applied to identified trials by three authors with disagreements resolved by consensus.
Assessment of study quality
Inclusion was limited to RCTs. The authors do not state how papers were assessed for validity, or how many of the reviewers performed the validity assessment.

Data extraction
Two authors independently extracted the following data using a standard data collection form: author; year of publication; patient characteristics; interventions; study design; eligibility criteria; duration of therapy; cholesterol measurements; outcome measures; and, where reported, type of stroke (hemorrhagic, embolic or thrombotic). A third author reviewed both sets of forms and disagreements were resolved by discussion and consensus. The net percentage of change in cholesterol level for the treatment group relative to the control group and the percentage change in cholesterol for either group were calculated. Odds ratios (OR) and 95% confidence intervals (CI) were computed for fatal, non-fatal, and total stroke outcomes. Where necessary, further information was obtained from the original investigators.

Methods of synthesis
How were the studies combined?
A conditional maximum likelihood pooled OR estimate (CMLE) and 95% CI and a Mantel-Haenszel pooled OR were calculated for total, non-fatal and fatal stroke, and coronary events.

How were differences between studies investigated?
Heterogeneity was assessed using an exact test for heterogeneity and a Breslow-Day chi-squared test for homogeneity.

A chi-squared test for between-group heterogeneity was used to compare differences in results between primary and secondary prevention trials.

Weighted linear regression was preformed using OR for individual trials for fatal, non-fatal, and total stroke outcomes as dependent variables and the initial total and LDL cholesterol levels and net percentage decrease in total and LDL cholesterol as the independent variables. Weighted univariate regression was used to assess the relation of the OR and absolute risk reduction for stroke across a range of baseline cardiac event rates.

Results of the review
Thirteen RCTs were included in the meta-analysis (19,921 patients).

CMLE and Mantel-Haenszel methods produced similar results. Only CMLE estimates and exact tests of homogeneity were reported.

Overall.

Total stroke: statistically significant reduction in statin treated patients. OR = 0.70 (95% CI: 0.57, 0.86). Nonfatal stroke: statistically significant reduction in statin treated patients OR = 0.64 (95% CI: 0.51, 0.79).

Fatal stroke: no statistically significant difference between groups. OR = 1.25 (95% CI: 0.71, 2.24).

No evidence of heterogeneity was found for any stroke outcome (total P = 0.5067, nonfatal P = 0.5257, fatal P = 0.6749).

Primary prevention (4 RCTs, 7808 patients): no statistically significant difference between groups for any stroke outcome.

Total stroke OR = 0.85 (95% CI: 0.57, 1.28).

Non-fatal stroke OR = 0.84 (95% CI: 0.54, 1.29).
Fatal stroke OR = 1.00 (95% CI: 0.27, 3.73).

Secondary prevention (9 RCTs, 12113 patients): statistically significant reduction in statin treated patients for total stroke and non-fatal stroke outcomes with no statistically significant difference found between groups for fatal stroke.

Total stroke OR = 0.65 (95% CI: 0.51, 0.82).
Non-fatal stroke OR = 0.57 (95% CI: 0.44, 0.75).
Fatal stroke OR = 1.34 (95% CI: 0.69, 2.62).

No significant univariate association was found between relative odds of stroke (total, fatal, non-fatal) and the mean initial cholesterol level, mean net cholesterol reduction, or baseline risk of cardiac events. A significant association was found between absolute risk reduction for total and non-fatal stroke outcomes for increase in baseline risk of cardiac events. Supporting results were presented.

Cardiac events (11 RCTs, 19247 patients): statistically significant reduction in statin treated patients OR = 0.67 (95% CI: 0.62, 0.73). No significant within group heterogeneous detected.

**Authors’ conclusions**
The available evidence clearly shows that HMG-CoA reductase inhibitors reduce the morbidity associated with strokes in patients at increased risk of cardiac events. Data from 13 placebo-controlled trials suggest that on average one stroke is prevented for every 143 patients treated with statins over a 4-year period.

**CRD commentary**
The aims were stated and inclusion criteria specified in terms of study design, participants, intervention, and outcomes (though measures used to assess outcomes were not described). Methods used to select primary studies and extract data were described. Some relevant details of primary studies were presented in either tabular or text format. Statistical heterogeneity was assessed and sensitivity analyses were conducted. The discussion includes consideration of the following limitations of the review: only one trial provided data on the pathology of stroke type; the study populations were younger, healthier and predominately white and had a lower overall case-fatality than the general stroke population; and data was aggregated from a wide diversity of patients.

Only one database was searched, and although pharmaceutical companies were contacted, it is possible that some relevant studies were omitted. It was not stated whether any language restrictions were applied to the literature search. Validity was not formally assessed though only double blind RCTs were included. It was not reported whether data were extracted on an intention-to-treat basis and no mention was made of rates of withdrawal or adverse reactions. The wide diversity of included patients and the differences between the included population and the general stroke population must be considered when interpreting the conclusions. The evidence would be strengthened by the incorporation of a formal assessment of validity in the review and an assessment of adverse reactions.

**Implications of the review for practice and research**
Practice: The authors state that the best available evidence supports the use of statins to prevent morbidity associated with stroke, and that benefits of statins on coronary morbidity and mortality far outweigh their impact on stroke events.

Research: The authors state that further research will need to focus on defining the pathology of strokes observed in patients on statin medication, to better understand the impact of lipid-lowering therapy on cerebrovascular disease.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.