Cholesterol-lowering interventions and stroke: insights from a meta-analysis of randomized controlled trials


CRD summary
The review concluded that statins were the most effective cholesterol-lowering treatments for decreasing the risk of total and non-fatal strokes. A relationship was observed between lowering of total cholesterol and low-density lipoprotein cholesterol and reductions of total strokes. The reliability of the authors’ conclusions is unclear because of a lack of information on the methodological quality of the included trials.

Authors’ objectives
To determine the effectiveness of various cholesterol-lowering treatments on the risk of stroke and their relationship with the extent of cholesterol lowering.

Searching
PubMed was searched from January 2000 to April 2009. Search terms were reported. Studies were retrieved from four previous systematic reviews published between 1996 and 2002. Reference lists of retrieved articles and relevant recent reviews were searched for additional studies.

Study selection
Randomised controlled trials (RCT) of at least 100 patients that compared single cholesterol-lowering treatments with either placebo or no treatment were eligible for inclusion. Trials needed to report incidence of stroke. Follow-up needed to be at least six months. Studies with crossover designs were excluded.

The review included RCTs published from 1966 to 2008. Mean follow-up was 3.5 years. Mean age of patients was 61 years. Sixty per cent of participants were male. The mean pre-treatment level of total serum cholesterol was 224mg/dL. Patients with a history of smoking, diabetes, hypertension (approximately half of the included patients), myocardial infarction and stroke were included. The primary clinical outcomes evaluated were incidence of total, fatal and non-fatal-stroke as defined in each trial. Cholesterol-lowering agents were statins, fibrates and other drugs. Dietary interventions and surgical interventions were used.

Three reviewers independently performed study selection in duplicate; any disagreements were resolved by a fourth reviewer and through discussion.

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

Data extraction
Data were extracted independently by three reviewers to calculate odds ratios (OR) or relative risks (RR) and 95% confidence intervals on incidence of stroke. The reviewers used intention-to-treat data where possible. Any disagreements between reviewers were resolved by a fourth reviewer and through discussion.

Methods of synthesis
Pooled odds ratios and 95% confidence intervals were calculated using a Mantel-Haenszel random-effects model for the effects of treatments on serum cholesterol. \( \chi^2 \) was used to evaluate heterogeneity. Planned sensitivity analyses examined the effects of statins on outcomes and baseline characteristics. Pooled relative risks were used to determine the effects of interventions on risk of stroke according to the risk of death of the control group populations recruited in each trial. Meta-regression analyses were used to explore the relationship of cholesterol reduction to total stroke.

Results of the review
Seventy-eight trials (n=266,973 participants) were included in the review; 11 were open trials and 67 trials were
All cholesterol-lowering treatments (dietary interventions and surgery included) were associated with decreases in incidence of all strokes (OR 0.88, 95% CI 0.83 to 0.94; 80 trials) and non-fatal stroke (OR 0.87, 95% CI 0.81 to 0.94; 44 trials). Significant statistical heterogeneity was observed ($\chi^2=9.496$ for total strokes and $\chi^2=12.466$ for non-fatal strokes). No significant differences were observed between all treatments and placebo/control in fatal strokes (66 trials).

Use of statins was found to significantly decrease the incidence of total strokes (OR 0.85, 95% CI 0.78 to 0.92; 49 RCTs; n=148,296 participants) and non-fatal strokes (OR 0.81, 95% CI 0.74 to 0.89). No differences were observed between statins and placebo/control for incidence of fatal strokes.

No differences were observed in incidence risk of total strokes and non-fatal strokes with fibrates and other cholesterol-lowering interventions.

A 10% reduction of low-density lipoprotein cholesterol was associated with a significant 4% reduction in the relative risk of strokes. A 10% reduction of total cholesterol was significantly associated with an 8% reduction in total stroke.

Planned sensitivity analyses assessed the efficacy of cholesterol-lowering treatments on various subgroups and showed that benefits of cholesterol-lowering interventions on strokes were observed when reduction of serum cholesterol was more than 2% to 3%.

**Authors' conclusions**
Statins are the most effective cholesterol-lowering treatments for decreasing the risk of total and non-fatal strokes. Benefits of statins appear to be proportional, with an observed relationship between lowering of total cholesterol and low-density lipoprotein cholesterol and reduction of total stroke.

**CRD commentary**
The review addressed a clear question. Inclusion criteria were clearly stipulated. One appropriate database was used for the searches. A previous review by the same authors was used to search for further studies. Use of only one database may mean that potentially relevant studies were missed. The lack of specific searches for unpublished studies risked publication bias. It was unclear whether language restrictions were applied, so there may have been a risk of language bias. Steps were taken to minimise errors and bias for study selection and data extraction.

The authors did not assess methodological quality of the included trials, so the reliability of the results could not be verified adequately. The authors conducted appropriate subgroup and sensitivity analyses to explore sources of heterogeneity in the pooled results. Some limitations of the results due to uncertainties related to losses to follow-up were correctly acknowledged by the authors.

The reliability of the authors’ conclusions is unclear because of a lack of information on the methodological quality of the included trials.

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

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