Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis

Law M R, Wald N J, Rudnicka A R

CRD summary
This review concluded that statins can reduce risk of ischaemic heart disease (IHD) events by 61% and stroke by 17% compared with placebo in people with high blood lipid levels, and that any possible excess of haemorrhagic stroke is outweighed by protection against IHD events and thromboembolic stroke. Reporting and methodological issues make it difficult to assess the reliability of the conclusions.

Authors' objectives
To determine by how much statins, of different doses, type and treatment duration, lower serum concentrations of low-density lipoprotein (LDL) cholesterol and the incidence of ischaemic heart disease (IHD) and stroke.

Searching
To find RCTs of statin trials, the authors searched MEDLINE (from 1982 to 2001), the Cochrane Library and ISI Web of Science using generic and trade names of six statins as keywords or textwords, as well as terms for finding clinical trials. The reference lists of relevant studies were checked and pharmaceutical companies were asked to identify trials of statins.

To find studies that reported IHD events and cholesterol reduction, the literature search (above) was expanded to include other lipid-lowering intervention studies; no details were given.

Study selection
Study designs of evaluations included in the review
For assessing statin treatments and the effect on LDL cholesterol reduction, only double-blind RCTs (including crossover studies) were sought. Crossover trials in which the order of treatment and placebo periods were not randomised were excluded.

For assessing IHD events in relation to the reduction in LDL cholesterol concentration, double-blind RCTs of any duration (including crossover studies) were sought.

Specific interventions included in the review
Three inclusion criteria were given for each part of the analysis.

1. Comparisons of fixed-dose statins, (atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin and simvastatin) with placebo were sought. Studies of less than 2 weeks' duration and those with variable doses or combinations of lipid-lowering drugs were excluded. The median duration of the included studies was 8 weeks (90% range: 4, 48). In the included studies, the doses of the individual drugs ranged from 2.5 to 80 mg; full details were given on the authors' website (Wolfson Institute; accessed 15/05/2004). See Web Address at end of abstract.

2. The authors also looked for any studies of LDL-lowering treatment. These included statins (as above), fibrates, niacin, bile resins, diet and ileal bypass surgery. Studies were excluded if risk factors other than serum cholesterol were changed, cholesterol reduction was less than 0.2 mmol/L, there was no untreated control group, or the study recorded fewer than five IHD events.

3. Studies that reported blood LDL concentrations and stroke outcomes were sought. Details of the interventions, if any, were not reported.

Participants included in the review
Studies on participants of any age or disease profile were sought. Studies on people with chronic renal failure or organ transplantation were excluded.

In the included statin studies, most of the participants were healthy individuals with above average blood lipid levels: the median LDL was 4.8 (90% range: 3.2, 7.4) in the treated group and 4.6 (90% range: 3.0, 6.8) in the control group. Some of the participants had high blood-pressure, diabetes or IHD. The mean age ranged from 34 to 76 years.

In the longer-term studies of any lipid-lowering intervention, 52% of the participants had existing vascular disease.

Outcomes assessed in the review
The outcomes assessed from randomised controlled trials (RCTs) of statins were serum concentrations of total cholesterol and LDL, according to the treatment dose and pre-treatment cholesterol levels.

For studies of LDL-lowering interventions, the authors looked for the number of IHD events (defined as death and nonfatal myocardial infarction) in relation to the reduction in LDL concentrations and the duration of treatment. Subsequent events (after the first) and ‘silent’ infarctions were ignored. The numbers of IHD events and the changes in LDL (adjusted for placebo) separately for years 1, 2, 3 to 5, and 6 or more (of the study) were sought.

Adverse events associated with statin use were also reported.

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 data extraction.

Effect of statin treatment: the authors calculated the reduction in serum LDL cholesterol for a given dose as the change in the treated group minus that in the placebo group. In crossover trials this was calculated as the end treatment concentration minus the end placebo concentration. Methods for calculating standard errors and statistical analysis were reported in an additional publication (see Other Publications of Related Interest no.1). Standard errors for change in LDL, if not reported, were estimated from standard errors before and after treatment. If data to calculate variance were unavailable, the variance was estimated from the average in all studies that reported it.

Effect of serum LDL reductions on IHD events: the authors calculated the absolute change in serum LDL cholesterol concentration in the treatment group minus that in the placebo group. Where LDL cholesterol levels were not reported, total cholesterol was used. In each study, the number of IHD events and changes in LDL cholesterol (adjusted for placebo) were calculated separately for years 1, 2, 3 to 5, and 6 or more.

Methods of synthesis
How were the studies combined?
Trials of statins and LDL cholesterol reduction: methods for calculating standard errors and statistical analyses were described in an accompanying paper (see Other Publications of Related Interest no.1). The authors used regression models in this paper, whereas in the current review they seem to have calculated weighted mean differences and percentage reductions in LDL cholesterol concentration, along with 95% confidence intervals (CIs), according to the type of statin and dose. Absolute reductions in LDL were estimated by interpolation of cumulated dose estimates and were standardised to the pre-treatment mean serum LDL concentrations in the trials (i.e. 4.8 mmol/L).

Serum cholesterol reduction by any intervention: the odds ratios (treated/placebo) of IHD events, stratified by duration of scheduled intervention, were calculated using the random-effects model of DerSimonian and Laird. Each result was
standardised to an LDL cholesterol reduction of 1.0 mmol/L by raising the observed odds ratio to the power of (1.0 divided by the observed LDL cholesterol reduction).

How were differences between studies investigated?
The authors did not say what method was used to assess heterogeneity, although they did report the results of testing. The outcomes were reported according to the daily dose of different statins. Differences in the outcomes were also reported according to the time of drug administration (morning or evening) and pre-treatment levels of LDL.

Results of the review

Studies of statins: 164 RCTs (approximately 38,000 participants) were included.

Studies of lipid-lowering treatments: 58 longer term RCTs (more than 148,000 participants) were included. Of these, 31 were studies on statins that were also included in the analysis of the effects of statins.

Statins significantly reduced serum LDL cholesterol. The estimated mean reductions for individual drugs at maximum doses of 80 mg/day were: atorvastatin 2.64 mmol/L (95% CI: 2.31, 2.96), fluvastatin 1.58 mmol/L (95% CI: 1.40, 1.76), lovastatin 2.15 mmol/L (95% CI: 1.86, 2.43), pravastatin 1.60 mmol/L (95% CI: 1.46, 1.74), rosuvastatin 2.80 mmol/L (95% CI: 2.63, 2.97), simvastatin 2.01 mmol/L (95% CI: 1.83, 2.19).

For each individual drug there appeared to be a linear relationship between dose and reduction in LDL (i.e. as the dose increased so did the effect). This was demonstrated by fitting a straight line to the results with estimates made by interpolation of points on the straight line and standardisation to average LDL cholesterol pre-treatment concentrations. Rosuvastatin 5 mg/day, atorvastatin 10 mg/day, lovastatin 40 mg/day and atorvastatin 40 mg/day all reduced LDL levels by approximately 35% (1.8 mmol/L). Full details of all the results were given in the paper.

Longer term interventions to reduce serum cholesterol showed a reduction in the risk of IHD events. The calculated odds ratios were not presented in either the paper or on the website. The reduction in risk calculated for a 1.0 mmol/L reduction in LDL was 11% (95% CI: 4, 18) at 1 year, 24% (95% CI: 17, 30) at 2 years, 33% (95% CI: 28, 37) at 3 to 5 years, and 36% (95% CI: 26, 45) at the sixth and subsequent years.

In trials grouped by levels of LDL reduction (mean values of 0.5, 1.0 and 1.6 mmol/L), the IHD events were reduced by 20, 31 and 51%, respectively, after 2 years.

The authors stated that taking into account the reduction in LDL cholesterol and duration of treatment, there was no significant residual heterogeneity in the 58 studies of statins and other interventions for lowering cholesterol. The original odds ratios and heterogeneity tests were not presented.

Data from 48 RCTs of statins reported no excess risk of adverse reactions in the group given statins, compared with placebo, when the outcome was 'any adverse event'. The absolute risk of rhabdomyolysis was low: in RCTs there were 8 cases in the statin-treated group and 5 cases in the placebo group. None reported serious illness or death attributable to this cause. No cases of liver failure were reported in the RCTs either. Full details of the adverse effects were given in the paper.

Authors' conclusions

Statins can reduce the risk of IHD events by an estimated 61% and the overall risk of stroke by 17%. Any possible excess of haemorrhagic stroke is greatly outweighed by the protective effect against IHD events and thromboembolic stroke.

CRD commentary

This was a complex review with an additional publication and extra data provided on the BMJ website (see Web Address at end of abstract) and the authors’ own website (see Other Publications of Related Interest). Part of this paper was an update of a previous review (see Other Publications of Related Interest no.2). The aims were clearly described. The search terms for studies other than those on statins were not reported, and few search terms were used; it is
therefore possible that studies were missed. EMBASE was not searched so studies published in European languages may also have been missed. Full details of the process of the review (i.e. study selection, quality assessment and data extraction) were not provided, and the validity of the included studies was not reported. The results from poor-quality studies and the synthesis of them may not be reliable. Subjective decisions taken in the selection process and in assessing validity could also lead to bias. There was little detail about the participants in any of the studies; this could affect the generalisability of the results.

In the analysis of 164 trials, variance was estimated for some trials and this could lead to bias in the results. Many 'results' and the authors' conclusions were based on adjusted and extrapolated data and estimates, rather than data arising directly from the included studies. For example, the relation of lipid-lowering treatments to IHD was calculated using odds ratios. However, the odds ratios were not presented; standardised measures based on adjusted estimates of the odds ratios to an equivalent LDL reduction of 1.0 mmol/L were presented instead. There was obvious heterogeneity in the results of this analysis, as the authors stated that once any effects of reduction in LDL cholesterol and duration of treatment were taken into account no heterogeneity remained. It would have been informative to have seen the original analysis, with odds ratios and heterogeneity tests, before adjustment.

The authors used information from different types of studies and data from indirect comparisons to draw their conclusions. They argued that statins lower cholesterol levels and they provided useful information about the effects of differing doses and types of statins. They went on to describe the effects of lowering cholesterol on IHD events and haemorrhagic and stroke events. They were selective in choosing only those studies where 5 or more IHD events had occurred. The studies included in this part of the analysis were on any type of lipid-lowering treatment and also included cohort studies. These results may not be as reliable as data from long-term RCTs of statin treatment and its effects on IHD and stroke events.

The authors have a stated conflict of interest in that they have filed a patent application on the formula of a combined pill to simultaneously reduce four cardiovascular risk factors.

**Implications of the review for practice and research**

**Practice:** The authors stated that it may be prudent to use moderate doses of commonly used older drugs for general use. This would also be cheaper as some statins are now off patent.

**Research:** The authors did not state any implications for further research.

**Bibliographic details**


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http://bmj.bmjournals.com/cgi/content/full/326/7404/1423

**Other publications of related interest**


This additional published commentary may also be of interest. Rosenson RS. Lowering LDL cholesterol reduces risk of

Additional data relating to this study are available on the following website: http://www.smd.qmul.ac.uk/wolfson/bpchol (accessed 15/05/2004).

Indexing Status
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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.