Meta-analysis of the cardiovascular benefits of intensive lipid lowering with statins

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CRD summary
The authors stated that intensive lipid lowering therapy with statins significantly reduced risk of stroke, major coronary events and cardiovascular or coronary heart disease deaths in individuals at high risk of cardiovascular events. The review was largely well conducted, but the unknown methodological quality of included trials limits conclusive evidence of the review’s reliability.

Authors’ objectives
To evaluate the effects of lipid lowering therapy using higher-dose statins.

Searching
PubMed, EMBASE and The Cochrane Library were searched from 1966 to 2009. Search terms were reported. Reference lists and related links of relevant papers were reviewed for further studies.

Study selection
Eligible studies were primary and secondary prevention large randomised controlled trials (RCTs) with at least 12 months post-intervention follow-up. Eligible trials primarily compared intensive versus less intensive lipid-lowering effects of statins in people at high risk of vascular events. Data had to be available individually on the outcomes of stroke, major coronary events and deaths related to cardiovascular or coronary heart disease. Drug-induced adverse events were eligible. The target for low density lipoprotein cholesterol (LDL-C) had to be less than 2.1mmol/L; trials with targets of 2.5mmol/L or more were excluded.

The included statins were simvastatin, atorvastatin, pravastatin and rosuvastatin; in some studies they were compared with placebo. Doses ranged from 10mg to 80mg. Mean age of participants was 63 years. Definitions of major cardiovascular events varied and were reported in the paper.

Three reviewers independently selected studies for inclusion. Discrepancies were resolved by consensus.

Assessment of study quality
There was no reported assessment of trial quality.

Data extraction
Data were extracted to enable calculation of odds ratios (OR) and 95% confidence intervals (CIs).

Three reviewers independently extracted data. Discrepancies were resolved by consensus.

Methods of synthesis
Odds ratios (OR) were pooled in random-effects meta-analyses. Statistical heterogeneity was assessed using $\chi^2$. Sensitivity analyses excluded placebo-controlled trials and one trial that represented primary prevention.

Results of the review
Seven RCTs (50,972 participants) were included in each of the meta-analyses. Mean follow-up ranged from one to 4.9 years. Two trials were placebo controlled.

Stroke events were significantly reduced by intensive lipid lowering with statins (OR 0.80, 95% CI 0.71 to 0.89), as were major coronary events (OR 0.74, 95% CI 0.65 to 0.83) and mortality from cardiovascular or coronary heart disease (OR 0.84, 95% CI 0.74 to 0.95). All results remained statistically significant following removal of trials in the sensitivity analysis.

There was no statistically significant difference between groups in relation to treatment discontinuation. Liver enzyme elevation was significantly increased as a result of intensive lipid lowering (OR 3.96, 95% CI 2.08 to 7.53).
When all studies were included, significant heterogeneity was found for major coronary events, liver enzyme elevation and treatment discontinuation. There was no statistically significant heterogeneity when the placebo-controlled trials were removed.

**Authors' conclusions**
In those at high risk of cardiovascular events, intensive lipid lowering therapy with statins to LDL-C level less than 2.1mmol/L significantly reduced risk of stroke, major coronary events and cardiovascular or coronary heart disease deaths compared to LDL-C level 2.1mmol/L or more.

**CRD commentary**
The review question was clear. Inclusion criteria were broad for interventions, but potentially reproducible for all aspects. Data sources included some relevant sources, but the possibility of publication bias could not be ruled out. The processes of study selection and data extraction were conducted with sufficient attempts to minimise error and bias. The absence of any reported quality assessment made the reliability of included trials unclear. Some study details were presented, but there was little information on participant characteristics and this limited the interpretation of generalisability. The chosen method of synthesis appeared to be appropriate. Statistical heterogeneity was assessed and explored.

The review was largely well conducted, but the unknown methodological quality of included trials means that some caution is warranted when assessing the reliability of the authors' conclusion.

**Implications of the review for practice and research**
**Practice:** The authors stated that physicians should consider the risks and benefits of high-dose statins and monitor liver enzymes and other adverse events.

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

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