Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials

Cholesterol Treatment Trialists’ (CTT) Collaboration

CRD summary
This meta-analysis of individual patient data found that reducing low-density lipoprotein cholesterol with statins reduced the annual rate of heart attack, revascularisation and stroke by about 20% for each 1mmol/litre reduction achieved. These conclusions reflected the strong evidence presented and are likely to be reliable and applicable to a wide range of patients.

Authors' objectives
To assess the safety and efficacy of more versus less intensive lowering of low density lipoprotein (LDL) cholesterol with statins.

Searching
As reported in the study protocol, potentially eligible studies were identified prospectively by computer-aided literature searches, manual searches of journals, examination of reference lists of trials and review articles, examination of abstracts and conference proceedings, by collaboration with the trial register of the International Committee on Thrombosis and Haemostasis and by contacting colleagues, collaborators and drug manufacturers.

Study selection
Randomised controlled trials (RCTs) of more versus less intensive statin regimens and of statins versus control were eligible for the review. Trials had to have at least 1,000 participants and a treatment duration of at least two years. Prespecified outcomes of interest were cause-specific mortality, major coronary event, coronary revascularisation, stroke, major vascular event (major coronary event, revascularisation or stroke) and new cancer diagnosis.

Included studies compared a statin with a different statin, the same statin at a lower dose, usual care, placebo or no treatment. The more intensive statin regimens used atorvastatin, simvastatin or pravastatin at doses increasing to 80mg/day. The percentage of women in included trials varied from 0% to 68%, people with diabetes from less than 1% to 100% and people with prior coronary heart disease from 0% to 100%.

The authors did not state explicitly how trials were selected for the meta-analysis.

Assessment of study quality
Individual patient data (IPD) and summary data were checked for consistency and completeness as reported in the study protocol. Queries were referred to the principal investigator of the trial concerned.

Data extraction
Individual patient data were used to derive the effect of treatment on disease event rates in each trial (rate ratio, RR), calculated from the logrank observed-minus-expected (o-e) statistic and its variance weighted by the absolute LDL cholesterol difference in that trial at one year. Results were reported as effects per 1mmol/L reduction in LDL cholesterol. Data were analysed on an intention-to-treat basis.

Methods of synthesis
Pooled rate ratios (unweighted or per mmoL/L in LDL cholesterol) and associated 95% or 99% confidence intervals (CIs) were calculated by meta-analysis. Subgroup analyses were used to investigate the effects of various prognostic factors and of baseline LDL cholesterol. Risk reductions in subgroups were compared by X² tests for heterogeneity or trend as appropriate.

Results of the review
Five RCTs of more versus less intensive statin regimens (39,612 participants and median follow-up of 5.1 years) and 21 RCTs of statin versus control (129,526 participants and median follow-up of 4.8 years) were included. Three eligible trials with 11,342 participants were excluded because individual patient data were unavailable.

Compared with less intensive regimens, more intensive regimens produced a statistically significant reduction in major vascular events (RR 0.85, 95% CI 0.82 to 0.89). Major coronary events (RR 0.87, 95% CI 0.81 to 0.93), revascularisation (RR 0.81, 95% CI 0.76 to 0.85) and stroke of any kind (RR 0.86, 95% CI 0.77 to 0.96) were all significantly reduced by the more intensive regimen.

Across all trials there was a significant reduction in major vascular events per 1mmol/L reduction in LDL cholesterol (RR 0.78, 95% CI 0.76 to 0.80) and this was found in all types of patient, including those with low LDL cholesterol concentrations (lower than 2mmmol/L) on the less intensive or control regimen. All-cause mortality was significantly reduced by 10% per 1mmol/L reduction in LDL cholesterol (RR 0.90, 95% CI 0.87 to 0.93), which largely reflected significant reductions in death from coronary heart disease (RR 0.80, 99% CI 0.74 to 0.87) and other cardiac causes (RR 0.89, 99% CI 0.81 to 0.98). Even at low LDL cholesterol concentrations, there were no significant differences in deaths from cancer or other non-vascular causes or in cancer incidence. There were more cases of rhabdomyolysis in the more intensive statin group (14 versus six cases, an observed excess of four per 10,000). Results of other analyses were reported.

**Authors' conclusions**
Further reductions in LDL cholesterol safely produced definite further reductions in the incidence of heart attack, revascularisation and stroke; each 1mmol/L reduction reduced the annual rate by just over 20%. There was no evidence of any threshold within the cholesterol range studied, which suggested that reduction of LDL cholesterol by 2-3mmol/L would reduce risk by about 40% to 50%.

**CRD commentary**
The meta-analysis had clear objectives and inclusion criteria. Eligible trials were located using a range of appropriate methods and selected for inclusion before any results were known. Three trials were excluded from the analysis because of a lack of individual patient data, but it was unlikely that inclusion of these trials would have affected the findings. Although not reported in this paper, the protocol specified the use of appropriate methods for checking individual patient data for consistency and resolving any queries. Statistical methods used for the meta-analysis seemed appropriate. Differences between trial populations were examined through a series of subgroup analyses, which showed that the findings were applicable to a wide range of participants. The authors' conclusions are likely to be reliable.

**Implications of the review for practice and research**
**Practice:** The authors stated that the primary goal for patients at high risk of occlusive vascular events should be to achieve the largest LDL cholesterol reduction possible without materially increasing myopathy risk.

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

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