The relationship between reduction in low-density lipoprotein cholesterol by statins and reduction in risk of cardiovascular outcomes: an updated meta-analysis

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CRD summary
This review found that, after treatment with statins, there was a significant positive relationship between the reduction in low-density lipoprotein cholesterol and reduction in the risk of major cardiovascular events. However, uncertainties about the methodologies used in the review and the absence of trial quality data mean that the reliability of the authors' conclusions is unclear.

Authors' objectives
To provide an updated meta-analysis of the Cholesterol Treatment Trialists' (CTT) Collaboration systematic review (see Other Publications of Related Interest), by including trials published since 2005, to further quantify the relationship between reduction in low-density lipoprotein cholesterol by treatment with statins and reduction in cardiovascular risk.

Searching
MEDLINE, EMBASE, Derwent Drug File and the Cochrane Library were searched to December 2008 for English-language studies. Search terms were reported.

Study selection
Randomised trials in which statin treatment was compared with active-control (defined as the use of a statin comparator), a placebo or normal treatment, with more than one year of follow-up and enrolling more than 1,000 participants, were eligible for inclusion. No specific inclusion criteria were outlined for the participants and conditions to be included. Clinical outcomes to be examined included cardiovascular end-points of vascular mortality, major coronary events (classified as non-fatal myocardial infarction or coronary disease death), major vascular events (stroke, major coronary events, coronary revascularisation), and mean absolute changes in low-density lipoprotein cholesterol at one year.

Atorvastatin was the most common statin assessed in the included trials; other statins assessed were pravastatin, simvastatin, lovastatin, fluvastatin and rosuvastatin. Most trials compared statin with placebo, but comparisons with usual care and other active treatments were also included. Follow-up ranged from 1.9 to 5.6 years and the age of the reported participants ranged from 18 to 90 years. The included patients were from primary and secondary prevention populations. Most trials included diabetic patients.

The reviewers did not state how the studies were selected for the review, or how many reviewers performed the study selection.

Assessment of study quality
The authors did not assess the validity of the included trials.

Data extraction
Data were extracted on the outcomes specified above and combined into a meta-analysis.

The reviewers did not state how the data were extracted for the review, or how many reviewers performed the data extraction.

Methods of synthesis
Random-effects meta-regression was applied to the mean absolute changes in low-density lipoprotein cholesterol at one year and the respective relative risks (RR) and corresponding 95% confidence intervals (CI) of the cardiovascular endpoints and major vascular events. The log relative risk of an event was regressed against the mean reduction in low-
density lipoprotein cholesterol between statins, (atorvastatin, simvastatin, pravastatin and rosvastatin) and their comparators (active statin treatment, placebo or usual care). To account for the precision of the relative risk estimate from each trial, each trial was weighted using the inverse-variance of the log relative risk. The $r^2$ statistic was also calculated to provide an estimate of the heterogeneity accounted for by reductions in low-density lipoprotein cholesterol.

**Results of the review**

Twenty-five trials (n=155,613 participants) were included in the review. Events occurring included 6,321 vascular deaths, 23,791 major vascular events, 11,357 major coronary events and 4,717 strokes. The mean follow-up was 4.2 years.

**Primary analysis** (24 trials): For every 25-mg/dL (0.65mmol/L) reduction in low-density lipoprotein cholesterol, the proportionate reduction in risks for the following outcomes were: vascular mortality 11% (RR 0.89, 95% CI 0.87 to 0.92; $r^2=0.75$), major coronary events 16% (RR 0.84, 95% CI 0.82 to 0.86; $r^2=0.87$), major vascular events 14% (RR 0.86, 95% CI 0.84 to 0.88; $r^2=0.84$) and fatal and non-fatal strokes 10% (RR 0.90, 95% CI 0.86 to 0.94; $r^2=0.47$). For every 1.0mmol/L reduction in low-density lipoprotein cholesterol, the proportionate risk reductions were 16% for vascular mortality, 20% for major coronary events, 23% for major vascular events and 15% for fatal and non-fatal strokes.

**Secondary analysis** (25 trials, including results from a trial of patients with heart failure): For every 25-mg/dL (0.65mmol/L) reduction in low-density lipoprotein cholesterol, the proportionate reductions in risks for the following outcomes were: vascular mortality 10% (RR 0.90; 95% CI 0.87, 0.94, $r^2=0.56$), major vascular events 13% (RR 0.87; 95% CI 0.84, 0.90, $r^2=0.76$), major coronary events 15% (RR 0.85; 95% CI 0.82, 0.88, $r^2=0.76$), and fatal and non-fatal stroke 9% (RR 0.91; 95% CI 0.87, 0.95, $r=0.45$).

The results were similar when the analyses were stratified by primary or secondary prevention, but no data were given for these analyses.

**Authors’ conclusions**

There was a significant and positive relationship between reduction in low-density lipoprotein cholesterol and reduction in the risk of major cardiovascular events. These results further quantify the relationship between low-density lipoprotein cholesterol and cardiovascular risk, and support and extend the findings of the previous Cholesterol Treatment Trialists’ Collaboration review, which limited analyses to placebo-controlled trials published prior to 2005.

**CRD commentary**

This review was designed to update and expand the results of a previous systematic review. Few criteria for inclusion were stipulated and no specific inclusion criteria were outlined for the participants and conditions. However, one trial was excluded because the patient population were subjects with heart failure, classified by the reviewers as a distinct disease subgroup. The literature search was confined to English-language studies and no attempts were made to identify unpublished studies; so relevant studies may have been missed and language/publication biases could not be ruled out. Steps taken to minimise errors and bias were not reported for any aspects of the review process.

Relevant trial details, in terms of treatment comparisons, participants and outcomes were reported, and the statistical analyses used seemed appropriate. However, no details were provided on trial quality, which made it difficult to assess the reliability of the results. This made it difficult to draw any conclusions from the evidence presented, so the reliability of the authors' conclusions is unclear.

Two authors disclosed consultancy services with Pfizer Australia Pty Ltd; three authors disclosed holding stock and/or stock options in Pfizer; one author received honoraria from Pfizer Australia Pty Ltd.

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

**Practice:** The authors did not state any implications for practice.

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