Association between change in high density lipoprotein cholesterol and cardiovascular disease morbidity and mortality: systematic review and meta-regression analysis


CRD summary
This review and meta-regression concluded that increasing the amount of high density lipoprotein cholesterol with lipid modifying treatment did not reduce the risk of coronary heart disease events and death or all-cause deaths. Results supported recommendations for reducing low density lipoprotein cholesterol with lipid-modifying interventions. This was a well-conducted review and the authors' conclusions were likely to be reliable.

Authors' objectives
To investigate the association between changes in high density lipoprotein (HDL) cholesterol with lipid-modifying treatment and coronary heart disease-related morbidity and mortality.

Searching
MEDLINE, EMBASE, CINAHL, Cochrane Central Register of Controlled Trials and AMED were searched up to October 2006 with no language restrictions. Full search details were available from the authors. References of relevant papers and experts in the field were contacted in order to identify any additional papers.

Study selection
Randomised controlled trials (RCTs) were eligible for inclusion if they: compared any lipid-modifying agent or diet with placebo or usual care; compared a more intensive with a less intensive lipid-modifying treatment regimen; targeted a reduction in cardiovascular risk; and followed patients for at least six months. Studies were required to report mortality or myocardial infarctions separately for treatment groups.

Excluded studies were those that: did not report change from baseline or follow-up concentrations of HDL cholesterol and low density (LDL) lipoprotein cholesterol; and those with serious questions about the integrity of the data.

The following classes of intervention were included in the review: statins, fibrates, resins, combinations with niacin, n-3 fatty acids, diet/surgery, acyl-CoA:-cholesterol acyltransferase (ACAT) inhibitors, probucol, glitazones, hormones and torcetrapib (plus statin).

Median follow-up was 34 months (interquartile range 24 to 54). Where reported, mean age of participants ranged from 42 to 75 years. Mean baseline HDL ranged from 32 mg/dL to 62 mg/dL. Mean baseline LDL ranged from 84 mg/dL to 279 mg/dL. The proportion of people with prior history of coronary heart disease and current status for diabetes and hypertension varied substantially between trials. Outcomes of interest included change in HDL, change in LDL and change in triglycerides for total deaths, coronary heart disease deaths and coronary heart disease events (combined outcome of non-fatal myocardial infarction and coronary heart disease death).

Two reviewers independently selected studies for inclusion in the review; any disagreements were resolved by consensus or third-party arbitration.

Assessment of study quality
Study quality was assessed using the following criteria: concealment of allocation; blinding of patients, caregivers, or clinical outcome assessors; adherence to the intention-to-treat (ITT) principle; stopping early for benefit; and the proportion of patients lost to follow-up. Two reviewers independently assessed studies for methodological quality.

Data extraction
Change from baseline lipid concentrations for each trial were calculated. Risk ratios (RRs) and their associated 95% confidence intervals (CIs) were calculated for clinical outcomes of interest. Data was extracted using standardised pre-
In extracting data regarding coronary heart disease death, the hierarchy used was: coronary heart disease death; fatal myocardial infarction; fatal cardiac events; fatal cardiovascular events. Where trials had multiple treatment arms, the control group was used as comparator for all treatment arms.

Two reviewers independently extracted data from the included studies.

**Methods of synthesis**

Studies were combined in a meta-analysis using a random-effects model. Summary estimates were reported as RRs and their associated 95% CIs. Meta-regression was used to investigate the association between change in HDL and LDL cholesterol and the RR of death or a CHD event (as a univariate analysis and also after adjusting for drug class). The interaction between change in cholesterol and drug class was assessed. Model assumptions were checked and $R^2$ was used to assess the proportion of variability explained by the model.

Analyses were repeated using percentage change in cholesterol and yielded similar results (absolute change was reported). Pre-specified sensitivity analyses were performed, focusing on: trials that used interventions known to raise HDL cholesterol (excluding trials using n-3 fatty acids, low fat diets and probucol); trials specifically chosen to raise HDL cholesterol (fibrates and niacin combinations); and trials of patients with renal failure. In addition, trials with agents associated with harmful effects such as torcetrapib or hormones were excluded, as were trials with less than one year follow-up or two years or less follow-up.

**Results of the review**

One hundred and eight RCTs were included in the review (n=299,310); three trials had multiple treatment arms. Sixty two were statin trials (n=157,151). Nine were fibrate trials (n=22,370). Three were resin trials (n=4,005). Six were combination with niacin trials (n=779). Nine were n-3 fatty acids trials (n=13,768). Five were diet/surgery trials (n=62,645). Two were ACAT inhibitor trials (n=717). Two were probucol trials (n=481). Two were glitazones trials (n=9,589). Nine were hormones trials (n=25,710). Two were torcetrapib (plus statin) trials (n=2,095).

The weighted mean change in LDL cholesterol was -23 mg/dL (SD 19). The weighted mean change in HDL cholesterol was 1.7 mg/dL (SD 3.1), and the weighted mean change in triglycerides was -15 mg/dL (SD 18). HDL cholesterol was raised by most classes of intervention except n-3 fatty acids, low-fat diets, ACAT inhibitors and probucol. Almost all classes of intervention reduced LDL cholesterol except n-3 fatty acids and glitazones. Compared to less intensive statin treatment, high-dose statin treatment (80 mg daily simvastatin or atorvastatin) was found to slightly decrease HDL cholesterol (weighted mean change -0.23 mg/dL (SD 0.83); statin treatment as a whole moderately increased HDL cholesterol (weighted mean change 1.6 mg/dL (SD 1.5)).

**Meta-regression**

A reduction in LDL cholesterol was associated with a statistically significant reduction in the risk of a CHD event with a 10 mg/dL reduction leading to a RR reduction of 7.2% (95% CI: 3.1% to 11.3%, p=0.001) for coronary heart disease death, 4.4 per cent (95% CI: 1.6% to 7.2%, p=0.002) for total deaths and 7.1 per cent (95% CI: 4.5% to 9.8%, p<0.001) for CHD events (adjusted for change in HDL cholesterol and different drug classes). No significant association of change in HDL cholesterol after adjusting for changes in LDL cholesterol and drug class was found.

**Sensitivity analyses**

Change in LDL cholesterol remained significantly associated with risk for coronary heart disease events, explaining a greater variability in trials that had a longer follow-up (R² 0.41 for trials with a follow-up of at least six months, 0.46 for trials with a follow-up of more than one year and 0.51 for trials with a follow-up of more than two years). Change in LDL cholesterol remained a significant predictor for coronary heart disease events in a multivariable model adjusted for change in HDL cholesterol, change in triglycerides and class of drug (relative risk reduction 7.4%, 95% CI: 4.4, 10.4; p<0.001). No associations between change in HDL cholesterol or triglycerides and risk of coronary heart disease events (after adjusting for LDL cholesterol) were found in the models analysed.
Authors' conclusions
Simply increasing the amount of circulating HDL cholesterol did not reduce the risk of coronary heart disease events, coronary heart disease deaths or total deaths. Results of the review supported recommendations that the primary goal for lipid modifying interventions was reduction in LDL cholesterol.

CRD commentary
The review question was supported by clear inclusion criteria. Several databases were searched and the authors made some attempts to locate unpublished material. There were no language restrictions. Methods used to select studies, extract data and assess study quality were likely to minimise the possibility of reviewer error or bias. The statistical analysis appeared appropriate and the authors investigated several potential sources of heterogeneity. A source of potential bias in this review was that around one third of studies had to be excluded as they did not report changes in cholesterol. Many of the results presented came from a meta-regression and it should be remembered that associations derived from meta-regressions are observational and thus have a weaker interpretation. Overall this was a well-conducted review. The authors' conclusions were a reasonable interpretation of the evidence presented.

Implications of the review for practice and research
Practice: The results of the review supported recommendations from clinical guidelines that emphasised targeting primarily LDL cholesterol in the prevention of cardiovascular morbidity and mortality.

Research: The authors suggested that future research should prospectively consider the results of assays to measure HDL function and then investigate evidence of pharmacological effects on patient important outcomes in long-term RCTs. The results of this project needed to be confirmed with an individual patient data meta-analysis from trials testing lipid-modifying interventions.

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