Meta-analysis of the relationship between non-high-density lipoprotein cholesterol reduction and coronary heart disease risk


CRD summary
This review concluded that most lipid-modifying monotherapies showed an approximate one-to-one relationship between the lowering of non-high-density lipoprotein cholesterol and coronary heart disease. There were multiple shortcomings, but a very large number of patients in randomised trials were included. The authors' conclusions may be reliable, but confirmation with individual patient data is required.

Authors' objectives
To determine the relationship between the lowering of non high-density lipoprotein (HDL) cholesterol and the reduction in coronary heart disease risk, for various lipid-modifying therapies.

Searching
MEDLINE was searched for articles from 1966 to May 2008; the search terms were not reported. English-language journals, the authors' reference files, and references of identified articles, reviews, and meta-analyses were also searched.

Study selection
Randomised controlled trials (RCTs) that evaluated the effects of diet, statins, niacin, fibrates, bile acid sequestrants, or surgery, compared with an active or placebo control, were eligible for inclusion. Apart from those assessing diet, trials were required to be blinded and all trials were required to have blinded outcome assessment. Eligible trials assessed total cholesterol and HDL or non-HDL cholesterol to within 1mg per dL at least once after baseline; the intervals for measurements were not fixed and averages over the trial were permitted. Trials of statins were required to report clinical events and to have a minimum duration of two years.

Trials in patients with serious noncardiovascular diseases or conditions were excluded from the review. Stroke events, coronary revascularisation, and diagnoses of unstable angina were not included as outcomes. Coronary heart disease outcomes were death related to coronary heart disease or nonfatal myocardial infarction. Included studies assessed statins, fibrates, niacin, a bile acid sequestrant, diet and ileal bypass surgery. The information reported on study populations was very limited.

The authors did not state how the papers were selected for the review, nor how many reviewers performed the selection.

Assessment of study quality
The authors did not state that they assessed validity, beyond requiring randomisation and blinding of outcome assessors and (in most trials) participants for inclusion.

Data extraction
Two reviewers independently performed the data extraction. Relative risks and standard errors were estimated from the total numbers of participants and the number of cases of nonfatal myocardial infarction and deaths from coronary heart disease in the treatment and control groups. Participant characteristics were extracted, but were not reported.

Methods of synthesis
Where more than one trial assessed an intervention, trials were combined using random-effects Bayesian meta-analysis with vague prior distributions for the parameters. The outcome was the log of the relative risk and the explanatory factors were the mean length of follow-up and the difference between groups in their mean HDL cholesterol levels. This was used to estimate the relationship between a 1% reduction in non-HDL cholesterol and the risk of a coronary heart disease event. Statistical heterogeneity was assessed using the Cochran Q statistic. Bayesian models were also used to evaluate the relationship between non-HDL cholesterol and coronary heart disease for different types of trial
(primary prevention, secondary prevention, or in patients with diabetes).

**Results of the review**

Thirty RCTs (n=132,021 patients) were included in the review. Fourteen trials assessed statins (n=100,827), seven assessed fibrates (n=21,647), six assessed niacin (n=4,445), one assessed a bile acid sequestrant (n=3,806), one assessed diet (n=458), and one ileal bypass surgery (n=838).

In statin trials, a 1% decrease in non-HDL cholesterol was associated with an estimated 4.5 year relative risk of a coronary heart disease event of 0.99 (95% Bayesian CI 0.98 to 1.00), which was a 1% decrease in relative risk. This translated into a relative risk of 0.78 (95% Bayesian CI 0.64 to 0.94) for a 25% decrease in non-HDL cholesterol. Trials of fibrates did not differ from statin trials (Bayes factor K=0.49) and no statistical heterogeneity was detected among them (p=0.68). In niacin trials there was evidence of heterogeneity (p=0.038). The largest trial, with 88% of patients, showed a 17% reduction in non-HDL cholesterol after 6.2 years and a 17% reduction in coronary heart disease risk, while the five smaller trials showed no consistent relationships between the variables.

There was little support for differences between different types of trial, in the relationship between the reduction in non-HDL cholesterol and the risk of coronary heart disease events.

**Authors' conclusions**

Reduction in non-HDL cholesterol was an important target for coronary heart disease prevention therapy. Most lipid-modifying drugs, when used as monotherapy, showed approximately a one-to-one relationship between the lowering of the percentage of non-HDL cholesterol and the reduction in the risk of coronary heart disease.

**CRD commentary**

The review question and the inclusion criteria were clear. Only one database was searched, which increases the chances that some relevant trials were not included in the review. No systematic search for unpublished studies was reported and it is not clear whether language restrictions were applied. These factors increase the chances of publication and language biases being present. The authors used methods designed to reduce bias and error in the extraction of data, but these were not reported in the selection of trials. While two quality criteria were used for inclusion, no further assessment of trial validity was undertaken and only limited information was available on trial reliability. The authors stated that they extracted data on patient characteristics, but these were not reported. Without important details of other coronary heart disease risk factors, such as age, gender, and smoking status, it is not possible to assess the comparability of the trials and the generalisability of the results. The use of Bayesian meta-analysis to combine the trials appeared to be appropriate and reasonable steps were taken to explore potential heterogeneity. The results were not consistently reported with pooled outcomes given for only some of the meta-analyses and it is therefore not clear if the authors' conclusions reflected the results of the review.

There were multiple shortcomings, including a limited search process and a lack of reporting of the trial details, but the review did include a very large number of patients in randomised trials, which met some basic quality criteria. The authors' conclusions may be reliable, but confirmation with individual patient data is required.

Two authors reported financial relationships with a number of pharmaceutical companies.

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

**Practice**: The authors stated that their findings supported the use of non-HDL cholesterol as an important target of therapy, as recommended by the National Cholesterol Education Program (NCEP), Adult Treatment Panel III and the American Diabetes Association/American College of Cardiology consensus report on lipoprotein management.

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

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