Cholesterol reduction and clinical benefit: are there limits to our expectations?

Fager G, Wiklund O

Authors' objectives
To assess the clinical benefits of cholesterol-lowering regimens.

Searching
The authors do not state what sources were searched or the strategies used.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) with greater than 50 reported events.

Specific interventions included in the review
Cholesterol-lowering regimes including dietary interventions, the control of tobacco smoking and hypertension, and the use drug treatments (clofibrate (with or without nicotinic acid), cholestyramine, gemfibrozil, pravastatin and simvastatin). For the purposes of the analysis, the type of cholesterol-lowering regimen was ignored.

Participants included in the review
Patients undergoing cholesterol-lowering treatments using any drug and/or dietary interventions for primary or secondary prevention.

Outcomes assessed in the review
Reduction in major coronary heart disease (CHD) events defined as definite CHD deaths or nonfatal myocardial infarction. Trials were excluded if monitoring of progression of atherosclerosis was the major objective or if they only reported mortality data.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the authors performed the selection.

Assessment of study quality
The authors do not state that they assessed quality.

Data extraction
The authors do not state who, or how many of the authors, extracted the data.

A standardised benefit was calculated from the individual data to show which cumulative or additional percentage of CHD reduction could be expected per percent reduction in total cholesterol (TC) in strata of relative TC reductions or of reference (control) TC values.

Methods of synthesis
How were the studies combined?
The percentage difference between control and treatment groups (reduction) in major CHD events in the nine largest (n≥2000) trials was plotted against percent difference (reduction) in TC. The regressions for these trials and for all trials were calculated separately on log-transformed data. Curves derived from the regression equations were introduced in the plot.
In the primary studies, the observed CHD incidences were compared with incidences estimated from the non-intervened prospective studies by level of TC achieved in primary prevention trials. The achieved TC values were used in the regression equation.

For the secondary trials, the results from control groups of the trials were used as non-intervened data to calculate the regression equation, and then the estimated incidences in the treated groups were calculated as was done with the primary studies.

**How were differences between studies investigated?**

Differences in CHD incidences between study groups were tested with two-way ANOVA with studies as co-variates. Paired data were tested using Student's paired t-tests.

Relationships were tested using with linear regression analysis with logarithmic transformations. 95% confidence intervals (CIs) were calculated and a value of p less than or equal to 0.5 was considered to be statistically significant.

**Results of the review**

Seven primary prevention and 9 secondary prevention RCTs were included in the review. The total number of person-years-of experience (PYE) was almost 355,000 in the control groups and 348,000 in the intervention groups, with about 12% in secondary prevention trials. Altogether there were 4,456 major CHD events (54% in primary prevention trials) registered in the control groups and 3,642 (59% in primary prevention trials) in the treatment groups.

The mean follow-up times were 6.2 (95% CI: 4.9, 10.0) years in primary prevention trials and 4.4 (95% CI: 3.3, 6.2) in secondary prevention trials.

For major CHD events, ANOVA in the primary prevention trials showed statistically different results between control and intervention groups (p = 0.021) as well as between individual studies (p = 0.011). The mean incidence in control groups was 10.0 (95% CI: 6.7, 13.2) and in the intervention groups 7.6 (95% CI: 5.3, 9.9) events per 1000 PYE.

For major CHD events, ANOVA in the secondary prevention trials showed statistically different results between control and intervention groups (p = 0.005). The mean incidence in control groups was 59.2 (95% CI: 44.1, 74.3) and in the intervention groups 46.9 (95% CI: 36.9, 57.0) events per 1000 PYE.

The percentage change in CHD levelled off exponentially with increasing percentage change in TC indicating that the degree of clinical benefit becomes less and less for additional decreases in TC. The regression was statistically significant for the nine large trials (R-squared = 0.73, p = 0.003). For all 16 trials the regression was also statistically significant (R-squared = 0.39, p = 0.010). The two regression curves were almost superimposable.

**Authors' conclusions**

The current results support the clinical benefit from cholesterol-lowering therapy and show that the type of therapy is less important than the degree of cholesterol reduction. The clinical benefit is 6 times better in secondary than in primary prevention and is doubled in cohorts with severe compared with mild hypercholesterolemia.

**CRD commentary**

The authors have stated their research question and inclusion and exclusion criteria. There is no report on the process of literature search or the selection of articles. The authors have not made any quality assessment of the included trials and do not report how the data was extracted for the review. This missing data makes it difficult to replicate the review. It is also not possible to evaluate the review for biases in the authors' selection, inclusion and evaluation of the individual studies or of their reporting of results.

The statistics used to combine the studies are appropriate and very well reported, and differences between groups and between studies have been investigated and discussed.
Although the conclusions follow from the reported results, because of the missing information the review should be viewed with some caution.

**Implications of the review for practice and research**
The authors did not state any implications for further research and practice.

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