Low-density lipoprotein-dependent and -independent effects of cholesterol-lowering therapies on C-reactive protein: a meta-analysis

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CRD summary
This review concluded that most of the anti-inflammatory effect of statins and other low-density lipoprotein (LDL)-lowering therapies is related to the magnitude of the reduction in LDL. The evidence supports the author’s conclusions, but it is difficult to assess the reliability of the findings given the poor reporting of both the review methods and the individual studies.

Authors’ objectives
To assess the relationship between the low-density lipoprotein (LDL) cholesterol dependent and independent effects of cholesterol-lowering therapies on changes in C-reactive protein (CRP) in healthy or stable individuals.

Searching
MEDLINE was searched up to August 2005 for articles in English; the search terms were reported. Relevant systematic reviews and the reference lists of retrieved articles were screened for additional studies.

Study selection
Randomised controlled trials (RCTs) that compared the effects of cholesterol-lowering interventions on levels of LDL and CRP with placebo, in healthy or clinically stable individuals, were eligible for inclusion. Studies excluded from the review were those that assessed: risk factors; histopathology; participants with conditions known to elevate inflammation processes (e.g. vasculitis, infection, acute coronary syndromes); single-dose therapies or therapies lasting less than 2 weeks; herbal treatments; the use of low-sensitivity CRP assays (lower limits less than >0.5 mg/L); and non-LDL lowering therapies or diets. Most of the included studies assessed statin-only therapies, with the remainder mainly assessing statin and ezetimibe combination therapies; a small number of studies assessed ezetimibe-only therapies and non-statin therapies including fish oil, niacin, diet and fibrate. The median duration of therapy was 12 weeks (range: 4 to 270). The median age of the included participants was 58 years (range: 35 to 63), the median baseline LDL was 153 mg/dL (range: 105 to 188) and the median baseline CRP was 2.2 mg/L (range: 0.2 to 5.0).

Study authors and assay manufacturers were contacted if there was any doubt about the sensitivity of the CRP assay used, or about any other aspect of the study which could affect its eligibility.

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

Assessment of study quality
Aspects of study quality were extracted and recorded for each study: type of study design (randomised controlled trial, crossover or parallel design), blinding, use of an intention-to-treat analysis and completeness of follow-up.

The author did not state how the quality assessment was performed.

Data extraction
The average mean differences in LDL and CRP over the study period, as a percentage change from baseline levels, were extracted or estimated from final and baseline data. The variance of the within-group changes was estimated using standard deviations or standard errors (where reported) or calculated using published statistical methods. The difference in mean change (placebo minus treatment) was calculated for each study.

The author did not state how many reviewers performed the data extraction.
Methods of synthesis
Estimates were pooled using both random-effects and fixed-effect analyses. Statistical heterogeneity was assessed using the $\chi^2$ statistic. Potential sources of heterogeneity were investigated using subgroups based on participant characteristics. A subgroup analysis of trials directly comparing statins was also carried. The correlation between change in CRP and LDL was estimated using a weighted correlation coefficient. This was explored further using a meta-regression analysis alone, and after adjusting for treatment type and study characteristics. Publication bias was assessed using funnel plots and the Begg and Egger test of bias.

Results of the review
Twenty-three placebo-controlled RCTs (median sample size of 55; range: 35 to 63) with 57 treatment groups were included in the review. The majority of the studies used a parallel-group design (52 treatment groups).

Forty treatment groups had less than 15% attrition. Further details about the quality of the trials was not reported.

Across all interventions, the pooled reduction in CRP in comparison with placebo was 28% (95% confidence interval, CI: 26, 30). However, significant statistical heterogeneity was detected ($p<0.0001$) and the effect size was less with the fixed-effect model (16%) than with the random-effects model. Significantly greater reductions in CRP were reported for statin-ezetimibe combinations and statin-only therapies versus other LDL-lowering therapies, and for 80 mg/day statin versus lower statin doses. A dose relationship with greater LDL reduction was also observed with increasing statin dosages. Study type, duration of the intervention and study sample size had no impact on the change in CRP after adjusting for change in LDL. The meta-regression model showed a significant correlation between change in CRP and change in LDL (correlation, $r=0.80$, $p<0.001$). Overall, 89% to 98% of the reduction in CRP was related to the effects of the statin, independent of the reduction in LDL.

The funnel plot and Begg's analysis showed a significant risk of publication bias. However, stratification for median reduction in LDL showed no evidence of bias, suggesting that the overall result was due to differences in LDL reduction across the various studies, rather than directly related to publication bias.

Authors' conclusions
The majority of the anti-inflammatory effect of statins and other LDL-lowering therapies is related to the magnitude of the reduction in LDL. LDL cholesterol should therefore remain the primary measure of efficacy.

CRD commentary
This review answered a clear review question, but only carried out a limited search of the literature. The risk of publication bias was assessed and considered to be low, but relevant studies may still have been missed through the inclusion of only English language articles and the fact that only one main data source was searched. There may also be a risk of reviewer error and bias, but this is difficult to assess as the review methods were not reported. This was, however, a single author review, which suggests that the study selection, quality assessment and data extraction processes might not have been independently verified. Some aspects of study validity were reported, but without further details it is difficult to assess the reliability of the review data. In addition, few individual study details were reported and only a brief overview of mean and median study characteristics was available to the reader. Consideration was, however, given to the potential differences between studies: further statistical analyses were conducted to investigate possible sources of statistical heterogeneity and the relationships between key variables. Overall, the evidence supports the author's conclusions, but it is difficult to assess the reliability of the findings given the poor reporting of both the review methods and the individual studies.

Implications of the review for practice and research
Practice: The author stated that this review ‘supports the concept of intensive LDL lowering to achieve maximum reductions in inflammation to stabilise atherosclerotic plaque’.

Research: The author stated that LDL cholesterol is the primary target for the prevention of cardiovascular disease, and that it should be the primary outcome measure for assessing the efficacy of statins and non-statin LDL-lowering therapies.
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