Are treatment targets for hypercholesterolemia evidence based? Systematic review and meta-analysis of randomised controlled trials

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CRD summary
This review concluded that recommendations to consider statins as a first-line drug treatment for hypercholesterolaemia were evidence-based. There was no firm evidence regarding when to start statin treatment and what target low-density lipoprotein cholesterol level should be attained. The authors' conclusions are likely to be reliable. The possibility of publication bias should be borne in mind.

Authors' objectives
To identify the evidence regarding treatment target values for low-density lipoprotein (LDL) cholesterol levels in children with familial hypercholesterolaemia and assess the effects of statins on improving surrogate markers of coronary artery disease.

Searching
MEDLINE, CINAHL and The Cochrane Library were searched from inception to December 2007 without language restrictions. Search terms were reported. Reference lists of relevant publications were screened for additional studies.

Study selection
Randomised controlled trials (RCTs) and quasi-RCTs that compared statin with placebo or no treatment in children (aged eight to 18 years) with heterozygous familial hypercholesterolaemia were eligible for inclusion. Studies that used lipid-lowering co-medication or unblinded treatment were excluded. Review outcomes included changes in total cholesterol, LDL cholesterol, high-density lipoprotein cholesterol, apolipoprotein B, apolipoprotein A, blood pressure and adverse events.

The included studies evaluated the statins: atorvastatin, lovastatin, pravastatin and simvastatin. Dose and duration of treatment varied between trials. All included patients were diagnosed with probable or definite heterozygous familial hypercholesterolaemia and only a portion had a genetically proven diagnosis. Study duration ranged from 12 to 104 weeks. Most studies recruited children who were already compliant with a recommended low-fat diet; both intervention and control groups were maintained on this diet during the trial period.

Two reviewers independently assessed studies for inclusion.

Assessment of study quality
Study quality was assessed using criteria of allocation concealment, blinding of investigators, participants, outcome assessors and data analysts, intention-to-treat analysis and loss to follow-up.

The authors did not state how many reviewers performed validity assessment.

Data extraction
For continuous outcomes, means and standard deviations were extracted to enable calculation of mean differences (MDs) and 95% confidence intervals (CIs). For dichotomous outcomes, event rates were extracted to enable calculation of relative risks (RRs) and 95% CIs.

Two reviewers independently performed data extraction. Any disagreement was resolved by discussion.

Methods of synthesis
Studies were combined in meta-analyses. Pooled relative risks and weighted mean differences (WMDs), with 95% CIs,
were calculated. Statistical heterogeneity was assessed using $X^2$ and $I^2$. Results of both random-effects and fixed-effect models were presented where there was substantial heterogeneity ($I^2>50\%$), otherwise only the results of the fixed-effect model were presented. The authors did not assess publication bias using a funnel plot due to the small number of studies.

**Results of the review**

Seven trials were included in the review (n=884 patients). All trials used adequate randomisation. Only two trials had an adequate method of allocation concealment. All trials were double blinded, and used intention-to-treat analyses. Loss to follow-up rates of trials ranged from zero to 17%.

Compared with placebo, significant reductions in total cholesterol were observed for lovastatin (WMD -21.88, 95% CI -30.98 to -12.78; two trials) and pravastatin (WMD -39.82, 95% CI -74.80 to -4.84; two trials). Significant heterogeneity was found for both outcomes ($I^2=61\%$ and $I^2=97\%$).

Compared with placebo, significant reductions in LDL cholesterol was observed for lovastatin (WMD -25.72; 95% CI -36.40 to -15.05; two trials) and pravastatin (WMD -43.10, 95% CI -69.85, to -16.35; two trials). Significant heterogeneity was found for both outcomes ($I^2=70\%$ and $I^2=94\%$). There were no significant differences in high-density lipoprotein cholesterol between the treatment and placebo groups.

The evidence on target values for LDL cholesterol levels in children was limited to one study that demonstrating that 60% of the children in the treatment group reached the target LDL cholesterol level of less than 130mg/dL. None of the children in the placebo group reached this target LDL cholesterol level.

The evidence of the effect of statins on surrogate markers of atherosclerosis (carotid intima-media thickness, flow-mediated dilation) was limited to two studies. Further results were reported, as were adverse events.

**Authors' conclusions**

Recommendations to consider statins as a first-line drug treatment for hypercholesterolaemia were evidence-based. There was no firm evidence regarding when to start statin treatment or what target LDL cholesterol level should be attained.

**CRD commentary**

This review's inclusion criteria were clear. Relevant databases were searched. Efforts were made to find published studies. Unpublished studies were not sought, which increased potential for publication bias. No language restriction was applied to the search, which minimised the risk of language bias. Steps were made to minimise reviewer biases and errors in the processes of study selection and data extraction; it was unclear whether quality assessment was performed in duplicate. Appropriate criteria were used to assess study quality. Statistical heterogeneity was assessed and appropriate methods were used to pool the results.

The authors' conclusions are likely to be reliable. The possibility of publication bias and the small number of included studies should be borne in mind.

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

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

**Research:** The authors stated that future trials should study high-risk groups such as obese and diabetic patients and incorporate composite end points; these may help define treatment guidelines.

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