Statin treatment for children and adolescents with heterozygous familial hypercholesterolaemia: a systematic review and meta-analysis

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CRD summary
This review assessed the efficacy and safety of statin therapy in children and adolescents for the treatment of hypercholesterolaemia. The authors concluded that statin mono-therapy was efficacious and well tolerated in the short-term. Despite some limitations, the authors’ conclusions appear to follow from the results presented.

Authors’ objectives
To determine the efficacy and safety of statin (HMG-CoA reductase inhibitor) treatment in children and adolescents with heterozygous familial hypercholesterolaemia.

Searching
MEDLINE, EMBASE, the Cochrane Library and Current Controlled Clinical Trials were searched from 1986 to July 2006, without language restrictions. Search terms were reported. References from relevant articles were checked and experts in the field contacted to identify any additional studies.

Study selection
Studies of statin treatment in patients (≤20 years) with heterozygous hypercholesterolaemia, that reported clinical data as primary outcomes, were eligible for inclusion in the review. Case reports were excluded from the review.

Study designs included in the review were randomised controlled trials (RCTs), prospective case series, a parallel matched non-randomised trial, a cross-over trial and a time series comparison. Interventions included in the review were: pravastatin, simvastatin, lovastatin, atorvastatin; further details are reported in the review.

For the RCTs, follow-up ranged from six to 96 weeks (median duration of treatment was 27 weeks). All RCTs identified participants either by a minimum low density lipoprotein (4.0mmol/L) and at least one parent having a clinical, or molecular diagnosis of familial hypercholesterolaemia, or a positive low density lipoprotein receptor gene mutation.

In included studies, participants’ ages ranged from four to 18 years (eight to 18 years for the RCTs). Most studies included both genders but two studies included only males. Primary outcomes measures were mean change from baseline in low density lipoprotein, high density lipoprotein, and total cholesterol and triglycerides. A number of other outcomes, including laboratory biochemistry, cardiovascular and adverse events, were also reported.

One reviewer reviewed titles and abstracts and selected articles for inclusion in a preliminary short-list, and two reviewers independently selected studies for inclusion in the review from this short-list. Any disagreements were resolved through consensus between three reviewers.

Assessment of study quality
The quality of the RCTs was assessed using the Jadad scale. This scale considers reported randomisation, allocation concealment, drop-outs and withdrawals, and a maximum score of 5 points could be awarded to each study.

It was not clear how the papers were assessed for validity or how many reviewers performed the validity assessment.

Data extraction
Mean and standard deviation of change in low density lipoprotein cholesterol were calculated for both the intervention and placebo groups for change from baseline to follow-up. Unadjusted low density lipoprotein and high density lipoprotein cholesterol, triglyceride, apolipoprotein A1, and apolipoprotein B data (change from baseline to follow-up) were included in the pooled analysis. Data from cross-over trials and time-series comparisons were excluded.
Information was derived, where possible, from graphical presentations if the text or tables did not report numerical data. Where comparison groups with different statin doses were reported, data from the higher dose was used.

Two reviewers extracted data from the primary studies.

**Methods of synthesis**

Studies were pooled in a meta-analysis, and summary estimates were reported as weighted mean differences with 95% confidence intervals. It was not clear whether a fixed-effect or random-effects model was used. Data were pooled where two or more studies presented data in a uniform format with appropriate measures of distribution. Statistical heterogeneity was assessed using the $\chi^2$ test and the $I^2$ statistic.

**Results of the review**

Eighteen studies were included in the review: eight RCTs (n=947 patients); one parallel matched non-randomised trial (n=16 patients); one cross-over trial (n=40), one time series comparison (n=69 patients); and seven prospective case series (n=137 patients). The median Jadad score for the RCTs was 3.5 (range 1 to 5).

**Low density lipoprotein**: Six RCTs reported absolute mean change in low density lipoprotein cholesterol. A reduction in low density lipoprotein cholesterol was found with statin therapy compared with placebo (1.89 mmol/L, 95% confidence interval (CI): 1.58 to 2.19). Evidence of significant statistical heterogeneity was found. Five RCTs reported efficacy of statin therapy as relative mean percentage change of low density lipoprotein cholesterol. A significant reduction in low density lipoprotein cholesterol from baseline was found with statin treatment compared with placebo (weighted mean difference -32.46%, 95% CI: -40.66 to -24.27). Evidence of significant statistical heterogeneity was found.

**High density lipoproteins**: Pooled results for high density lipoprotein found a significant absolute increase (0.05 mmol/L, 95% CI: 0.01 to 0.10) and an increase in relative mean change (weighted mean difference 3.36%, 95% CI: 0.76 to 5.96) with statin use compared to placebo. No statistically significant between group differences were found for absolute reduction or relative mean percentage change in apolipoprotein AI (-0.03 g/L, 95% CI: -0.17 to 0.10 ) and weighted mean difference (1.33%, 95% CI: -1.32 to 3.98).

**Triglycerides**: No statistically significant between group differences were found at follow-up for mean percentage change in triglyceride levels (weighted mean difference -2.99, 95% CI: -17.64 to 11.65), based on three RCTs. There was no evidence of significant statistical heterogeneity.

**Apolipoproteins**: An absolute reduction (0.62 g/L, 95% CI: 0.52 to 0.72) and relative reduction (27.7%, 95% CI: 20.6 to 34.8) were found in apolipoprotein B with statin use compared with placebo. Evidence of significant statistical heterogeneity was found. Too few trials reported apolipoprotein II and lipoprotein(a) to enable results to be pooled.

**Adverse events**: One RCT found that statin therapy significantly attenuated the progression of carotid medial thickness (p=0.02) and another RCT found that statin therapy improved endothelial function (p=0.05). No statistically significant differences between intervention and placebo were found for clinical or laboratory adverse reactions.

**Authors’ conclusions**

In the short-term, statin mono-therapy in children and adolescents was efficacious and well tolerated for the treatment of hypercholesterolaemia, but safety in longer-term use remained unclear. Current evidence supported use for children at highest cardiovascular risk.

**CRD commentary**

The review was supported by clear inclusion criteria and several databases were searched for relevant studies. The search was not restricted by language, although the authors do not appear to have assessed the possibility of publication bias. Methods used to select studies and extract data were mostly likely to minimise reviewer error and bias. It is unclear whether similar methods were used to assess study quality. Only the quality of the RCTs were assessed (total scores were reported). Further details regarding the included participants might have been useful in order to better assess generalisability. Only RCTs were included in the main analysis, and the authors appeared to base their conclusion...
on these results. Standard meta-analytic methods were used to combine studies, but, although the authors stated that a fixed-effect model was used, forest plot presentations indicate that a random-effects model was used. Statistical heterogeneity was found for a number of models and the authors did not attempt to assess possible reasons for this heterogeneity. Overall, despite some limitations in the review, the authors' conclusions seem to follow from the results presented.

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

**Practice:** Current evidence supports short-term statin therapy for children at highest cardiovascular risk. Results from longer-term on-going trials may extend these indications.

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

**Funding**

Post-graduate Institute of Medicine grant, University of Colombo, Sri Lanka.

**Bibliographic details**


**PubMedID**

17097660

**DOI**

10.1016/j.atherosclerosis.2006.09.030

**Original Paper URL**

http://www.atherosclerosis-journal.com/article/S0021-9150(06)00595-8/abstract

**Indexing Status**

Subject indexing assigned by NLM

**MeSH**

Adolescent; Child; Female; Humans; Hydroxymethylglutaryl-CoA Reductase Inhibitors /therapeutic use; Hyperlipoproteinemia Type II /drug therapy; Male; Randomized Controlled Trials as Topic; Treatment Outcome

**AccessionNumber**

12008005044

**Date bibliographic record published**

30/09/2008

**Date abstract record published**

05/08/2009

**Record Status**

This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.