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TABLE OF CONTENTS

HEADER . . . 1
ABSTRACT . . . 1
PLAIN LANGUAGE SUMMARY . . . 2
SUMMARY OF FINDINGS FOR THE MAIN COMPARISON . . . 4
BACKGROUND . . . 7
OBJECTIVES . . . 7
METHODS . . . 7
RESULTS . . . 9
Figure 1. . . . 12
DISCUSSION . . . 15
AUTHORS' CONCLUSIONS . . . 19
ACKNOWLEDGEMENTS . . . 19
REFERENCES . . . 19
CHARACTERISTICS OF STUDIES . . . 25
DATA AND ANALYSES . . . 40
Analysis 1.1. Comparison 1 Statins versus control, Outcome 1 Change in carotid intima-media thickness (mm). . . . 41
Analysis 1.2. Comparison 1 Statins versus control, Outcome 2 Change in serum LDL cholesterol level (%). . . . 42
Analysis 1.3. Comparison 1 Statins versus control, Outcome 3 Change in puberty (Tanner stage ≧ 1 level). . . . 43
Analysis 1.4. Comparison 1 Statins versus control, Outcome 4 Change in aspartate aminotransferase levels (> 3x ULN). 44
Analysis 1.5. Comparison 1 Statins versus control, Outcome 5 Change in alanine aminotransferase levels (> 3x ULN). 45
Analysis 1.6. Comparison 1 Statins versus control, Outcome 6 Myopathy: Change in creatine kinase levels (> 10x ULN). 46
Analysis 1.7. Comparison 1 Statins versus control, Outcome 7 Change in flow-mediated dilatation of brachial artery (%). 47
Analysis 1.8. Comparison 1 Statins versus control, Outcome 8 Change in serum total cholesterol levels (%). . . . 47
Analysis 1.9. Comparison 1 Statins versus control, Outcome 9 Change in serum HDL cholesterol levels (%). . . . 49
Analysis 1.10. Comparison 1 Statins versus control, Outcome 10 Change in serum triglyceride levels (%). . . . 50
Analysis 1.11. Comparison 1 Statins versus control, Outcome 11 Adverse events. . . . 51
WHAT'S NEW . . . 51
HISTORY . . . 52
CONTRIBUTIONS OF AUTHORS . . . 52
DECLARATIONS OF INTEREST . . . 53
SOURCES OF SUPPORT . . . 54
DIFFERENCES BETWEEN PROTOCOL AND REVIEW . . . 54
INDEX TERMS . . . 54

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[Intervention Review]

Statins for children with familial hypercholesterolemia

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ABSTRACT

Background

Familial hypercholesterolemia is one of the most common inherited metabolic diseases and is an autosomal dominant disorder meaning heterozygotes, or carriers, are affected. Those who are homozygous have severe disease. The average worldwide prevalence of heterozygous familial hypercholesterolemia is at least 1 in 500, although recent genetic epidemiological data from Denmark and next generation sequencing data suggest the frequency may be closer to 1 in 250. Diagnosis of familial hypercholesterolemia in children is based on elevated total cholesterol and low-density lipoprotein cholesterol levels or DNA-based analysis, or both. Coronary atherosclerosis has been detected in men with heterozygous familial hypercholesterolemia as young as 17 years old and in women with heterozygous familial hypercholesterolemia at 25 years old. Since the clinical complications of atherosclerosis occur prematurely, especially in men, lifelong treatment, started in childhood, is needed to reduce the risk of cardiovascular disease. In children with the disease, diet was the cornerstone of treatment but the addition of lipid-lowering medications has resulted in a significant improvement in treatment. Anion exchange resins, such as cholestyramine and colestipol, were found to be effective, but they are poorly tolerated. Since the 1990s studies carried out on children aged 6 to 17 years with heterozygous familial hypercholesterolemia have demonstrated significant reductions in their serum total and low-density lipoprotein cholesterol levels. While statins seem to be safe and well-tolerated in children, their long-term safety in this age group is not firmly established. This is an update of a previously published version of this Cochane Review.

Objectives

To assess the effectiveness and safety of statins in children with heterozygous familial hypercholesterolemia.

Search methods

Relevant studies were identified from the Group's Inborn Errors and Metabolism Trials Register and Medline.

Date of most recent search: 20 February 2017.

Selection criteria

Randomized and controlled clinical studies including participants up to 18 years old, comparing a statin to placebo or to diet alone.

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Data collection and analysis

Two authors independently assessed studies for inclusion and extracted data.

Main results

We found 26 potentially eligible studies, of which we included nine randomized placebo-controlled studies (1177 participants). In general, the intervention and follow-up time was short (median 24 weeks; range from six weeks to two years). Statins reduced the mean low-density lipoprotein cholesterol concentration at all time points (moderate quality evidence). Serum aspartate and alanine aminotransferase, as well as creatinine kinase concentrations, did not differ between treated and placebo groups at any time point (low quality evidence). The risks of myopathy (low quality evidence) and clinical adverse events (moderate quality evidence) were very low and also similar in both groups. In one study simvastatin was shown to improve flow-mediated dilatation of the brachial artery (low quality evidence), and in another study treatment with pravastatin for two years induced a significant regression in carotid intima media thickness (low quality evidence).

Authors' conclusions

Statin treatment is an effective lipid-lowering therapy in children with familial hypercholesterolemia. No significant safety issues were identified. Statin treatment seems to be safe in the short term, but long-term safety remains unknown. Children treated with statins should be carefully monitored and followed up by their pediatricians and their care transferred to an adult lipidologist once they reach 18 years of age. Large long-term randomized controlled trials are needed to establish the long-term safety issues of statins.

PLAIN LANGUAGE SUMMARY

Statins for children with inherited high blood cholesterol

Review question

We reviewed the evidence for the effectiveness and safety of statins in children with inherited high blood cholesterol.

Background

Familial hypercholesterolemia is an inherited disease in which the blood cholesterol level is high. Vascular disease, i.e. furring up of the blood vessels, often occurs at an earlier age than usual, especially amongst men. Thus lifelong therapies, started in childhood, to reduce blood cholesterol are needed. In children with familial hypercholesterolemia, diet has been the main treatment option. Medications, such as cholestyramine and colestipol, have been used effectively, but due to their unpleasant taste they are poorly tolerated and treatment plans are not followed. The advent of statin therapy for children has improved treatment and this review updates the previous published version.

Search date

The evidence is current to: 20 February 2017.

Study characteristics

The review included 9 studies with 1177 people with heterozygous familial hypercholesterolemia aged between 4 and 18 years of age. Studies compared different statin treatments with a substance which contains no medication (termed placebo) and people were selected for one treatment or the other randomly. The studies lasted from 12 weeks to 104 weeks.

Key results

In general, the intervention and follow-up time was short (median 24 weeks; range from six weeks to two years). Statins reduced the mean low-density lipoprotein cholesterol concentration at all time points (moderate quality evidence). The levels of the liver enzymes, serum aspartate and alanine aminotransferase, and the muscle enzyme, creatinine kinase, did not differ between treated and placebo groups at any time point (low quality evidence). The risks of myopathy (disease of muscle tissue) and side-effects were very low and similar in both groups (low quality evidence). Two of the statins, simvastatin and pravastatin, were shown to have a positive effect on two of the major blood vessels typically affected by raised cholesterol levels (low quality evidence).

Quality of the evidence

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Blinding (performance bias and detection bias) was not present in any studies. In two studies information on how the participants were allocated to treatment groups (selection bias) was clearly presented, but this information was not clearly stated in the remaining seven studies. There is a lack of information whether investigators knew which treatment group participants would be put into (selection bias) and or whether selective reporting (reporting bias) occurred, but it is very unlikely. In conclusion, it can be stated all the studies appeared to be well run and we do not think any of the above-mentioned factors influenced the results in a negative way. Quality of evidence varied from moderate (change in serum low-density lipoprotein (LDL) cholesterol and adverse events) to low (change in blood vessel wall (carotid intima-media) thickness, change in measures if growth and maturation, liver dysfunction, myopathy and change in blood wall (endothelial) function).

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SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Statins compared with placebo for children with familial hypercholesterolemia

Patient or population: children with familial hypercholesterolemia
Settings: outpatients
Intervention: statins
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Statins				
Change in carotid intima-media thickness (mm) - At 2 years Follow-up: 2 years	The mean change in carotid intima-media thickness was 0.005 mm in the placebo group	The mean change in carotid intima-media thickness was 0.01 mm lower (0.03mm lower to 0.00mm lower) in the stains group	NA	211 (1 study)	⊕⊕○○ **low**[1]	
Change in serum LDL cholesterol level (%) - At end of follow-up Follow-up: up to 48 weeks	The mean change in serum LDL cholesterol level ranged from a 5% increase to a 4% decrease across placebo groups	The mean change in serum LDL cholesterol level was 32.15% lower (34.90% lower to 29.40% lower) in the stains group	NA	669 (6 studies)	⊕⊕⊕○ **moderate**[1,2]	Heterogeneity: I^2 = 89% This outcome was also reported at at 1 month (228 participants, 3 studies), 6 months (528 participants, 4 studies) and at 1 year (254 participants, 2 studies). All pooled results were in favour of statins; the latter two analyses were also very heterogeneous (I^2 > 85%)

Change in measures of growth and maturation: change in puberty proportion with Tanner stage ≧ 1 level - At 2 years Follow-up: 2 years	**636 per 1000**	**604 per 1000** (489 to 750 per 1000)	**RR 0.95** (95% CI 0.77 to 1.18)	211 (1 study)	⊕⊕◯◯ **low**[1,3]	This outcome was also reported at at 6 months (355 participants, 2 studies) and at 1 year (139 participants, 1 study) Results of analysis at all time points showed no significant differences between statins and placebo
Liver dysfunction: proportion with changed aspartate aminotransferase or alanine aminotransferase levels (> 3x ULN) - At all time points Follow-up: up to 2 years	There were two cases of changed aspartate aminotransferase levels and no cases of changed alanine aminotransferase levels in the placebo groups (at all time points)	There were four cases of changed aspartate aminotransferase levels and four cases of changed alanine aminotransferase levels in the statins groups (at all time points)	See comment	up to 924[4] (7 studies)	⊕⊕◯◯ **low**[1,5]	There were no significant differences between the number of cases at any time point for either measurement and confidence intervals of pooled results were wide due to very low numbers of events
Myopathy: proportion with changed serum creatine kinase levels (>10x ULN) - At all time points Follow-up: up to 1 year	There were two cases of changed serum creatine kinase levels in the placebo groups (at all time points)	There were five cases of changed serum creatine kinase levels in the placebo groups (at all time points)	See comment	up to 669[4] (6 studies)	⊕⊕◯◯ **low**[1,5]	There were no significant differences between the number of cases at any time point and confidence intervals of pooled results were wide due to very low numbers of events
Change in endothelial function: Change in flow-mediated dilatation of brachial artery (%) Follow-up: up to 1 year	The mean change in flow-mediated dilatation of brachial artery was 1.2% in the placebo group	The mean change in flow-mediated dilatation of brachial artery was 2.70% higher (0.42% to 4.98% higher) in the statins group	NA	50 (1 study)	⊕⊕◯◯C **low**[1]	

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Adverse events - At one year Follow-up: up to 1 year	**399 per 1000**	**402 per 1000** (323 to 502 per 1000)	**RR 1.01** (95% CI 0.81 to 1.26)	276 (2 studies)	⊕⊕⊕○ **moderate**[1]	This outcome was also reported at at 1 months (248 participants, 2 studies) and at 6 months (416 participants, 3 studies) Results of analysis at all time points showed no significant differences between statins and placebo

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **NA**: not applicable; **RR**: risk ratio; **ULN**: upper limit of normal

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

1. Downgraded once due to unclear risk of bias: methods of allocation concealment not described for any included studies and method of randomisation not described for more than half of the included studies.
2. Downgraded once due to inconsistency: a large amount of statistical heterogeneity present, despite studies being clinically comparable.
3. Downgraded once due to applicability: unclear whether changes in puberty are due to a treatment effect of the statins or due to natural changes in puberty of the age group.
4. Some studies contributed data to more than one time point, participants only counted once at the first time point reported.
5. Downgraded once due to imprecision: wide confidence intervals of pooled effects due to very low numbers of events.

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BACKGROUND

Description of the condition

Familial hypercholesterolemia (FH) is one of the most common inherited metabolic diseases and, as an autosomal dominant condition, may be either homozygous or heterozygous. Homozygous FH is the more severe form with a prevalence of at least one case in a million but will not be considered in this review. The average worldwide prevalence of heterozygous FH individuals has been estimated to be at least about 1 in 500 individuals (Goldstein 1995; Nordestgaard 2013), although recent genetic epidemiological data from Denmark and next generation sequencing data suggest the frequency may be closer to 1 in 250 (Sjouke 2015; Benn 2016; Khera 2016; Pang 2016; Wald 2016). Mutations in one of three genes that encode proteins involved in clearance of low-density lipoprotein (LDL) cholesterol from the blood are known to cause FH. The most common mutations in FH diminish the number of cellular LDL receptors (*LDLR*) and render their function defective. This results in a lifelong elevation of serum LDL cholesterol which is two- to three-fold higher among FH heterozygotes than among non-FH people. the other two known causative mutations are the apolipoprotein B (*APOB*) gene that causes defective binding of the LDL particle to the LDL-receptor and the gain of function mutation in the proprotein convertase subtilisin/kexin 9 (*PCSK9*) gene. Currently, over 1700 different *LDLR* mutations have been reported (Leigh 2016) but only one common *APOB* and one common *PCSK9* mutation are seen (Humphries 2006a). Serum LDL cholesterol levels in untreated FH children are typically above 4 mmol/L (Wray 1996).

Coronary stenosis has been detected in men with FH as young as 17 years and in women with FH as young as 25 years of age (Mabuchi 1989). Indeed, early atherosclerosis, as determined by increased carotid intima-media thickness, is detectable in untreated FH children from the second decade of life (Tonstad 1996; Hoffmann 2002; Wiegman 2004).

Description of the intervention

It is necessary to start lifelong lipid-lowering measures in childhood in order to reduce the risk of cardiovascular disease in later life. Diet has so far been the main mode of treatment for children with FH (Poustie 2001; McCrindle 2012). Anion exchange resins, such as cholestyramine and colestipol, have been found to be effective but are unpalatable, poorly tolerated and therefore poorly adhered to by the patients (O'Connor 1990; Tonstad 1996).

Statins (3-hydroxy-3-methyl-glutaryl coenzyme A reductase inhibitors), are inhibitors of the rate-controlling enzyme in cholesterol synthesis, and have been available for lowering plasma LDL levels since the 1980s (Goldstein 1979; Goldstein 1990). Since the 1990s studies with statins have been carried out amongst children with FH aged 6 to 17 years and demonstrated a significant reduction in LDL levels (Knipscheer 1996).

Why it is important to do this review

The major serious side-effect of statin therapy is myopathy, defined as muscle pain with serum creatine kinase concentrations of more than 1000 U per liter and in its extreme form rhabdomyolsis. These fortunately occur rarely (Bradford 1991; Joy 2009) and statins appear to be safe and well-tolerated in adults. While there is no evidence these adverse effects occur more commonly in children than adults, the long-term safety of statins amongst children is not well documented.

This review is an update of previously published versions of this Cochrane Review (Vuorio 2010; Vuorio 2014).

OBJECTIVES

To assess the effectiveness and safety of statins in children with heterozygous FH.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized and non-randomized but controlled clinical studies with systematic allocation.

Types of participants

Children and adolescents aged up to 18 years of age (at start of study) with clinical diagnosis of heterozygous FH based on genetic testing or clinical criteria (the level of serum total cholesterol is higher than the age-adjusted normal upper limit and at least one parent has been diagnosed with hypercholesterolemia).

Types of interventions

Active treatment with a statin (e.g. lovastatin, simvastatin, pravastatin, fluvastatin, rosuvastatin, atorvastatin, pitavastatin) compared to control treatment with another statin, or with placebo, or with other lipid-lowering agents (fibric acids, resins), or with diet alone or with no treatment.

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Types of outcome measures

The ultimate goal of treatment with statins is to reduce the incidence of morbidity and mortality from cardiovascular diseases. These outcomes are rare in childhood, therefore, we used surrogate end points for assessing effectiveness. The 'change' means the difference between the values at the beginning and at the end of follow-up. We report the means of both absolute (mmol/L) and relative (%) changes in lipids between groups.

We grouped outcome data into those measured at one month, at six months (± two weeks), at one year (± four weeks) and at two years. These are time points commonly used in clinical studies for evaluating drug effects and there was no statin-specific reason for the selection.

Primary outcomes

1. Change in carotid intima-media thickness
2. Change in serum LDL cholesterol level
3. Change in measures of growth and maturation, e.g. age of onset of puberty

Secondary outcomes

1. Liver dysfunction: change in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels
2. Myopathy: change in serum creatine kinase (CK) levels
3. Rhabdomyolysis (degeneration of skeletal muscle tissue) or death due to rhabdomyolysis
4. Change in endothelial function (measured by flow-mediated dilation of the brachial artery)
5. Change in serum total and high-density lipoprotein (HDL) cholesterol and triglyceride (TG) level
6. Quality of life
7. Compliance to study medication
8. Other adverse events which may be associated with statins

Search methods for identification of studies

There were no restrictions regarding language or publication status.

Electronic searches

Relevant studies were identified from the Group's Inborn Errors of Metabolism Trials Register using the terms: (*Hypercholesterolemia*:ti,ab,kw,mh,emt,misc1) AND (*Statin*:ti,ab,kw,mh,emt,misc 1).

The Inborn Errors of Metabolism Trials Register is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (updated with each new issue of the Cochrane Library), weekly searches of MEDLINE and the prospective hand-searching of one journal - J*ournal of Inherited Metabolic Disease*. Unpublished work is identified by searching through the abstract books of the Society for the Study of Inborn Errors of Metabolism conference and the SHS Inborn Error Review Series. For full details of all searching activities for the register, please see the relevant section of the Cochrane Cystic Fibrosis and Genetic Disorders Group's website.

Date of most recent search: 20 February 2017.

Searching other resources

Additionally, we searched the references of retrieved reviews and original articles.

Data collection and analysis

Selection of studies

Two authors (AV, JK) independently assessed potentially eligible studies for their suitability for inclusion in the review. We resolved any disagreements by discussion.

Data extraction and management

The same two authors (AV, JK) independently extracted data from the studies using a study selection and data extraction form modified for this review. We resolved any disagreements by discussion. We present treatment with all statins combined as a single intervention when comparing to control or placebo. We did not undertake any formal subgroup analyses because the statins studied differed between studies.

When study reports presented standard errors (SE), we converted these to standard deviations (SD = SE x¬ square root of n). For several outcomes for one study, we combined the results of three intervention groups by using n-weighted averages of means and SDs (Knipscheer 1996). The respective equations are described in chapter 7 of the*Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a).

Assessment of risk of bias in included studies

We originally assessed the methodological quality of included studies based on a method as described by Jüni (Jüni 2001). We have now related our judgements to the current Cochrane risk of bias tool, so that assessments of adequate relate to low risk of bias, inadequate to high risk of bias and unclear to unclear risk of bias (Higgins 2011b).

We independently assessed the following aspects of quality: generation of the allocation sequence (assessed as adequate, inadequate or unclear); concealment of allocation (assessed as adequate, inadequate or unclear); the degree of blinding; and the appropriateness of the statistical analyses (i.e. intention-to-treat or per protocol).

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Measures of treatment effect

For binary outcomes, the results are presented as risk ratios (RR) with 95% confidence intervals (CIs). For continuous outcomes, the results are presented as mean differences (MD) with 95% CIs.

Unit of analysis issues

There were no special unit-of-analysis issues. Cross-over and cluster-randomized studies do not have a suitable design for the interventions being considered and we feel they are unlikely to be used in the future.

Dealing with missing data

There were no or only few missing data in the included studies.

Assessment of heterogeneity

The I^2 statistic was used to test the impact of heterogeneity between studies (Higgins 2003). We considered levels of heterogeneity as follows:

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

Assessment of reporting biases

The use of a funnel plot to investigate the possibility of publication bias was not feasible due to the small number of included studies; for a funnel plot analysis, a minimum of 10 studies is required.

Data synthesis

Where feasible, we combined data using a fixed-effect model of analysis.

Subgroup analysis and investigation of heterogeneity

We planned to explore possible sources of methodological heterogeneity, such as study quality or design and completeness of follow-up. We also planned to consider possible sources of clinical heterogeneity, such as sex and age of the participants and the interventions being compared. We would have investigated these using subgroup analyses; however, this was not feasible due to the small number of included studies. If more studies are available for future updates of this review and we identify heterogeneity, we will consider undertaking those subgroup analyses listed above.

Summary of findings and quality of the evidence (GRADE)

In a post hoc change from protocol, we have presented a summary of findings tables for the comparison of statins versus placebo for children with FH (Summary of findings for the main comparison). The following outcomes were reported in the tables (chosen based on relevance to clinicians and consumers): change in carotid intima-media thickness; change in serum LDL cholesterol level; change in measures of growth and maturation, e.g. age of onset of puberty, liver dysfunction; change in aspartate and alanine aminotransferase levels; myopathy; change in serum creatine levels; change in endothelial function (measured by flow-mediated dilation of the brachial artery); other adverse events which may be associated with statins.

Outcomes were presented in the summary of findings table at the end of follow-up or latest reported follow-up time.

We determined the quality of the evidence using the GRADE approach; and downgraded evidence in the presence of a high risk of bias in at least one study, indirectness of the evidence, unexplained heterogeneity or inconsistency, imprecision of results, high probability of publication bias. We downgraded evidence by one level if they considered the limitation to be serious and by two levels if very serious.

RESULTS

Description of studies

For further details please see the tables (Characteristics of included studies; Characteristics of excluded studies).

Results of the search

We found 25 potentially eligible studies of statins for treating children with FH. Nine randomized controlled studies were eligible for inclusion. Reasons for excluding the remaining studies are provided in a table (Characteristics of excluded studies).

Included studies

Statins versus placebo

Nine randomized placebo-controlled studies were included, with a total of 1177 children. The earliest study was published in 1996 (Knipscheer 1996) and the most recent in 2015 (Braaskamp 2015a).

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Study design

Six studies had a multicentre design (Stein 1999; de Jongh 2002a; McCrindle 2003; Clauss 2005; Avis 2010; Braaskamp 2015a); the remaining studies were undertaken at a single centre (Knipscheer 1996; Couture 1998; Wiegman 2004). The studies included a run-in phase with a fat-restricted diet lasting from four weeks to three months. Only Wiegman averaged two measurements to obtain the baseline LDL cholesterol level (Wiegman 2004), all other studies carried out a single measurement.

The sizes of the study populations varied. Four studies had more than 100 children per treatment arm (de Jongh 2002a; McCrindle 2003; Wiegman 2004; Avis 2010). The remaining studies were much smaller, with group sizes ranging from 18 to 64. In general, the intervention and follow-up time was short, median 24 weeks (range from six weeks to two years).

Study participants

As inclusion criteria, three studies defined lower and upper limits for LDL cholesterol, required the participant to be at Tanner stage II (small amount of long, downy hair with slight pigmentation at the base of the penis and scrotum or on labia majora) or higher at the start of the study, and required FH to be present in the family (Stein 1999; McCrindle 2003; Clauss 2005). Three studies had criteria for LDL cholesterol lower limits and required FH to be present in the family but did not have any criteria for sexual development (Knipscheer 1996; de Jongh 2002a; Wiegman 2004). One study based the inclusion on LDL cholesterol level and a positive DNA diagnosis of the participating child (Couture 1998). In addition, McCrindle had a criterion for the upper level of serum TG levels (McCrindle 2003); Wiegman required a positive DNA diagnosis in the first-degree relative of the participating child and used premature CVD in close relatives as an inclusion criterion (Wiegman 2004); and Knispcheer required that clinical manifestations of premature atherosclerosis had to be present before the age of 50 years in the first or second-degree relatives (Knipscheer 1996). In one study either DNA-based or clinical criteria were required in addition to specific criteria for the fasting LDL cholesterol value and for female Tanner stage (Avis 2010). In the most recent study either documented genetic effect or LDL-C $\geqq$ 160 mg/dL or LDL-C > 130 mg/dL and male, early CVD in family, HDL-C < 45 mg/dL, TG > 150 mg/dL, lipoprotein(a) > 75 nmol/L, type 2 diabetes mellitus diagnosed and blood pressure > 95th percentile for age and height were required (Braaskamp 2015a).

Exclusion criteria were aimed at excluding children with concomitant diseases which elevate lipid levels or medications that could interact with statins and thus included homozygous FH; diabetes mellitus; anorexia nervosa; kidney, liver or thyroid disorders; concomitant other dyslipidemias; immunosuppressant drugs; or drugs that are potent inhibitors of cytochrome P-450 3A4. Lifestyle was not generally considered at inclusion, e.g. there were no criteria regarding alcohol consumption and only one study excluded smokers.

The age of the study participants ranged from 6 years to 18 years; 51% were males. The mean (SD) baseline LDL cholesterol in the study groups varied from 5.28 (1.08) mmol/L (de Jongh 2002a) to 6.48 (0.98) mmol/L (Stein 1999).

Study interventions

Two studies used lovastatin with daily doses of 40 mg (Stein 1999; Clauss 2005), one pravastatin with doses of 5 mg to 20 mg (Knipscheer 1996), one pravastatin with doses of 20 mg to 40 mg (Wiegman 2004), one simvastatin with a dose of 20 mg (Couture 1998), one simvastatin with a dose of 40 mg (de Jongh 2002a), one atorvastatin with doses of 10 mg to 20 mg (McCrindle 2003), one rosuvastatin with doses of 5 mg to 20 mg (Avis 2010) and one pitavastatin with doses of 1 mg to 4 mg (Braaskamp 2015a).

Outcome measures

Only four studies mentioned compliance as monitored by counting tablets (Couture 1998; Wiegman 2004; Clauss 2005; Avis 2010). Although one important exclusion criterion was the use of drugs that are potent inhibitors of cytochrome P-450 3A4 like macrolide antibiotics and ketoconazole, it was unclear how their use was monitored and avoided.

Changes in LDL cholesterol during the treatment were measured in all studies. The primary efficacy outcome in eight studies was an absolute or percentage change in LDL cholesterol (Knipscheer 1996; Couture 1998; Stein 1999; de Jongh 2002a; McCrindle 2003; Clauss 2005; Avis 2010; Braaskamp 2015a). In one study it was the change from baseline in mean carotid intima-media thickness (IMT) (Wiegman 2004). Four studies reported absolute LDL cholesterol concentrations and the mean percentage change in LDL cholesterol at the end of follow-up (Knipscheer 1996; McCrindle 2003; Clauss 2005; Avis 2010) and one reported the mean percentage change in LDL cholesterol (Couture 1998;). Of the studies reporting absolute and mean percentage change, two reported the mean percentage change in LDL cholesterol at the end of follow-up (Stein 1999; de Jongh 2002a), one reported mean percentage change but not SD for this change (Braaskamp 2015a), one reported the mean absolute changes in LDL cholesterol during follow-up (Wiegman 2004), and one reported the relative difference between the mean LDL values in the beginning and at the end of the study (Avis 2010). The study of Wiegman was therefore excluded from the follow-up LDL cholesterol analyses, which were carried out either by using LDL cholesterol concentrations or percentage reduction at the end of the follow-up**.** Five studies explicitly reported that they used the Friedewald formula to calculate LDL cholesterol (Knipscheer 1996; Couture 1998; Wiegman 2004; Clauss 2005; Avis 2010).

Clinically significant elevation in hepatic transaminase (AST or ALT) levels, possibly related to hepatotoxicity, was defined as more

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than three times the upper limit of normal (ULN). This measurement was reported in eight studies (Knipscheer 1996; Stein 1999; de Jongh 2002a; McCrindle 2003; Wiegman 2004; Clauss 2005; Avis 2010; Braaskamp 2015a). Clinically significant CK elevation related to possible myopathy or rhabdomyolysis (or both) was defined as more than 10 times the ULN. This measurement was reported in seven studies (Knipscheer 1996; Stein 1999; de Jongh 2002a; McCrindle 2003; Clauss 2005; Avis 2010; Braaskamp 2015a).

The effect of statins on puberty (defined as an increase in the Tanner stage) was reported in only three studies (de Jongh 2002a; McCrindle 2003; Wiegman 2004). Height and weight measurements were carried out in some studies, but due to the short follow-up time, it is not possible to draw any further conclusions on their changes and are not examined in the present analysis.

Six studies reported adverse events (Knipscheer 1996; Stein 1999; de Jongh 2002a; McCrindle 2003; Clauss 2005) with one not separating treated participants from controls (Braaskamp 2015a). Muscular adverse events were reported as either myalgia or myopathy.

Given cholesterol is a precursor of steroid and sex hormones, four studies reported the results of plasma levels of these hormones (Stein 1999; de Jongh 2002a; Wiegman 2004; Clauss 2005). The differences between the treatment and placebo groups, although statistically significant, were small. Normal variability of these hormones is large at this age; thus we considered the differences to be of no clinical significance but exact significance is unknown.

Change in thickness of carotid intima was examined in only one study (Wiegman 2004).

There were no reports on quality of life.

Excluded studies

Of the 17 excluded studies, 13 did not have controls (Lambert 1996; Raal 1997; Stein 1999; Athyros 2002; Dirisamer 2003; Hedman 2003; Sinzinger 2004; Hedman 2005; van der Graaf 2006; Carreau 2011; Gandelman 2011; Braaskamp 2015b; Langslet 2016), one was carried out with a combination of colestipol resin and a statin (McCrindle 2002), one did not have clearly defined controls (Stefanutti 1999), one was not randomized (Braaskamp 2015c) and in one participants had homozygous FH (Stein 2016).

Risk of bias in included studies

In the original version of this review, methodological quality was assessed based on a method as described by Jüni (Jüni 2001). We primarily focused on the following aspects of study design: method and concealment of allocation, treatment and control group comparability at baseline, use of intention-to-treat analysis, and blinding. Loss to follow-up was reported heterogeneously and was difficult to grade. There was no indication to suspect selective reporting in any of the studies. For this update, these judgements have been related to the current risk of bias tool as described in chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b). Please refer to the risk of bias graph (Figure 1).

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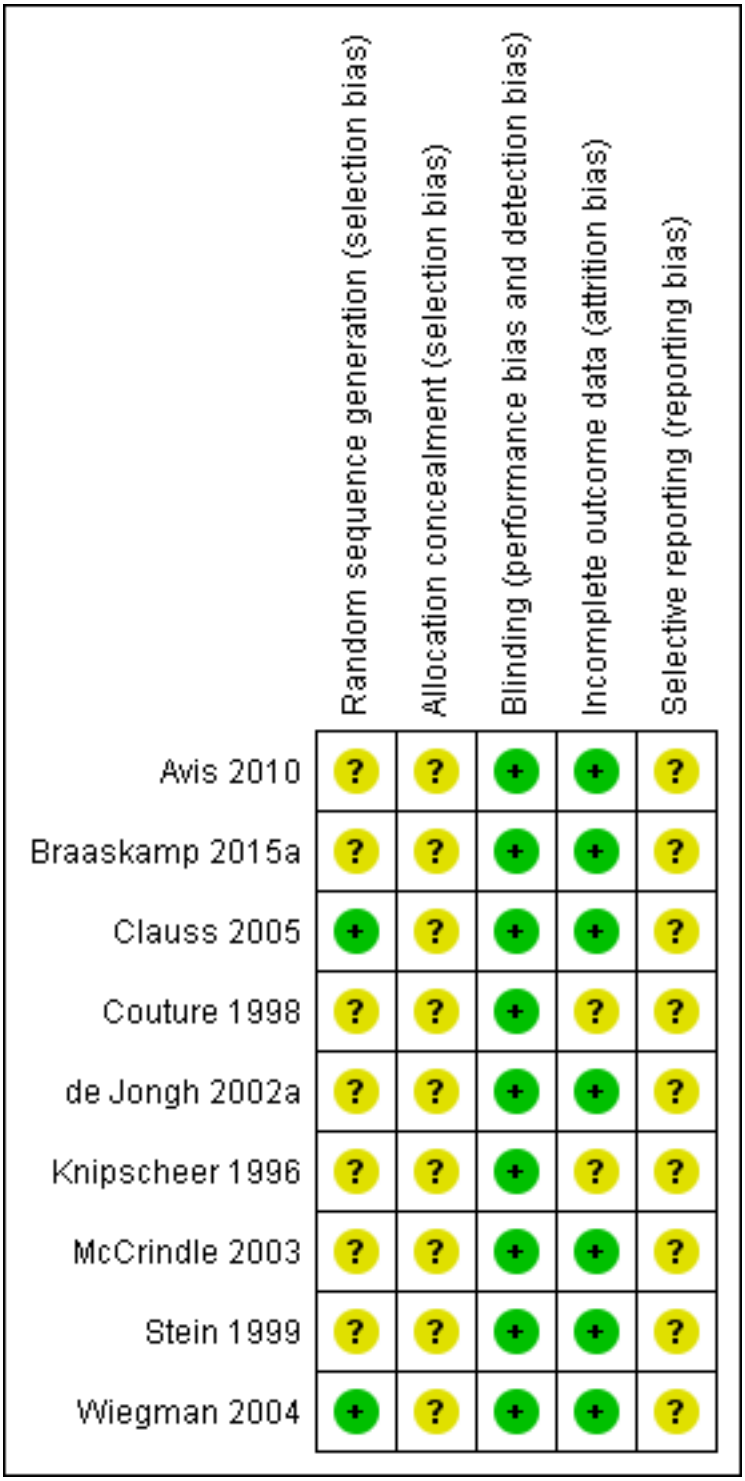
Figure 1. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



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Allocation

Generation of allocation sequence

The generation of the allocation sequence was adequate in two studies since the sequence was computer-generated (Wiegman 2004; Clauss 2005). In two studies (unclear risk), it was stated that groups were stratified but the randomization procedure was not described (Knipscheer 1996; Avis 2010). The remaining five studies were described as randomized, but no further details of the process were given (also unclear risk of bias) (Couture 1998; Stein 1999; de Jongh 2002a; McCrindle 2003; Braaskamp 2015a).

Concealment of allocation

None of the included studies described how the allocation sequence was concealed from the investigators, the outcome assessors or the participants in the study (unclear risk of bias). However, one study (Avis 2010) reported randomisation was stratified by center, and there was one multicenter study (Braaskamp 2015a); both of these were assumed to have been centrally randomised.

Blinding

All studies were described as double blind, indicating that participants and those participating in treatment procedures were blinded to treatment (low risk).

Incomplete outcome data

Dropout rates were reported in seven studies (low risk of bias) (Stein 1989; de Jongh 2002a; McCrindle 2003; Wiegman 2004; Clauss 2005; Avis 2010; Braaskamp 2015a); these were low, varying from 2% (McCrindle 2003) to 8% (Stein 1999). Two studies did not present a report on dropout rates (unclear risk of bias) (Knipscheer 1996; Couture 1998).

Effects of interventions

See: **Summary of findings for the main comparison**
Please refer to the 'Summary of Findings table' for explanations of the assessments of the quality of the evidence (Summary of findings for the main comparison).

Statins versus placebo

Primary outcomes

1. Change in thickness of carotid intima

One study reported on this outcome (Wiegman 2004). This study showed that two years of pravastatin therapy induced a small but significant regression of IMT compared to placebo which was -0.01 mm (95% CI -0.03 to -0.00) (low quality evidence) (Analysis 1.1).

2. Change in serum LDL cholesterol level

Five studies reported the difference between mean relative reductions of serum LDL cholesterol levels (de Jongh 2002a; Knipscheer 1996; Stein 1999; McCrindle 2003; Clauss 2005). One study reported only changes in absolute lipid levels (Wiegman 2004), one study reported lipid levels in graph form only (Couture 1998); LDL cholesterol data from these two studies were not analysed. One study reported LDL cholesterol levels using the relative difference between the mean LDL values in the beginning and at the end of the study (Avis 2010) and one study reported LDL cholesterol mean percentage change without SD (Braaskamp 2015a).
At one month (three studies) the pooled estimate of the difference in mean relative reductions was -24.59% (95% CI -30.11 to -19.08) (Braaskamp 2015a; Clauss 2005; Knipscheer 1996), at six months (four studies) it was -34.97% (95% CI -37.51 to -32.44) (Clauss 2005; de Jongh 2002a; McCrindle 2003; Stein 1999) and at one year (two studies) it was -26.94% (95% CI -31.64 to -22.23) (de Jongh 2002a; Stein 1999) (Analysis 1.2).
The difference in mean relative reductions in LDL cholesterol concentration at end of follow-up (median 24 weeks) between those treated with statins and those with a placebo varied from -21% to -41%. The pooled estimate of the difference in mean relative reductions at the end of follow-up (six studies) was -32.15% (95% CI -34.90 to -29.40) (moderate quality evidence) (Braaskamp 2015a; Clauss 2005; de Jongh 2002a; Knipscheer 1996; McCrindle 2003; Stein 1999) (Analysis 1.2).
The studies can be considered clinically comparable even though the results showed statistical heterogeneity. This heterogeneity was present at six months (I^2 = 86%) and at one year (I^2 = 81%), but not at one month. The heterogeneity is most likely due to multiple factors such as variation in statin type, statin dosage and duration of study.

3. Change in measures of growth and maturation

Three studies reported measures of growth (de Jongh 2002a; McCrindle 2003; Wiegman 2004). The effect of statins on puberty was measured by the change in Tanner stage. McCrindle reported percentage of groups experiencing an increase in Tanner stage and we calculated the number of events from this in order to enter data into the meta-analysis. The pooled estimate of the RR at six

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months (two studies) was -0.99 (95% CI -0.66 to 1.50) (de Jongh 2002a; McCrindle 2003), at one year (one study) 0.89 (95% CI 0.51 to 1.54) (de Jongh 2002a) and at two years (one study) 0.95 (95% CI 0.77 to 1.18) (low quality evidence) (Wiegman 2004) (Analysis 1.3).

Secondary outcomes

1. Liver dysfunction

a. Change in AST levels

Seven studies reported levels of AST (Knipscheer 1996; Stein 1999; de Jongh 2002a; McCrindle 2003; Wiegman 2004; Clauss 2005; Braaskamp 2015a). At one month there were no cases reported (Braaskamp 2015a; Knipscheer 1996), at six months (four studies) the estimate of the RR was 2.40 (95% CI 0.29 to 19.85) (Clauss 2005; de Jongh 2002a; McCrindle 2003; Stein 1999), at one year (two studies) 2.03 (95% CI 0.08 to 49.09) (de Jongh 2002a; Stein 1999) and at two years (one study) 0.21 (95% CI 0.01 to 4.23) (low quality evidence) (Wiegman 2004) (Analysis 1.4).

b. Change in ALT levels

Seven studies reported levels of ALT (Stein 1989; Knipscheer 1996; de Jongh 2002a; McCrindle 2003; Wiegman 2004; Clauss 2005; Braaskamp 2015a). There were no cases reported at one month (Braaskamp 2015a; Knipscheer 1996) or at two years (Wiegman 2004). At six months (four studies) the estimate of the risk ratio was 2.03 (95% CI 0.24 to 16.95) (Clauss 2005; de Jongh 2002a; McCrindle 2003; Stein 1999) and at one year (two studies) 2.03 (95% CI 0.08 to 49.09) (low quality evidence) (de Jongh 2002a; Stein 1999) (Analysis 1.5).

2. Myopathy: change in serum CK levels

Six studies reported the change in serum CK levels (Stein 1989; Knipscheer 1996; de Jongh 2002a; Clauss 2005; Avis 2010; Braaskamp 2015a). At one month (three studies) the pooled estimate of the RR was 3.23 (95% CI 0.18 to 58.84) (Avis 2010; Braaskamp 2015a; Knipscheer 1996), at six months (two studies) it was RR 0.22 (95% CI 0.01 to 5.28) (Clauss 2005; de Jongh 2002a) and at one year (two studies), RR 0.67 (95% CI 0.04 to 10.57) (low quality evidence) (de Jongh 2002a; Stein 1999) (Analysis 1.6).

3. Rhabdomyolysis

There were no reported cases of rhabdomyolysis.

4. Change in endothelial function

The change in endothelial function was reported in a sub-study of the 2002 de Jongh study, among 28 participants treated with statins and 22 treated with placebo (de Jongh 2002a). The absolute change in relative flow-mediated dilatation of brachial artery was 2.70% (95% CI 0.42 to 4.98) (low quality evidence) (de Jongh 2002a) (Analysis 1.7).

5. Change in serum total cholesterol, HDL cholesterol and TG levels

a. Change in serum total cholesterol levels

Five studies reported the difference between mean relative reductions of serum total cholesterol levels (Stein 1989; Knipscheer 1996; de Jongh 2002a; McCrindle 2003; Clauss 2005). One study reported mean relative reductions of serum total cholesterol levels but not the SDs (Braaskamp 2015a).

At one month (three studies) the pooled estimate of the difference in mean relative reductions was -18.31% (95% CI -22.55 to -14.06) (Braaskamp 2015a; Clauss 2005; Knipscheer 1996), at six months (four studies) -24.28% (95% CI -26.09 to -22.47) (Clauss 2005; de Jongh 2002a; McCrindle 2003; Stein 1999) and at one year (two studies) -27.60% (95% CI -30.64 to -24.57) (de Jongh 2002a; Stein 1999) (Analysis 1.8).

The difference in mean relative reductions in total cholesterol concentration at the end of the follow-up (median 24 weeks) between those treated with a statin and those with a placebo varied from -17% to -32%. The pooled estimate of the difference in mean relative reductions at the end of follow-up (six studies) was -26.53% (95% CI -28.54 to -24.51) (Braaskamp 2015a; Clauss 2005; de Jongh 2002a; Knipscheer 1996; McCrindle 2003; Stein 1999) (Analysis 1.8).

The studies can be considered clinically comparable even though the results showed statistical heterogeneity. This heterogeneity was not present at one month, but it was present at six months (I^2 = 87%) and at one year (I^2 = 95%).

b. Change in serum HDL cholesterol levels

Five studies reported the difference between mean relative reductions of serum HDL cholesterol levels (Knipscheer 1996; Stein 1999; de Jongh 2002a; Clauss 2005; McCrindle 2003). One study reported HDL cholesterol levels using the relative difference between the mean HDL values in the beginning and at the end of

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the study (Avis 2010) and one study reported mean percentage change in HDL cholesterol without SD (Braaskamp 2015a).
At one month (three studies) the pooled estimate of the difference in mean relative change was 3.00% (95% CI -2.47 to 8.47) (Braaskamp 2015a; Clauss 2005; Knipscheer 1996), at six months (four studies) 4.18% (95% CI 1.54 to 6.82) (Clauss 2005; de Jongh 2002a; McCrindle 2003; Stein 1999) and at one year (two studies) 2.56% (95% CI -1.17 to 6.29) (de Jongh 2002a; Stein 1999) (Analysis 1.9).
The difference in mean relative reductions in HDL cholesterol concentration at the end of the follow-up (median 24 weeks) between those treated with statins and those with a placebo varied from 0% to 5%. The pooled estimate of the difference in mean relative changes at the end of follow-up (six studies) was 3.11% (95% CI 0.55 to 5.67) (Braaskamp 2015a; Clauss 2005; de Jongh 2002a; Knipscheer 1996; McCrindle 2003; Stein 1999) (Analysis 1.9).

c. Change in serum TG levels

Four studies reported the difference between mean relative reductions of serum TG levels (Knipscheer 1996; Stein 1999; McCrindle 2003; Clauss 2005). One study reported TG levels using the relative difference between the mean TG values in the beginning and at the end of the study (Avis 2010) and one study reported mean percentage change without the SD (Braaskamp 2015a).
At one month (three studies) the pooled estimate of the difference in mean relative change was 10.31% (95% CI -5.11 to 25.74) (Braaskamp 2015a; Clauss 2005; Knipscheer 1996), at six months (three studies) -9.34% (95% CI -18.90 to 0.22) (Clauss 2005; McCrindle 2003; Stein 1999) and at one year (one study) 0.00% (95% CI -18.09 to 18.09) (Stein 1999) (Analysis 1.10).
The difference in the mean relative reductions in TG concentration at the end of follow-up (median 24 weeks) between those treated with statins and those with a placebo varied from -7% to 16%. The pooled estimate of the difference in mean relative reductions at the end of follow-up (five studies) was -3.27% (95% CI -12.03 to 5.50) (Braaskamp 2015a; Clauss 2005; Knipscheer 1996; McCrindle 2003; Stein 1999) (Analysis 1.10).

6. Quality of life

No study reported this outcome.

7. Compliance

Compliance was reported in one study by tablet counting (Wiegman 2004) and it was found most children adhered to the protocol, i.e. 84% of tablets were taken for the full length of the two-year study.

8. Adverse events

Six studies reported clinical adverse events (Knipscheer 1996; Stein 1999; de Jongh 2002a; McCrindle 2003; Clauss 2005; Avis 2010). At one month (two studies) the estimate of the RR was 0.86 (95% CI 0.65 to 1.13) (Avis 2010; Knipscheer 1996), at six months (three studies) 1.02 (95% CI 0.82 to 1.27) (Clauss 2005; de Jongh 2002a; McCrindle 2003) and at one year (two studies) 1.01 (95% CI 0.81 to 1.26) (moderate quality evidence) (de Jongh 2002a; Stein 1999) (Analysis 1.11).

DISCUSSION

Summary of main results

We analysed nine randomised placebo-controlled studies in children with heterozygous familial hypercholesterolaemia (FH). The studies showed a clinically significant reduction in both serum total cholesterol and low-density lipoprotein (LDL) cholesterol among children treated with a statin compared with those treated with a placebo. In addition, statin therapy slightly increased serum high-density lipoprotein (HDL) cholesterol and slightly decreased serum triglyceride concentration; however, when compared with the substantial change in serum LDL cholesterol, these changes are likely to be of minor importance. The magnitude of LDL cholesterol lowering varied from study to study, most likely due to different statins and doses and possibly due to different definitions about true monogenic heterozygous FH. We did not do any formal subgroup analyses because the choice of statin treatment was heterogeneous between studies.
Endothelial dysfunction represents one of the earliest stages of atherogenesis, and has a clear predictive value for future cardiovascular disease. A number of studies have shown that endothelial function measured as flow-mediated dilation is impaired in children with FH (de Jongh 2002b; Vlahos 2014). The effect of simvastatin on flow-mediated dilatation of the brachial artery in children with FH was reported in one study (de Jongh 2002a). It was found that simvastatin therapy restored endothelial function in the studied participants (50 children with FH; 9 to 18 years). Clearly more studies are needed to confirm this result in children with FH.
In addition to early changes in the function of the arterial endothelium in children with FH, which result from the high LDL cholesterol concentration in the blood, accumulation of the LDL cholesterol in the subendothelial space of the carotid arterial wall leads to increased intima-media thickness (IMT) of the carotid arteries (Tonstad 1996). Carotid IMT represents the combined intima and media thickness of the arterial wall, and numerous studies have shown that this surrogate marker of atherosclerotic vessel wall change is a reliable indicator of clinical outcomes later in life

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(Koeijvoets 2005). Accordingly, studies examining the sensitivity of this surrogate marker to risk intervention are important. We found only one study that used carotid IMT as the primary efficacy outcome in children with FH treated with statins (Wiegman 2004). The authors found that two years of pravastatin therapy induced a small but significant regression in mean change in IMT between statin-treated and placebo groups in children with FH. This clearly encouraging result calls for further studies with pravastatin or other statins.

In the largest study, all children were from families where a molecular diagnosis had been made in one parent and where the recruited child had LDL cholesterol twice greater than 4.0 mmol/L. The authors judged this to mean the child had a greater than 99.6% chance of having inherited the family mutation (Wiegman 2004).This sample is therefore highly likely to consist of all FH individuals. In the most recent study (Braaskamp 2015a), all children had a mutation in *LDLR* or *APOB* genes or had a parent where the mutation had been identified, and thus all of these children have molecularly defined monogenic FH. In all the other studies, children were recruited as having LDL cholesterol above a cut-off point which varied between the studies (Starr 2008). The other criterion was having a first degree relative, either with elevated LDL cholesterol, or with a family history of premature coronary artery disease. It is therefore likely the vast majority of the children in the studies included in this review have monogenic FH, but it cannot be ruled out that a small percentage (not more than 10%) may not have.

Although in the majority of studies published in recent years molecular testing was performed and only mutation-positive participants recruited, the diagnosis of FH was not confirmed by direct molecular testing of the children in some of the earlier studies included in this review. Although idiopathic elevated LDL cholesterol levels occur less frequently in children than in adults, this raises the question of whether only a proportion of the children in the earlier studies have true monogenic FH. This may affect the conclusions made above, since the lipid-lowering response to a statin may be different in mutation carriers compared to those with a polygenic cause of their phenotype. In adults with a clinical diagnosis of "Definite" FH a causative mutation can be found in between 70% to 80% of individuals, while only around 30% of people with a clinical diagnosis of "Possible" FH carry a causative mutation (Graham 2005; Humphries 2006b; Futema 2013). It is now known that in people with a clinical diagnosis of FH but with no detectable mutation in any of the three common FH genes there is a polygenic (not a monogenic) cause of their phenotype (Talmud 2013), and they have been incorrectly been given the diagnosis of FH. This polygenic cause has also been demonstrated to explain the elevated LDL-C levels in children with a diagnosis of FH where no mutation can be found (Futema 2015).

In the absence of molecular confirmation, it is possible to estimate the probable dilution of monogenic FH children with children with a polygenic aetiology from family studies. There is a considerable overlap in LDL-cholesterol levels in the mutation-carrying and non-mutation carrying siblings of a parent with FH, such that using the intersection between the two peaks of LDL-cholesterol levels observed results in a false positive diagnostic rate of 6% to 8% (Kwiterovich 1974; Leonard 1976). Thus selecting children as "FH" based only on having a parent with FH and elevated LDL-C levels may have resulted in the inclusion of 6% to 8% non-mutation carriers, in earlier studies where no DNA testing was carried out. Based on this we can conclude that the earlier published estimates of the effect of statin treatment in children with a clinical diagnosis of FH where no molecular testing had been performed are unlikely to have been significantly influenced by the incorrect inclusion of non-monogenic individuals.

The importance of distinguishing between monogenic and polygenic elevation of LDL cholesterol is whether children with a monogenic cause might have a much smaller than average LDL cholesterol-lowering response than children whose hypercholesterolaemia is due to polygenic causes. Although we are not aware of any data addressing this directly in children, there is evidence that adults with a clinical diagnosis of FH without a detected mutation have a better response to statins than those in which a mutation has been found (Sun 1998; Heath 1999). Another issue to consider is that children with different *LDLR* mutations, or in those where FH is caused by mutations in the *APOB* or *PCSK9* genes, may respond differently to statins. There is no direct evidence for this in children, but adults carrying the *APOB* mutation have been reported to respond better to statins than those carrying an *LDLR* mutation (Myant 1993) or a *PCSK9* mutation (Humphries 2006b). Furthermore, the class of *LDLR* mutation can affect the untreated LDL cholesterol levels (Humphries 2006b; Futema 2013) and affect the response to statins (Couture 1998; Vohl 2002; Miltiadous 2005). These variations according to mutations are pertinent because founder effects are seen in many countries, e.g. South Africa (Kotze 1993), Finland (Vuorio 2001) and Holland, (Umans 2002). Thus the variability in the prevalence of different mutations and molecular causes of FH across countries may contribute to a small extent to between-study differences in response but although there may be a small overestimate of the response in statin-sensitive mutation-carrying FH children, it is unlikely to be more than 5% (van der Graaf 2011).

Recent guidelines vary in their recommendations as to when statin treatment should be started between 8 years to 14 years (McCrindle 2007; SIGN 2007; Daniels 2008; NICE 2008; Descamps 2011; Goldberg 2011; Sullivan 2012). None of the guidelines recommended statins before the age of eight years in cases of heterozygous FH (Vuorio 2013). In regard to dosing, this varied considerably between the studies. In the earliest study, children with FH were treated with pravastatin doses from 5 mg/day to 20 mg/day (Knipscheer 1996). In the later studies there was a tendency to use larger doses. Wiegman used pravastatin doses of 20 mg/day or 40 mg/day (Wiegman 2004), and de Jongh titrated simvastatin doses of up to 40 mg/day (equivalent dose of pravas-

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tatin, 80 mg/day) (de Jongh 2002a). McCrindle titrated atorvastatin doses from 10 mg/day up to 20 mg/day (equivalent dose of pravastatin, up to 80 mg/day) if the LDL cholesterol level remained over 3.4 mmol/L (McCrindle 2003). In this study the mean serum LDL cholesterol concentration among FH children treated with statins was 3.39 mmol/L at the end of follow-up. In the most recent study (Braaskamp 2015a), the 5 mg starting dose of rosuvastatin was titrated at 3-monthly intervals to a maximum tolerated dose of 10 mg (six- to nine-year olds) or 20 mg (10- to 17-year olds) to achieve an LDL-C goal of (2.85 mmol/L (110 mg/dL). In all cases the minimal effect dose is advised.

It has been estimated that elevations in aminotransferase levels over three times the upper limit of normal occur in less than 1% of adults on any statin (Cohen 2006). However, there was no increase in aminotransferase levels when compared with a placebo group in a recent meta-analysis (de Denus 2004), and adults with elevated aminotransferase levels during statin treatment do not appear to have a higher risk of liver dysfunction (Chalasani 2004). The risk of acute severe liver dysfunction in the general population with no statin medication is about one to two cases per million (Law 2006). Consequently, severe liver dysfunction is extremely rare and routine monitoring is recommended, but it will be effective only when it is active and includes not only laboratory test but also clinical follow-up (Golomb 2013). The studies of children with FH used liver transaminases as the method for detecting possible liver dysfunction. The putative risk of statin-induced severe acute liver dysfunction at this stage of life should be outweighed by the reduced cardiovascular risk achieved by statin treatment (NICE 2008). The most recent guidelines by the National Lipid Association's Statin Safety Assessment Task Force give some useful considerations (McKenney 2006). They underline the importance of monitoring any possible symptoms like abdominal pain related to liver dysfunction and advise to consider using a fractionated bilirubin for detection of liver dysfunction. This kind of monitoring was carried out systematically in only half of the studies we analyzed, and the monitoring protocol varied between the studies (Stein 1999; de Jongh 2002a; Wiegman 2004; Clauss 2005). None of the studies included fractionated bilirubin in their laboratory analysis. It can be concluded that even though liver dysfunction was not present in the included studies, the risk exists. Therefore, any new studies of children with FH should be planned so that possible hepatotoxicity symptoms are routinely monitored using standardized methods and, additionally, new laboratory standards should be used in detecting possible liver dysfunction.

The incidence of rhabdomyolysis has been estimated to be about 3.4 per 100,000 person-years in adults (Law 2006). Although this figure is very low, the lesson learned with cerivastatin should be keenly kept in mind (Pasternak 2002). The rate of fatal rhabdomyolysis with this drug was unexpectedly and exceptionally high; 16 to 80 times greater than with other statins (Staffa 2002) and even after excluding individuals treated simultaneously with gemfibrozil, the rate of fatal rhabdomyolysis was still 10 to 50 times higher than of other statins (Staffa 2002). All statins used so far in children with FH (atorvastatin, lovastatin, pravastatin, and simvastatin) appear to have a low risk of rhabdomyolysis as compared to adults, which is estimated to be about 0.08% to 0.09% of persons treated with these statins (Pasternak 2002). Since the mechanism of myopathy is not well understood, it is of the utmost importance to monitor adverse reactions and adjust the therapy accordingly (Pasternak 2002).

The terminology of clinical adverse events in the analyzed studies varied. The comparison between the studies would have been more reliable if the definition of adverse events had been standardized. It is important to note that some drugs that interact with statins (macrolide antibiotics and azole fungals) may have been consumed, thus altering the adverse event risk. In practice any interaction risk can be mitigated with patient education. Statin therapy combined with alcohol abuse potentially increases the risk of liver dysfunction. Alcohol consumption was not monitored in any of the included studies; however, alcohol abuse is uncommon in children but when adolescence is reached discussions about alcohol consumption should be had with the young person. It is unclear as to whether statins increase the risk of cataracts with about equal numbers of studies supporting the theory versus those against (Harris 1995; Cenedella 1996; Pedersen 1996; Chodick 2010; Hippisley-Cox 2010; Fong 2012; Leuschen 2013).

One of the potential long-term side effects of statin treatment in children with FH is the increased risk of developing type 2 diabetes (T2D) that has been noted in statin treatment of non-FH individuals. A meta-analysis of published randomised controlled trials in over 91,000 high risk individuals from the general population (Sattar 2010) reported statin therapy was associated with a 9% increase in the likelihood of new T2D during follow-up. Interestingly, a second meta-analysis showed pravastatin (40 mg/day) was associated with the lowest (7%), atorvastatin (80 mg/day) with an intermediate (15%) and rosuvastatin (20 mg/day) and simvastatin (40 mg/day) with the highest (25% and 21% respectively) risk of new onset T2D (Navarese 2013). The exact molecular mechanism of this statin-associated T2D risk is unknown (please refer to the references in Vuorio 2016), and it is unclear whether this is an on-target or off-target effect of the drug; that is, whether the dysglycaemic effect is a direct consequence of inhibition of HMG-CoA, the intended target of statins. Using the approach of Mendelian Randomisation, variants in the gene encoding HMG-CoA reductase (HMGCR, chr 5q13.3) associated with lower LDL-C were used as proxies for statin treatment. Both statin treatment and the genetic variants were associated with higher T2D risk and higher bodyweight, and the genetic variants with higher plasma glucose and insulin, and waist and hip circumferences (Swerdlow 2015). This directional concordance strongly suggested that the higher T2D risk caused by statin therapy is at least in part a direct consequence of HMG-CoA reductase inhibition. Reassuringly, many studies have reported that the prevalence of T2D is low in adults with FH, and in a study of over 63,000

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people from Holland (Besseling 2015), even in treated adults with FH the prevalence of T2D was significantly lower than in their unaffected relatives (1.75% versus 2.93%). Follow-up studies in adults (Skoumas 2014) and in children (Kusters 2014) are also reassuring, with 10-year follow-up in 194 statin-treated children (mean age at baseline 13 years) seeing one new case of T2D, with a similar incidence in their 83 non-FH siblings (Kusters 2014). It is clear that overall the benefits of statin treatment for preventing cardiovascular disease in people with FH far outweighs the modest potential risk of T2D. It is possible the dietary and lifestyle advice given to all people with FH encourages them to maintain an ideal body weight and thus to ameliorate any of the statin-associated risk of developing T2D. Based on published evidence it would appear that treatment with pravastatin is associated with the lowest risk, although long-term follow-up studies of treated FH children are needed to confirm this.

Relatively little is known about the potential statin-related neurologic side-effects such as sleep disturbances (Bays 2006), effects on cognitive function and peripheral neuropathy (Backes 2003; Chong 2004). In most cases, the onset of symptoms was reported within six months of commencing medication, and most of the peripheral neuropathies were confirmed by nerve conduction studies. The reports were related to all statins, and discontinuation of statin treatment improved the symptoms. In a recent review based on adult studies, peripheral neuropathy was concluded to be an idiosyncratic effect of statin use (Brass 2006). In the included studies Wiegman showed that there was no difference on academic performance between the statin treated and placebo group (Wiegman 2004).

Particularly important are the concerns related to any potential impact on sexual and physical maturation (McCrindle 2007). Long-term effects on maturation will need to be studied in longer and larger controlled follow-up studies. Physical maturation was followed in some studies by measuring height but this is unreliable in short-term studies. There is concern about pregnancy during statin treatment (McCrindle 2007) as statins can affect foetal development. Females of child-bearing age should receive counselling and contraceptive advice (Arambepola 2007; McCrindle 2007; NICE 2008; Nordestgaard 2013).

In summary, this review found statins to be an effective treatment for FH in children. It did not find any difference between the statin and control group in the proportion of participants who experienced a clinically significant increase in liver transaminase values (over three-fold increase in alanine transferase or aspartate aminotransferase) or creatine kinase values (over 10-fold increase). We did not find any significant difference between those treated with a statin and those treated with placebo with respect to their sexual maturation measured by the Tanner staging. Overall, the data suggest the risk of adverse events in children treated with statins is similar to that observed in statin-treated adults over the short term and the adverse event rate was the same between statin and placebo group. In the absence of long-term treatment and follow-up of children, it is not possible to rule out any long-term adverse effects. Our findings are similar to those reported in two systematic reviews (Arambepola 2007; Avis 2007).

Overall completeness and applicability of evidence

The quality of the data concerning change in serum LDL cholesterol and adverse events was, according to GRADE, classified as moderate. These data are applicable in the treatment of FH children. In conclusion, statins lowered LDL cholesterol effectively (advantage). Significant adverse events were not present during the statin treatment (potential harm).

Quality of the evidence

Blinding (performance bias and detection bias) was not present in any studies. Bias from random sequence generation (selection bias) was not present in two studies and the data were not clearly stated in seven studies. Bias from allocation concealment (selection bias) and selective reporting (reporting bias) can not totally be excluded, but it is very unlikely. In conclusion it can be stated that all the studies appeared to be well run and we do not think any above mentioned factors will influence the results in a negative way. Quality of evidence varied from moderate (change in serum LDL cholesterol and adverse events) to low (change in carotid intima-media thickness, change in measures if growth and maturation, liver dysfunction, myopathy and change in endothelial function).

Potential biases in the review process

A comprehensive literature search was carefully carried out and we consider that most controlled studies were identified. Study protocols varied between the included studies and data were presented slightly differently between the studies. In conclusion we found no potential bias in the review process.

Agreements and disagreements with other studies or reviews

Our findings are similar to those reported in two systematic reviews (Arambepola 2007; Avis 2007). In the Arabepola review, results of a parallel-group randomised placebo-controlled trial concerning heterozygous FH children with LDL and HDL cholesterol and triglycerides as outcomes were pooled using standard meta-analytical methods (Arambepola 2007). In the Avis review, they performed a meta-analysis of randomized, double-blind, placebo-controlled trials evaluating statin therapy in children aged 8 to 18 years with heterozygous FH and six studies (n = 798 children) with 12 to 104 weeks of treatment were included (Avis 2010).

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AUTHORS' CONCLUSIONS

Implications for practice

Statin treatment is an effective lipid-lowering therapy in children with heterozygous FH. No safety issues were identified in the short term up to two years. Since statin treatment in children with FH is not acutely or sub-acutely a life-saving treatment, it would be difficult to accept any clinically significant adverse events in this patient group. This treatment should be combined with regular pediatric follow-up and parents informed about potential side-effects and interaction with concomitant medication.

Implications for research

Much larger and longer-term randomized clinical trials are needed to ensure that statins are a safe therapy in the long term in children. Growth, neurological development, cognitive function and quality of life should be assessed during follow-up.

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* *Indicates the major publication for the study*

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Avis 2010

Methods	* Design: RCT * Randomization stratified by center * Blinding: double * Concealment of allocation: nr * Setting: 20 centers * Country: Netherlands, Canada, Norway, USA * Follow-up: 12 weeks
Participants	Individuals with HeFH (N = 177) * Diagnosis: documented genetic effect or LDL-C ≧ 190 mg/dL or LDL-C > 160 mg/dL and early CVD in family * Inclusion: age 10 - 17 years, HeFH, Tanner stage ≧ II, females at least 1 year post-menarche * Exclusion: nr * Base population: nr Age: 10 - 17 years Male: 55% Race: White populations 94% Height (mean): 164 cm Weight (mean): 58 kg BMI (mean): nr LDL-C (mean):? mmol/L (233 mg/dL)
Interventions	* Treatment: rosuvastatin in 3 treatment arms (n = 130), 5 mg daily (n = 42), 10 mg daily (n = 44) and 20 mg daily (n = 45) * Control: placebo (n = 46) * Run-in: diet only for 6 weeks * Diet: nr
Outcomes	LDL-C: Friedewald's formula TC HDLC TG ASAT ALAT CK Myopathy: myalgia Adverse events: adverse event
Notes	* Open-label phase for 40 weeks after the RCT, data not used in this review

Risk of bias

Bias	Authors' judgement	Support for judgement

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Avis 2010 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Described as stratified but randomization procedure not described
Allocation concealment (selection bias)	Unclear risk	nr
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Compliance: 87% Dropout: 2% Losses to follow-up: 1% Missing from analysis: 1%
Selective reporting (reporting bias)	Unclear risk	No indication to suspect selective reporting.

Braaskamp 2015a

Methods	* Design: RCT * Randomization stratified by age and baseline LDL-C * Blinding: double * Concealment of allocation: nr * Setting: 10 centers * Country: Netherlands, Greece, Norway, Italy, Spain, France * Follow-up: 12 weeks
Participants	Individuals with HeFH (N = 103) * Diagnosis: documented genetic effect or LDL-C ≧ 160 mg/dL or LDL-C > 130 mg/dL and male, early CVD in family, HDL-C < 45 mg/dL, TG > 150 mg/dL, lipoprotein (a) > 75 nmol/L, type 2 diabetes mellitus diagnosed and blood pressure > 95th percentile for age and height. * Inclusion: age 6 - 17 years, HeFH * Exclusion: nr * Base population: nr Age: 6 - 17 years Male: 45% Height (mean): 148 cm Weight (mean): 44 kg BMI (mean): 19.1 kg/m² LDL-C (mean): 232 mg/dL
Interventions	* Treatment: pitavastatin in 3 treatment arms (n = 76), 1 mg daily (n = 26), 2 mg daily (n = 26) and 4 mg daily (n = 24) * Control: placebo (n = 27) * Run-in: diet only for 5 weeks * Diet: nr

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Outcomes	LDL-C (SD for mean percentage change not reported) TC (SD for mean percentage change not reported) HDL-C (SD for mean percentage change not reported) TG (SD for mean percentage change not reported) ASAT ALAT CK Myopathy: myalgia Adverse events: (adverse event not reported separately for the treatment groups)
Notes	No indication to suspect selective reporting.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	nr; multicenter study, central randomization assumed.
Allocation concealment (selection bias)	Unclear risk	nr
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Compliance: nr Dropout: 3% Losses to follow-up: 0% Missing from analysis: 0%
Selective reporting (reporting bias)	Unclear risk	No indication to suspect selective reporting.

Clauss 2005

Methods	* Design: RCT * Randomization process: nr * Blinding: double * Concealment of allocation: by randomised numbers * Setting: 12 medical centers * Country: USA * Follow-up: 4 and 24 weeks
Participants	* Participants with HeFH (N = 54) * Diagnosis: 1 parent with FH, LDL-C > 4.1mmol/L * Inclusion: age 10 - 17 years; female; LDL-C 4.1-10.3 mmol/L on diet; TG < 4.0 mmol/L; postmenarchal > 1 year * Exclusion: pregnancy; under/overweight; HoFH; dyslipidemia I, III-V; DM, hypothy-

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	roidism; renal disorder; certain medication (immunosuppressants, corticosteroids, cytochrome P-450 inhibitors) * Base population: unclear; 81 individuals were screened * Age: 11 - 18 years * Male: 0% * Race: nr * Height (mean): 164 cm * Weight (mean): 60 kg * BMI (mean): 23 kg/m² * LDL-C (mean): 5.5 mmol/L
Interventions	* Intervention: lovastatin 40 mg daily; started with 20 mg for 4 weeks, then increased to 40 mg (n = 35) * Control: placebo (n = 19) * Drugs discontinued 6 - 8 weeks before randomisation; diet/placebo run-in for 4 weeks * AHA step 1 diet or similar instruction at baseline
Outcomes	LDL-C: enzymatic method, calculated Friedewald's formula TC: enzymatic method HDL-C: heparin-manganese chloride method TG: enzymatic method
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomization process by randomised numbers.
Allocation concealment (selection bias)	Unclear risk	nr
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Compliance: nr Dropout: 6% Losses to follow-up: 6% Missing from analysis: 0%
Selective reporting (reporting bias)	Unclear risk	No indication to suspect selective reporting.

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Couture 1998

Methods	* Design: RCT * Randomization process: nr * Blinding: double * Concealment of allocation: nr * Setting: 1 research clinic * Country: Canada * Follow-up: 6 weeks
Participants	* Individuals with HeFH (N = 63) * Diagnosis: unclear, LDL-C > 95th percentile on diet * Inclusion: age < 18 years; HeFH; LDL-C > 95th percentile on diet; * Exclusion: DM; anorexia; kidney, liver or thyroid disorder; delayed puberty * Base population: all potential participants screened * Age 8 - 17 years * Male 59% * Race: nr * Height (mean) 153 cm * weight (mean) 46 kg * BMI (mean) nr * LDL-C (mean) 5.8 mmol/L
Interventions	* Treatment: simvastatin 20 mg daily (n = 47) * Control: placebo (n = 16) * Run-in: placebo 4 weeks * Diet: AHA phase I, dietary counselling throughout the trial
Outcomes	LDL-C: enzymatic method, calculated Friedewald's formula TC: enzymatic method HDL-C: heparin-manganese chloride method TG: enzymatic method
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomized, process not reported.
Allocation concealment (selection bias)	Unclear risk	nr
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Compliance: nr Dropout: nr Losses to follow-up: 0%

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Couture 1998 (*Continued*)

		Missing from analysis: 0%
Selective reporting (reporting bias)	Unclear risk	No indication to suspect selective reporting.

de Jongh 2002a

Methods	* Design: RCT * Randomization process: nr * Blinding: double * Concealment of allocation: nr * Setting: 7 countries, 9 medical centers * Country: Canada, Costa Rica, France, Netherlands, New Zealand, Norway * Follow-up: 24 and 48 weeks
Participants	Individuals with HeFH (N = 175) * Diagnosis: 1 parent clinical FH, LDL-C > 4.1mmol/L * Inclusion: age ≤ 18 years; HeFH; LDL-C > 95th percentile; genetic diagnosis or family history of high LDL-C * Exclusion: smoking; vasoactive medication; serious illness; HT; DM * Base population: nr * Age: 10 - 17 years * Male 57% * Race: nr * Height (mean): nr *Weight (mean): nr * BMI (mean): 22 kg/m² * LDL-C (mean): 5.4 mmol/L
Interventions	* Treatment: simvastatin 40 mg daily (n = 101); started with 10 mg, doubled at every 8 weeks up to 40 mg * Control: placebo (n = 64) * Run-in: diet + placebo for 4 weeks * Diet: nr
Outcomes	LDL-C: enzymatic method TC: enzymatic method HDL-C: enzymatic method TG: enzymatic method FMD: on brachial artery by ultrasonography, method described (on subset of Dutch group) CRP method: nr ASAT method: nr ALAT method: nr CK method: nr Puberty: Tanner staging by clinical examination Myopathy: criteria nr Adverse events: drug-related clinical adverse event, criteria unclear, method: nr

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Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described as randomized, process not reported.
Allocation concealment (selection bias)	Unclear risk	nr
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Compliance: nr Dropout: 6% Losses to follow-up: 6% Missing from analysis: 6%
Selective reporting (reporting bias)	Unclear risk	No indication to suspect selective reporting.

Knipscheer 1996

Methods	* Design: RCT * Randomization: stratified * Blinding: double * Concealment of allocation: nr * Setting: no. of medical centers nr * Country: Netherlands * Follow-up: 12 weeks
Participants	Individuals with HeFH (N = 72) * Diagnosis: LDL-C > 95th percentile on diet and HC or early AS in family * Inclusion: age 8 - 16 years; HeFH ~ LDL-C > 95th %tile on diet; HC or early AS in family * Exclusion: major surgery within 3 months; drugs interfering with lipid metabolism; liver or renal dysfunction * Base population: nr Age: 8 - 16 years Male: 35% Race: 92% Height (mean): nr Weight (mean): 47 kg BMI (mean): nr LDL-C (mean): 6.5 mmol/L

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Interventions	* Treatment: pravastatin in 3 treatment arms (n = 53), 5 mg daily (n = 17?), 10 mg daily (n = 18?) and 20 mg daily (n = 18?) * Control: placebo (n = 18) * Run-in: diet + placebo for 8 weeks * Diet: lipid-lowering diet, pre-study diet evaluated with 5 day dietary recall
Outcomes	LDL-C: enzymatic method, Friedewald's formula TC: enzymatic method HDL-C: enzymatic method TG: enzymatic method ASAT: routine biochemistry ALAT: routine biochemistry CK: routine biochemistry Myopathy: myalgia, recorded by blinded physicians Adverse events: adverse event, recorded by blinded physicians
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described as stratified but randomization procedure not described
Allocation concealment (selection bias)	Unclear risk	nr
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Compliance: unclear Dropout: nr Losses to follow-up: 1% Missing from analysis: 1%
Selective reporting (reporting bias)	Unclear risk	No indication to suspect selective reporting.

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McCrindle 2003

Methods	* Design: RCT * Randomization process: nr * Blinding: double * Concealment of allocation: nr * Setting: 20 medical centers (6 USA, 5 Canada, 8 Europe, 1 South Africa) * Country: USA, Canada, Ireland, France, Spain, England, Sweden, Norway, South Africa * Follow-up: 26 weeks
Participants	* Individuals with HeFH (N = 187) * Diagnosis: FH or severe hypercholesterolemia and LDL-C > 4.9 mmol/L OR LDL-C > 4.1 mmol/L and family history of FH OR LDL-C > 4.1 mmol/L and premature CHD in 1°/2° relatives * Inclusion: age 10 - 17 years; HeFH or LDL-C ≧ 4.9 mmol/L or LDL-C ≧ 4.1 mmol/L with HC or early AS in family; Tanner ≧ II; LDL-C ≧ 4.1 mmol/L w/ diet during baseline phase * Exclusion: premenarche; pregnancy; under or overweight; liver or kidney disorder; HoFH; other clinical trial; hypersensitivity to statins * base population: nr Age: 10 - 17 years Male: 69% Race: 92% white Height (mean): nr Weight (mean): nr BMI (mean): nr LDL-C (mean): 5.7 mmol/L
Interventions	* Treatment: atorvastatin 10 - 20 mg daily (n = 140); median 20 mg, increased to 20 mg if LDL-C ≧ 3.4 mmol/L at 4 weeks * Control: placebo (n = 47) * Run-in: washout for 4 weeks before the trial; placebo/diet run-in for 4 weeks * Diet: NCEP step 1 diet; instructions in the beginning of the study
Outcomes	LDL-C: samples analyzed centrally TC: samples analyzed centrally HDL-C: samples analyzed centrally TG: samples analyzed centrally ALAT: >3 x ULN samples analyzed in a routine manner ASAT: >3 x ULN samples analyzed in a routine manner Puberty: increase in Tanner staging ≧ 1, clinical examination Adverse event: self-report or detected by the investigator
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

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McCrindle 2003 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Described as randomized, process not reported.
Allocation concealment (selection bias)	Unclear risk	nr
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Compliance: nr Dropout: 2% Losses to follow-up: 0% Missing from analysis: 0%
Selective reporting (reporting bias)	Unclear risk	No indication to suspect selective reporting.

Stein 1999

Methods	* Design: RCT * Randomization process: nr * Blinding: double * Concealment of allocation: nr * Setting: 14 pediatric clinics (13 USA, 1 Finland) * Country: USA, Finland * Follow-up: 24 and 48 weeks
Participants	* Participants with HeFH (N = 132) * Diagnosis: LDL-C > 4.9mmol/L and 1 parent LDL-C > 4.9mmol/l; or LDL-C > 5.7mmol/L and CAD death in 1 parent * Inclusion: age 10 - 17 years; LDL-C 4.9 - 13.0 mmol/L on diet and ≧ 1 parent with LDL-C ≧ 4.9 mmol/L with or LDL-C 5.7 - 13.0 mmol/L on diet and a parent died of CAD; (Tanner > I required later by FDA > 8 participants needed to discontinue) * Exclusion: delayed puberty; under/overweight; HoFH; secondary hyperlipidaemia; TG disorders * Base population: unclear * Age: 11 - 17 years * Male: 100% * Race: 93% * Height (mean): 159 cm * Weight (mean): 52 kg * BMI (mean): 21 kg/m² * LDLC (mean): 6.5 mmol/L
Interventions	* Treatment: lovastatin 40 mg in the evening (n = 63); started with 10 mg, increased to 20/40 mg at weeks 8/16 * Control: placebo (n = 59) * Run-in: diet for 4 months; placebo run-in for 4 weeks

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	* Diet: AHA pediatric diet; instructed, monitored and evaluated throughout trial
Outcomes	LDL-C: enzymatic method TC: enzymatic method HDL-C: heparin-manganese chloride method TG: enzymatic method ALAT > 3 x ULN: samples analyzed centrally ASAT > 3 x ULN: samples analyzed centrally CK > 10 x ULN: samples analyzed centrally Myalgia criteria: nr Adverse event: new or worsening clinical adverse event, not otherwise specified
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described as randomized, process not reported.
Allocation concealment (selection bias)	Unclear risk	nr
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Compliance: nr Dropout: 8% Losses to follow-up: 8% Missing from analysis: 8%
Selective reporting (reporting bias)	Unclear risk	No indication to suspect selective reporting.

Wiegman 2004

Methods	* Design: RCT * Randomization computer-generated in blocks of 8 * Blinding: double * Compliance monitored by tablet counting * Concealment of allocation: nr * Setting: 1 medical center * Country: Netherlands * Follow-up: 104 weeks

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Participants	* Participants with HeFH (N = 214) * Diagnosis: molecular diagnosis in parent and LDL-C > 4.0 mmol/L * Inclusion: age 10 - 17 years; female; 1 parent with FH and LDL-C 4.1-10.3 mmol/L on diet; TG < 4.0 mmol/L; postmenarchal > 1 year * Exclusion: pregnancy; under/overweight; HoFH; dyslipidaemia I, III-V; DM, hypothyroidism; renal disorder; certain medication (immunosuppressants, corticosteroids, cytochrome P-450 inhibitors) * Base population: unclear; 81 participants were screened * Age: 8 - 18 years * Male: 47% * Race: nr * Height (mean): 157 cm * Weight (mean): 49 kg * BMI (mean): 20 kg/m² * LDL-C (mean): 6.2 mmol/L
Interventions	* Treatment: pravastatin 20 to 40 mg daily in the evening depending on age (n = 104) * Control: placebo (n = 107) * Run-in: fat-restricted diet * Diet: fat-restricted diet; 7 d dietary records; evaluated
Outcomes	LDL-C: enzymatic method, calculated Friedewald's formula TC: enzymatic method HDL-C: naheparin-manganese chloride method TG: enzymatic method ALAT: > 3 x ULN, analysis method: nr ASAT: > 3 x ULN, analysis method: nr CPK: > 4 x ULN, analysis method: nr IMT: ultrasonography; method described Puberty: Tanner staging, clinical examination
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated in blocks of 8.
Allocation concealment (selection bias)	Unclear risk	nr
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Compliance: unclear Dropout: 5% Losses to follow-up: 1%

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		Missing from analysis: 1%
Selective reporting (reporting bias)	Unclear risk	No indication to suspect selective reporting.

AHA: American Heart Association
ALAT: alanine amino transferase
ASAT: aspartate amino transferase
BMI: body mass index
CAD: coronary artery disease
CK: creatine kinase
CRP: C-reactive protein
CVD: cardiovascular disease
DM: diabetes mellitus
FH: familial hypercholesterolemia
FMD: flow-mediated dilatation
HC: hypercholesterolemia
HDL-C: high-density lipoprotein cholesterol
HeFH: heterozygous familial hypercholesterolemia
HoFH: homozygous familial hypercholesterolemia
HT: hypertension
IMT: intima-media thickness
LDL-C: low-density lipoprotein cholesterol
NCEP: National Cholesterol Education Panel
nr: not reported
RCT: randomized controlled trial
TC: total cholesterol
TG: triglycerides
ULN: upper limit of normal

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Athyros 2002	Publication type letter, no control group, not enough information reported
Braaskamp 2015b	Cohort study.
Braaskamp 2015c	Clinical trial without randomization.
Carreau 2011	Cohort study.
Chan 2016	No control group without medication.

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(*Continued*)

Dirisamer 2003	Clinical trial, no control group.
Gandelman 2011	Clinical trial, no control group, open-label.
Hedman 2003	Clinical trial, no control group.
Hedman 2005	Clinical trial, no control group.
Lambert 1996	Clinical trial, no control group.
Langslet 2016	Clinical trial, no placebo control group
McCrindle 2002	Randomised cross-over trial, comparison unacceptable (i.e. combination of 2 active drugs): one intervention was 10 mg pravastatin plus 5 g colestipol and the other 10 g colestipol
Raal 1997	Clinical trial, no control group.
Sinzinger 2004	Cohort study.
Stefanutti 1999	Clinical trial, control diet alone, controls were not clearly defined, e.g. the diagnostic criteria for heterozygous FH not reported, only age of the participants given
Stein 1989	Cohort study.
Stein 2016	Participants had homozygous FH.
Tada 2016	No control group without medication.
Teramoto 2016	PCSK 9 inhibitor used as add-on therapy and also not only people with FH included
van der Graaf 2006	Clinical trial, no control group.

FH: familial hypercholesterolemia

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DATA AND ANALYSES

Comparison 1. Statins versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in carotid intima-media thickness (mm)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1 At 2 years	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Change in serum LDL cholesterol level (%)	6		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 At 1 month	3	228	Mean Difference (IV, Fixed, 95% CI)	-24.59 [-30.11, -19.08]
2.2 At 6 months	4	528	Mean Difference (IV, Fixed, 95% CI)	-34.97 [-37.51, -32.44]
2.3 At 1 year	2	254	Mean Difference (IV, Fixed, 95% CI)	-26.94 [-31.64, -22.23]
2.4 At end of follow-up	6	669	Mean Difference (IV, Fixed, 95% CI)	-32.15 [-34.90, -29.40]
3 Change in puberty (Tanner stage ≧ 1 level)	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 At 6 months	2	355	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.66, 1.50]
3.2 At 1 year	1	139	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.51, 1.54]
3.3 At 2 years	1	211	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.77, 1.18]
4 Change in aspartate aminotransferase levels (> 3x ULN)	7		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 At 1 month	2	175	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 At 6 months	4	538	Risk Ratio (M-H, Fixed, 95% CI)	2.40 [0.29, 19.85]
4.3 At 1 year	2	254	Risk Ratio (M-H, Fixed, 95% CI)	2.03 [0.08, 49.09]
4.4 At 2 years	1	211	Risk Ratio (M-H, Fixed, 95% CI)	0.21 [0.01, 4.23]
5 Change in alanine aminotransferase levels (> 3x ULN)	7		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 At 1 month	2	175	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.2 At 6 months	4	538	Risk Ratio (M-H, Fixed, 95% CI)	2.03 [0.24, 16.95]
5.3 At 1 year	2	254	Risk Ratio (M-H, Fixed, 95% CI)	2.03 [0.08, 49.09]
5.4 At 2 years	1	211	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Myopathy: Change in creatine kinase levels (> 10x ULN)	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 At 1 month	3	330	Risk Ratio (M-H, Fixed, 95% CI)	3.23 [0.18, 58.84]
6.2 At 6 months	2	229	Risk Ratio (M-H, Fixed, 95% CI)	0.22 [0.01, 5.28]
6.3 At 1 year	2	254	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.04, 10.57]
7 Change in flow-mediated dilatation of brachial artery (%)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7.1 At 6 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Change in serum total cholesterol levels (%)	6		Mean Difference (IV, Fixed, 95% CI)	Subtotals only

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8.1 At 1 month	3	228	Mean Difference (IV, Fixed, 95% CI)	-18.31 [-22.55, -14.06]
8.2 At 6 months	4	528	Mean Difference (IV, Fixed, 95% CI)	-24.28 [-26.09, -22.47]
8.3 At 1 year	2	254	Mean Difference (IV, Fixed, 95% CI)	-27.60 [-30.64, -24.57]
8.4 At the end of follow-up	6	669	Mean Difference (IV, Fixed, 95% CI)	-26.53 [-28.54, -24.51]
9 Change in serum HDL cholesterol levels (%)	6		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
9.1 At 1 month	3	228	Mean Difference (IV, Fixed, 95% CI)	3.0 [-2.47, 8.47]
9.2 At 6 months	4	528	Mean Difference (IV, Fixed, 95% CI)	4.18 [1.54, 6.82]
9.3 At 1 year	2	254	Mean Difference (IV, Fixed, 95% CI)	2.56 [-1.17, 6.29]
9.4 At the end of follow-up	6	669	Mean Difference (IV, Fixed, 95% CI)	3.11 [0.55, 5.67]
10 Change in serum triglyceride levels (%)	5		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
10.1 At 1 month	3	228	Mean Difference (IV, Fixed, 95% CI)	10.31 [-5.11, 25.74]
10.2 At 6 months	3	363	Mean Difference (IV, Fixed, 95% CI)	-9.34 [-18.90, 0.22]
10.3 At 1 year	1	110	Mean Difference (IV, Fixed, 95% CI)	0.0 [-18.09, 18.09]
10.4 At the end of follow-up	5	525	Mean Difference (IV, Fixed, 95% CI)	-3.27 [-12.03, 5.50]
11 Adverse events	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
11.1 At 1 month	2	248	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.65, 1.13]
11.2 At 6 months	3	416	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.82, 1.27]
11.3 At 1 year	2	276	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.81, 1.26]

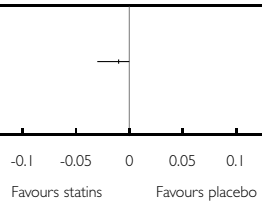
Analysis 1.1. Comparison 1 Statins versus control, Outcome 1 Change in carotid intima-media thickness (mm).

Review: Statins for children with familial hypercholesterolemia

Comparison: 1 Statins versus control

Outcome: 1 Change in carotid intima-media thickness (mm)

Study or subgroup	Statins N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 At 2 years						
Wiegman 2004	104	-0.01 (0.048)	107	0.01 (0.044)		-0.02 [-0.03, 0.00]



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Analysis 1.2. Comparison 1 Statins versus control, Outcome 2 Change in serum LDL cholesterol level (%).

Review: Statins for children with familial hypercholesterolemia

Comparison: 1 Statins versus control

Outcome: 2 Change in serum LDL cholesterol level (%)

Study or subgroup	Statins N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 At 1 month							
Braaskamp 2015a	76	-31 (0)	27	1 (0)			Not estimable
Clauss 2005	35	-23 (20)	19	3 (17)		29.7 %	-26.00 [-36.12, -15.88]
Knipscheer 1996	53	-27 (10)	18	-3 (13)		70.3 %	-24.00 [-30.58, -17.42]
Subtotal (95% CI)	**164**		**64**			**100.0 %**	**-24.59 [-30.11, -19.08]**
Heterogeneity: Chi^2 = 0.11, df = 1 (P = 0.75); I^2 =0.0%							
Test for overall effect: Z = 8.74 (P < 0.00001)							
2 At 6 months							
Clauss 2005	35	-27 (20)	19	5 (17)		6.3 %	-32.00 [-42.12, -21.88]
de Jongh 2002a	101	-38 (16)	64	-1 (11)		37.7 %	-37.00 [-41.12, -32.88]
McCrindle 2003	140	-40 (13)	47	0 (13)		34.8 %	-40.00 [-44.30, -35.70]
Stein 1999	63	-27 (16)	59	-3 (15)		21.2 %	-24.00 [-29.50, -18.50]
Subtotal (95% CI)	**339**		**189**			**100.0 %**	**-34.97 [-37.51, -32.44]**
Heterogeneity: Chi^2 = 21.81, df = 3 (P = 0.00007); I^2 =86%							
Test for overall effect: Z = 27.06 (P < 0.00001)							
3 At 1 year							
de Jongh 2002a	86	-41 (39)	58	0 (10)		29.7 %	-41.00 [-49.64, -32.36]
Stein 1999	61	-25 (16)	49	-4 (14)		70.3 %	-21.00 [-26.61, -15.39]
Subtotal (95% CI)	**147**		**107**			**100.0 %**	**-26.94 [-31.64, -22.23]**
Heterogeneity: Chi^2 = 14.49, df = 1 (P = 0.00014); I^2 =93%							
Test for overall effect: Z = 11.22 (P < 0.00001)							
4 At end of follow-up							
Braaskamp 2015a	76	-31 (0)	27	1 (0)			Not estimable
Clauss 2005	35	-27 (20)	19	5 (17)		7.4 %	-32.00 [-42.12, -21.88]
de Jongh 2002a	86	-41 (39)	58	0 (10)		10.1 %	-41.00 [-49.64, -32.36]
Knipscheer 1996	53	-27 (10)	18	-3 (13)		17.5 %	-24.00 [-30.58, -17.42]
McCrindle 2003	140	-40 (13)	47	0 (13)		41.0 %	-40.00 [-44.30, -35.70]
Stein 1999	61	-25 (16)	49	-4 (14)		24.0 %	-21.00 [-26.61, -15.39]
Subtotal (95% CI)	**451**		**218**			**100.0 %**	**-32.15 [-34.90, -29.40]**
Heterogeneity: Chi^2 = 37.92, df = 4 (P<0.00001); I^2 =89%							
Test for overall effect: Z = 22.92 (P < 0.00001)							

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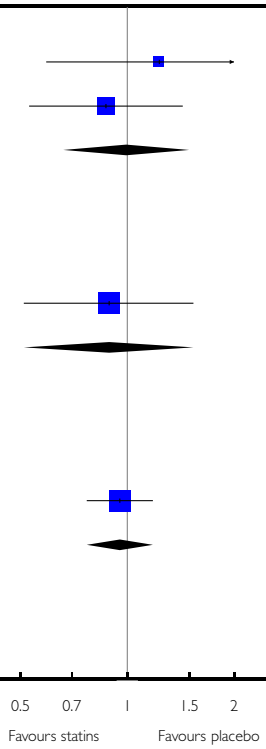
Analysis 1.3. Comparison 1 Statins versus control, Outcome 3 Change in puberty (Tanner stage ≧ 1 level).

Review: Statins for children with familial hypercholesterolemia

Comparison: 1 Statins versus control

Outcome: 3 Change in puberty (Tanner stage ≧ 1 level)

Study or subgroup	Statins n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 At 6 months					
de Jongh 2002a	18/104	9/64		33.2 %	1.23 [0.59, 2.57]
McCrindle 2003	39/140	15/47		66.8 %	0.87 [0.53, 1.43]
Subtotal (95% CI)	**244**	**111**		**100.0 %**	**0.99 [0.66, 1.50]**
Total events: 57 (Statins), 24 (Placebo)					
Heterogeneity: Chi^2 = 0.58, df = 1 (P = 0.44); I^2 =0.0%					
Test for overall effect: Z = 0.04 (P = 0.97)					
2 At 1 year					
de Jongh 2002a	21/83	16/56		100.0 %	0.89 [0.51, 1.54]
Subtotal (95% CI)	**83**	**56**		**100.0 %**	**0.89 [0.51, 1.54]**
Total events: 21 (Statins), 16 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.43 (P = 0.67)					
3 At 2 years					
Wiegman 2004	63/104	68/107		100.0 %	0.95 [0.77, 1.18]
Subtotal (95% CI)	**104**	**107**		**100.0 %**	**0.95 [0.77, 1.18]**
Total events: 63 (Statins), 68 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.44 (P = 0.66)					



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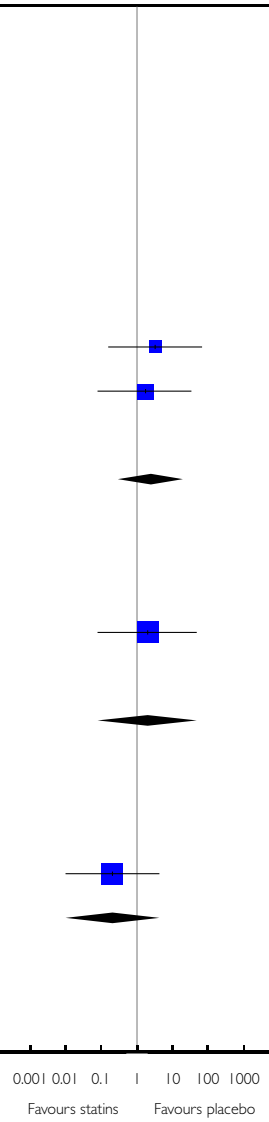
Analysis 1.4. Comparison 1 Statins versus control, Outcome 4 Change in aspartate aminotransferase levels (> 3x ULN).

Review: Statins for children with familial hypercholesterolemia

Comparison: 1 Statins versus control

Outcome: 4 Change in aspartate aminotransferase levels (> 3x ULN)

Study or subgroup	Statins n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 At 1 month					
Braaskamp 2015a	0/76	0/27			Not estimable
Knipscheer 1996	0/54	0/18			Not estimable
Subtotal (95% CI)	**130**	**45**			**Not estimable**
Total events: 0 (Statins), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 At 6 months					
Clauss 2005	0/35	0/19			Not estimable
de Jongh 2002a	2/106	0/69		44.8 %	3.27 [0.16, 67.12]
McCrindle 2003	2/140	0/47		55.2 %	1.70 [0.08, 34.83]
Stein 1999	0/63	0/59			Not estimable
Subtotal (95% CI)	**344**	**194**		**100.0 %**	**2.40 [0.29, 19.85]**
Total events: 4 (Statins), 0 (Placebo)					
Heterogeneity: $Chi^2 = 0.09$, df = 1 (P = 0.76); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.81 (P = 0.42)					
3 At 1 year					
de Jongh 2002a	1/86	0/58		100.0 %	2.03 [0.08, 49.09]
Stein 1999	0/61	0/49			Not estimable
Subtotal (95% CI)	**147**	**107**		**100.0 %**	**2.03 [0.08, 49.09]**
Total events: 1 (Statins), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.44 (P = 0.66)					
4 At 2 years					
Wiegman 2004	0/104	2/107		100.0 %	0.21 [0.01, 4.23]
Subtotal (95% CI)	**104**	**107**		**100.0 %**	**0.21 [0.01, 4.23]**
Total events: 0 (Statins), 2 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.02 (P = 0.31)					



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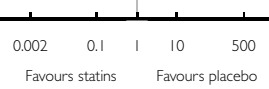
Analysis 1.5. Comparison 1 Statins versus control, Outcome 5 Change in alanine aminotransferase levels (> 3x ULN).

Review: Statins for children with familial hypercholesterolemia

Comparison: 1 Statins versus control

Outcome: 5 Change in alanine aminotransferase levels (> 3x ULN)

Study or subgroup	Statins n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 At 1 month					
Braaskamp 2015a	0/76	0/27			Not estimable
Knipscheer 1996	0/54	0/18			Not estimable
Subtotal (95% CI)	**130**	**45**			**Not estimable**
Total events: 0 (Statins), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 At 6 months					
Clauss 2005	0/35	0/19			Not estimable
de Jongh 2002a	2/106	0/69		44.8 %	3.27 [0.16, 67.12]
McCrindle 2003	1/140	0/47		55.2 %	1.02 [0.04, 24.65]
Stein 1999	0/63	0/59			Not estimable
Subtotal (95% CI)	**344**	**194**		**100.0 %**	**2.03 [0.24, 16.95]**
Total events: 3 (Statins), 0 (Placebo)					
Heterogeneity: Chi^2 = 0.27, df = 1 (P = 0.60); I^2 =0.0%					
Test for overall effect: Z = 0.65 (P = 0.51)					
3 At 1 year					
de Jongh 2002a	1/86	0/58		100.0 %	2.03 [0.08, 49.09]
Stein 1999	0/61	0/49			Not estimable
Subtotal (95% CI)	**147**	**107**		**100.0 %**	**2.03 [0.08, 49.09]**
Total events: 1 (Statins), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.44 (P = 0.66)					
4 At 2 years					
Wiegman 2004	0/104	0/107			Not estimable
Subtotal (95% CI)	**104**	**107**			**Not estimable**
Total events: 0 (Statins), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					



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Analysis 1.6. Comparison 1 Statins versus control, Outcome 6 Myopathy: Change in creatine kinase levels (> 10x ULN).

Review: Statins for children with familial hypercholesterolemia

Comparison: 1 Statins versus control

Outcome: 6 Myopathy: Change in creatine kinase levels (> 10x ULN)

Study or subgroup	Statins n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 At 1 month					
Avis 2010	4/130	0/46		100.0 %	3.23 [0.18, 58.84]
Braaskamp 2015a	0/76	0/27			Not estimable
Knipscheer 1996	0/37	0/14			Not estimable
Subtotal (95% CI)	**243**	**87**		**100.0 %**	**3.23 [0.18, 58.84]**
Total events: 4 (Statins), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.79 (P = 0.43)					
2 At 6 months					
Clauss 2005	0/35	0/19			Not estimable
de Jongh 2002a	0/106	1/69		100.0 %	0.22 [0.01, 5.28]
Subtotal (95% CI)	**141**	**88**		**100.0 %**	**0.22 [0.01, 5.28]**
Total events: 0 (Statins), 1 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.94 (P = 0.35)					
3 At 1 year					
de Jongh 2002a	1/86	1/58		100.0 %	0.67 [0.04, 10.57]
Stein 1999	0/61	0/49			Not estimable
Subtotal (95% CI)	**147**	**107**		**100.0 %**	**0.67 [0.04, 10.57]**
Total events: 1 (Statins), 1 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.28 (P = 0.78)					

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Analysis 1.7. Comparison 1 Statins versus control, Outcome 7 Change in flow-mediated dilatation of brachial artery (%).

Review: Statins for children with familial hypercholesterolemia

Comparison: 1 Statins versus control

Outcome: 7 Change in flow-mediated dilatation of brachial artery (%)

Study or subgroup	Statins N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 At 6 months						
de Jongh 2002a	28	3.9 (4.3)	22	1.2 (3.9)		2.70 [0.42, 4.98]

Analysis 1.8. Comparison 1 Statins versus control, Outcome 8 Change in serum total cholesterol levels (%).

Review: Statins for children with familial hypercholesterolemia

Comparison: 1 Statins versus control

Outcome: 8 Change in serum total cholesterol levels (%)

Study or subgroup	Statins N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 At 1 month							
Braaskamp 2015a	76	-25 (0)	27	1 (0)			Not estimable
Clauss 2005	35	-17 (15)	19	2 (13)		30.6 %	-19.00 [-26.67, -11.33]
Knipscheer 1996	53	-20 (8)	18	-2 (10)		69.4 %	-18.00 [-23.10, -12.90]
Subtotal (95% CI)	**164**		**64**			**100.0 %**	**-18.31 [-22.55, -14.06]**
Heterogeneity: Chi^2 = 0.05, df = 1 (P = 0.83); I^2 =0.0%							
Test for overall effect: Z = 8.45 (P < 0.00001)							
2 At 6 months							
Clauss 2005	35	-22 (15)	19	5 (13)		5.6 %	-27.00 [-34.67, -19.33]
de Jongh 2002a	101	-28 (13)	64	-1 (10)		26.5 %	-27.00 [-30.53, -23.47]

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Study or subgroup	Statins N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
McCrindle 2003	140	-31 (12)	47	-2 (10)		27.1 %	-29.00 [-32.48, -25.52]
Stein 1999	63	-21 (8)	59	-2 (8)		40.8 %	-19.00 [-21.84, -16.16]
Subtotal (95% CI)	**339**		**189**			**100.0 %**	**-24.28 [-26.09, -22.47]**
Heterogeneity: Chi^2 = 23.10, df = 3 (P = 0.00004); I^2 =87%							
Test for overall effect: Z = 26.23 (P < 0.00001)							
3 At 1 year							
de Jongh 2002a	86	-31 (12)	58	1 (10)		70.7 %	-32.00 [-35.61, -28.39]
Stein 1999	61	-20 (16)	49	-3 (14)		29.3 %	-17.00 [-22.61, -11.39]
Subtotal (95% CI)	**147**		**107**			**100.0 %**	**-27.60 [-30.64, -24.57]**
Heterogeneity: Chi^2 = 19.40, df = 1 (P = 0.00001); I^2 =95%							
Test for overall effect: Z = 17.81 (P < 0.00001)							
4 At the end of follow-up							
Braaskamp 2015a	76	-25 (0)	27	1 (0)			Not estimable
Clauss 2005	35	-22 (15)	19	5 (13)		6.9 %	-27.00 [-34.67, -19.33]
de Jongh 2002a	86	-31 (12)	58	1 (10)		31.1 %	-32.00 [-35.61, -28.39]
Knipscheer 1996	53	-20 (8)	18	-2 (10)		15.6 %	-18.00 [-23.10, -12.90]
McCrindle 2003	140	-31 (12)	47	-2 (10)		33.5 %	-29.00 [-32.48, -25.52]
Stein 1999	61	-20 (16)	49	-3 (14)		12.9 %	-17.00 [-22.61, -11.39]
Subtotal (95% CI)	**451**		**218**			**100.0 %**	**-26.53 [-28.54, -24.51]**
Heterogeneity: Chi^2 = 32.59, df = 4 (P<0.00001); I^2 =88%							
Test for overall effect: Z = 25.81 (P < 0.00001)							

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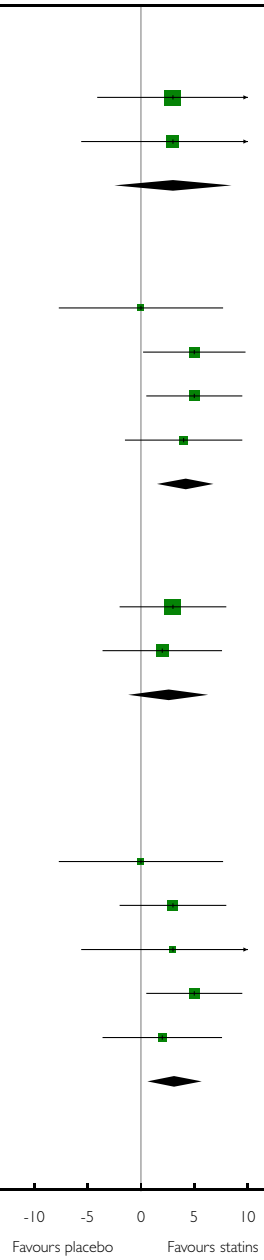
Analysis 1.9. Comparison 1 Statins versus control, Outcome 9 Change in serum HDL cholesterol levels (%).

Review: Statins for children with familial hypercholesterolemia

Comparison: 1 Statins versus control

Outcome: 9 Change in serum HDL cholesterol levels (%)

Study or subgroup	Statins N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 At 1 month							
Braaskamp 2015a	76	-1 (0)	27	1 (0)			Not estimable
Clauss 2005	35	5 (14)	19	2 (12)		59.1 %	3.00 [-4.12, 10.12]
Knipscheer 1996	53	7 (16)	18	4 (16)		40.9 %	3.00 [-5.56, 11.56]
Subtotal (95% CI)	**164**		**64**			**100.0 %**	**3.00 [-2.47, 8.47]**
Heterogeneity: Chi^2 = 0.0, df = 1 (P = 1.00); I^2 =0.0%							
Test for overall effect: Z = 1.07 (P = 0.28)							
2 At 6 months							
Clauss 2005	35	3 (15)	19	3 (13)		11.8 %	0.0 [-7.67, 7.67]
de Jongh 2002a	101	5 (14)	64	0 (16)		30.5 %	5.00 [0.22, 9.78]
McCrindle 2003	140	3 (15)	47	-2 (13)		34.8 %	5.00 [0.53, 9.47]
Stein 1999	63	5 (16)	59	1 (15)		23.0 %	4.00 [-1.50, 9.50]
Subtotal (95% CI)	**339**		**189**			**100.0 %**	**4.18 [1.54, 6.82]**
Heterogeneity: Chi^2 = 1.39, df = 3 (P = 0.71); I^2 =0.0%							
Test for overall effect: Z = 3.11 (P = 0.0019)							
3 At 1 year							
de Jongh 2002a	86	3 (15)	58	0 (15)		55.8 %	3.00 [-2.00, 8.00]
Stein 1999	61	1 (16)	49	-1 (14)		44.2 %	2.00 [-3.61, 7.61]
Subtotal (95% CI)	**147**		**107**			**100.0 %**	**2.56 [-1.17, 6.29]**
Heterogeneity: Chi^2 = 0.07, df = 1 (P = 0.79); I^2 =0.0%							
Test for overall effect: Z = 1.34 (P = 0.18)							
4 At the end of follow-up							
Braaskamp 2015a	76	-1 (0)	27	1 (0)			Not estimable
Clauss 2005	35	3 (15)	19	3 (13)		11.1 %	0.0 [-7.67, 7.67]
de Jongh 2002a	86	3 (15)	58	0 (15)		26.3 %	3.00 [-2.00, 8.00]
Knipscheer 1996	53	7 (16)	18	4 (16)		9.0 %	3.00 [-5.56, 11.56]
McCrindle 2003	140	3 (15)	47	-2 (13)		32.8 %	5.00 [0.53, 9.47]
Stein 1999	61	1 (16)	49	-1 (14)		20.8 %	2.00 [-3.61, 7.61]
Subtotal (95% CI)	**451**		**218**			**100.0 %**	**3.11 [0.55, 5.67]**
Heterogeneity: Chi^2 = 1.47, df = 4 (P = 0.83); I^2 =0.0%							
Test for overall effect: Z = 2.38 (P = 0.017)							



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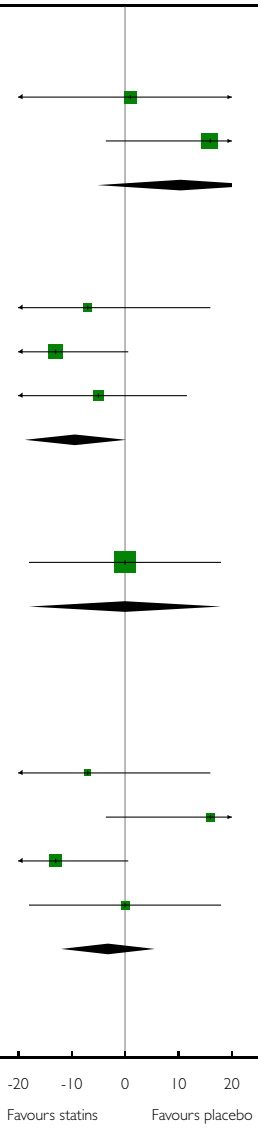
Analysis 1.10. Comparison 1 Statins versus control, Outcome 10 Change in serum triglyceride levels (%).

Review: Statins for children with familial hypercholesterolemia

Comparison: 1 Statins versus control

Outcome: 10 Change in serum triglyceride levels (%)

Study or subgroup	Statins N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 At 1 month							
Braaskamp 2015a	76	-5 (0)	27	2 (0)			Not estimable
Clauss 2005	35	-10 (36)	19	-11 (49)		37.9 %	1.00 [-24.05, 26.05]
Knipscheer 1996	53	4 (41)	18	-12 (35)		62.1 %	16.00 [-3.58, 35.58]
Subtotal (95% CI)	**164**		**64**			**100.0 %**	**10.31 [-5.11, 25.74]**
Heterogeneity: Chi² = 0.85, df = 1 (P = 0.36); I² =0.0%							
Test for overall effect: Z = 1.31 (P = 0.19)							
2 At 6 months							
Clauss 2005	35	-7 (40)	19	0 (42)		17.2 %	-7.00 [-30.07, 16.07]
McCrindle 2003	140	-12 (34)	47	1 (43)		50.0 %	-13.00 [-26.52, 0.52]
Stein 1999	63	6 (48)	59	11 (46)		32.8 %	-5.00 [-21.68, 11.68]
Subtotal (95% CI)	**238**		**125**			**100.0 %**	**-9.34 [-18.90, 0.22]**
Heterogeneity: Chi² = 0.58, df = 2 (P = 0.75); I² =0.0%							
Test for overall effect: Z = 1.92 (P = 0.055)							
3 At 1 year							
Stein 1999	61	6 (47)	49	6 (49)		100.0 %	0.0 [-18.09, 18.09]
Subtotal (95% CI)	**61**		**49**			**100.0 %**	**0.0 [-18.09, 18.09]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.0 (P = 1.0)							
4 At the end of follow-up							
Braaskamp 2015a	76	-5 (0)	27	2 (0)			Not estimable
Clauss 2005	35	-7 (40)	19	0 (42)		14.4 %	-7.00 [-30.07, 16.07]
Knipscheer 1996	53	4 (41)	18	-12 (35)		20.1 %	16.00 [-3.58, 35.58]
McCrindle 2003	140	-12 (34)	47	1 (43)		42.0 %	-13.00 [-26.52, 0.52]
Stein 1999	61	6 (47)	49	6 (49)		23.5 %	0.0 [-18.09, 18.09]
Subtotal (95% CI)	**365**		**160**			**100.0 %**	**-3.27 [-12.03, 5.50]**
Heterogeneity: Chi² = 5.94, df = 3 (P = 0.11); I² =49%							
Test for overall effect: Z = 0.73 (P = 0.47)							



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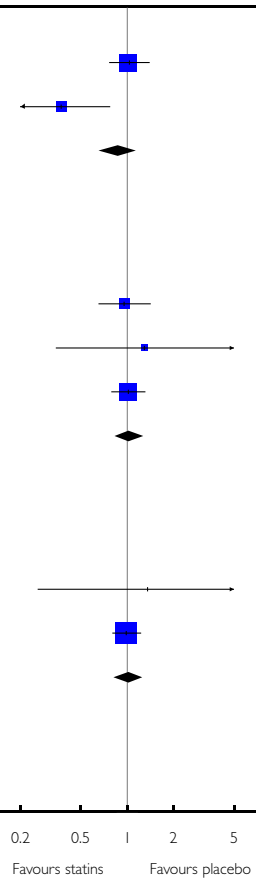
Analysis 1.11. Comparison 1 Statins versus control, Outcome 11 Adverse events.

Review: Statins for children with familial hypercholesterolemia

Comparison: 1 Statins versus control

Outcome: 11 Adverse events

Study or subgroup	Statins n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 At 1 month					
Avis 2010	73/130	25/46		73.2 %	1.03 [0.76, 1.40]
Knipscheer 1996	10/54	9/18		26.8 %	0.37 [0.18, 0.77]
Subtotal (95% CI)	**184**	**64**		**100.0 %**	**0.86 [0.65, 1.13]**
Total events: 83 (Statins), 34 (Placebo)					
Heterogeneity: Chi^2 = 6.58, df = 1 (P = 0.01); I^2 =85%					
Test for overall effect: Z = 1.10 (P = 0.27)					
2 At 6 months					
Clauss 2005	23/35	13/19		26.4 %	0.96 [0.65, 1.42]
de Jongh 2002a	6/106	3/69		5.7 %	1.30 [0.34, 5.03]
McCrindle 2003	88/140	29/47		67.9 %	1.02 [0.79, 1.32]
Subtotal (95% CI)	**281**	**135**		**100.0 %**	**1.02 [0.82, 1.27]**
Total events: 117 (Statins), 45 (Placebo)					
Heterogeneity: Chi^2 = 0.22, df = 2 (P = 0.90); I^2 =0.0%					
Test for overall effect: Z = 0.17 (P = 0.86)					
3 At 1 year					
de Jongh 2002a	4/86	2/58		4.8 %	1.35 [0.26, 7.13]
Stein 1999	48/67	47/65		95.2 %	0.99 [0.80, 1.23]
Subtotal (95% CI)	**153**	**123**		**100.0 %**	**1.01 [0.81, 1.26]**
Total events: 52 (Statins), 49 (Placebo)					
Heterogeneity: Chi^2 = 0.14, df = 1 (P = 0.71); I^2 =0.0%					
Test for overall effect: Z = 0.07 (P = 0.94)					



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WHAT'S NEW

Last assessed as up-to-date: 28 June 2017.

Date	Event	Description
28 June 2017	New citation required but conclusions have not changed	One new trial (107 participants) has been included in this update of the review (Braaskamp 2015a). However, this did not lead to any major changes in the conclusions of the review
28 June 2017	New search has been performed	One new trial has been included in this update of the review (Braaskamp 2015a). However, this did not lead to any major changes in the conclusions of the review

HISTORY

Protocol first published: Issue 1, 2007

Review first published: Issue 7, 2010

Date	Event	Description
3 July 2014	New search has been performed	One new trial has been included in the review update (Avis 2010). We are now using the definitions of statin-related myopathy provided by the U.S. Food and Drug Administration which relate to two clinical entities are used: (1) myopathy (creatine kinase over 10 x ULN); and (2) rhabdomyolysis (creatine kinase over 50 ULN and evidence of organ damage) (Joy 2009). One sub-study of the de Jongh 2002 study (de Jongh 2002b), previously listed as a separate included study, has been correctly linked under the de Jongh 2002 included study (de Jongh 2002a).
3 July 2014	New citation required but conclusions have not changed	One new trial has been included in this update of the review (Avis 2010). However, this did not lead to any major changes in the conclusions of the review
20 October 2008	Amended	Converted to new review format.
15 October 2007	New citation required and conclusions have changed	Substantive amendment

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CONTRIBUTIONS OF AUTHORS

Conceiving the review (AV02, PK01, SH01)

Designing the review (AV02, JK01, PK01, SH01)

Coordinating the review (AV02)

Data collection for the review (AV02, JK01)

Developing search strategy (JK01)

Undertaking searches (AV02, JK01)

Screening search results (AV02, JK01)

Organising retrieval of papers (AV02, JK01)

Screening retrieved papers against inclusion criteria (AV02, JK01)

Appraising quality of papers (AV02, JK01, PK01)

Abstracting data from papers (AV02, PK01)

Providing additional data about papers (JK01,SH01)

Data management for the review (JK01)

Entering data into RevMan (JK01)

Analysis of data (JK01)

Interpretation of data (AV02, JK01, TS01, PK01, SH01, AW, ST)

Providing a methodological perspective (JK01)

Providing a clinical perspective (AV02, G01, TS01, PK01, SH01, AW, ED,ST)

Providing a policy perspective (TS01, PK01, SH01)

Providing a consumer perspective

Writing the review (AV02, JK01, PK01)

Providing general advice on the review (TS01, PK01, SH01, AW, ST)

Securing funding for the review (AV02, JK01, PK01)

DECLARATIONS OF INTEREST

Disclosure issues and time periods:

None of the review authors is either employed by a drug company or is a member of the board of a drug company.

Some of the review authors have previously:

- been a guest lecturer in meetings arranged by a drug company;

- participated in an international conference, the travel expenses and participation fee sponsored by a drug company;

- been a member of the national advisory board of a drug company;

- been a clinical investigator in a statin trial.

Note: Drug company here means a company selling statins.

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SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We changed the age limit of participants from 17 years to 18 years. During the study selection, it became apparent several centres use 18 years as the cut off point for pediatric to adult services and we feel excluding these data would introduce a bigger bias to the review than changing the inclusion criteria.

Definitions of statin-related myopathy is now following U.S. Food and Drug Administration definitions and only two clinical entities are used: 1) myopathy (creatine kinase over 10 x upper limit of normal (ULN)) and rhabdomyolysis (creatine kinase over 50 ULN and evidence of organ damage) (Joy 2009).

We grouped outcome data into those measured at at six months (± two weeks), at one year (± four weeks) and at two years.

INDEX TERMS

Medical Subject Headings (MeSH)

*Heterozygote; Alanine Transaminase [blood]; Aspartate Aminotransferases [blood]; Brachial Artery [drug effects]; Carotid Intima-Media Thickness; Cholesterol, LDL [blood]; Creatine Kinase [blood]; Hydroxymethylglutaryl-CoA Reductase Inhibitors [adverse effects; *therapeutic use]; Hyperlipoproteinemia Type II [blood; *drug therapy; genetics]; Puberty [drug effects]; Randomized Controlled Trials as Topic; Vasodilation [drug effects]

MeSH check words

Adolescent; Child; Child, Preschool; Female; Humans; Male

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