

Section 12

NEED FOR STATINS IN CHILDREN - REVIEW

Prepared by: Basma Basha, Weill Cornell Medical College, Qatar, Julia Silveira, Weill Cornell Graduate School of Medical Sciences, and Marcus M. Reidenberg, Weill Cornell Medical College, New York, NY.

Primary Contact:

Dr. Marcus M. Reidenberg, MD, FACP
Professor of Pharmacology, Medicine, and Public Health
Weill Cornell Medical College
1300 York Ave. New York, NY 10065
(+) 212-746-6227
E-mail: mmreid@med.cornell.edu

SUMMARY AND CONCLUSION

This review of statin use in children was done to consider if a statin should be considered essential for children and added to the WHO Model List of Essential Medicines for Children. The data, presented in detail below prove that statins lower cholesterol in children just as they do in adults. The data show the same level and types of toxicity in children as seen in adults. Thus the issue is assessing whether heterozygous familial hypercholesterolemia, the best indication for statins in children, is “a priority health care need of a population, the public health relevance of this condition, and the evidence on efficacy and safety.”

The prevalence of heterozygous familial hypercholesterolemia is about 1 in 500 people. The Framingham Heart Study Cardiovascular Risk Assessment Tool (<http://hp2010.nhlbi.nih.net/atpiii/calculator.asp>) uses 20 as the youngest age for the calculation. Taking a total cholesterol of 300 mg/dl, high-density lipoprotein (HDL) of 35, systolic blood pressure of 120 and a non-smoker, the 10 year risk of a cardiovascular event is 1%. Using tables of values to calculate the risk score at: <http://www.framinghamheartstudy.org/risk/coronary.html> cannot be done for children because the lowest age in these tables is 30.

The duration of the randomized controlled trials in children showing change in blood lipids as the benefit ranged from 8 weeks to 3 years with the median being 6 months. Change in blood lipids was the only efficacy found. One study found a reduction of 0.01 mm in carotid intima thickness in pravastatin-treated children for 2 years compared to placebo-treated children [1] while another did not find any change after 3 years of atorvastatin [2].

Statin are certainly effective in secondary prevention of cardiovascular events. There is controversy about whether statins are effective for primary prevention [3-8]. This is not to question the concept that elevated concentrations of cholesterol in plasma cause atherosclerosis. It questions the idea that lowering the cholesterol by statins is effective in preventing or delaying cardiovascular events in children with high plasma cholesterol and no clinical evidence of atherosclerosis. The issue here is not whether people with familial hypercholesterolemia should or should not be given statins. The issue is whether there is enough evidence to start this drug therapy in children.

The current Cochrane Review [9], [Statin for the primary prevention of cardiovascular disease](#) by Fiona Taylor, Kirsten Ward, Theresa HM Moore, Margaret Burke, George Davey Smith, Juan P Casas, Shah Ebrahim, May, 2012 concludes:

“This current systematic review highlights the shortcomings in the published trials of statins for primary prevention. Selective reporting and inclusion of people with cardiovascular disease in many of the trials included in previous reviews of their role in primary prevention make the evidence impossible to disentangle without individual patient data. In people at high risk of cardiovascular events due to their risk factor profile (i.e. 20+ % 10-year risk), it is likely that the benefits of statins are greater than potential short term harms although long-term effects (over decades) remain unknown. Caution should be taken in prescribing statins for primary prevention among people at low cardiovascular risk.”

Given that:

1. the prevalence of heterozygous familial hypercholesterolemia is 1 in 500 people,
2. of 100 children with this condition, at most, 1 will have a cardiovascular event in 10 years (a 1% risk, considered very low risk by present standards), and

3. the long term risks to statin therapy as well as the benefits, if any, especially in children, have not been evaluated, it appears that statins do not meet the criteria for being an essential medicine for lifelong therapy for children.

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DETAILED DATA ABOUT EFFICACY

How search was conducted:

Search was done mainly looking at the randomized, double-blind, placebo-controlled clinical trials from reviews of statin use in children [1,2]. Also PubMed search was conducted with keywords “statin, children and familial hypercholesterolemia” or “statin, children and obesity”. Studies published after 2011 were found in PubMed using the search keys.

Effectiveness measures:

As main primary outcomes, change in carotid intima-media thickness, changes in serum low-density lipoprotein (LDL), HDL and total cholesterol and triglyceride level, and changes in measures of growth and maturation were reported in these studies (Table 1). The studies were followed up from 8 weeks up to 3 years.

Some studies reported the difference in mean relative reduction in thickness of carotid intima between those treated with placebo and those with statin treatment [3,4]. There was a reduction of 0.01mm in thickness for those treated with statin compared to placebo after two years of pravastatin treatment [3]. However, with atorvastatin, there was no difference in thickness after the treatment [4].

All studies reported the change in serum LDL cholesterol level after statin use [3-13]. Also there were studies reporting the change in absolute lipid levels, total cholesterol, triglycerides, and HDL cholesterol level [3-6,8-15].

Change in measures of growth and maturation was reported using the Tanner stage to see the effect of statins on puberty. Wiegman et al. reported onset of menstruation and testicular volumes were measured and saw no significant difference between the placebo and statin treated groups [3]. Serum hormone level such as estradiol and cortisol were reported in some studies and there was no significant effect after statin use [8,12,13].

Clauss et al. reported no change in vital signs (blood pressure and pulse rate), anthropomorphic measurements (height, weight, and BMI) and liver and muscle function after lovastatin treatment for 6 months [13].

Dose relationship:

Lambert et al conducted a study with 10, 20, 30, 40mg/dl and showed a dose-response relationship up to 30mg/dl [9].

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DETAILED DATA ABOUT TOXICITY

TOXICITY IN CHILDREN

How search was conducted:

The search used PubMed. The first strategy was “statins AND children”, then filtered by Child: birth – 18 years, Systematic Review, Meta-Analysis, Clinical Trial, Randomized Clinical Trial, Review, Humans, English. 175 papers were identified and manually searched for all that were relevant.

The next strategy used was using the “Mesh” Database feature, for “Hydroxymethylglutaryl-CoA Reductase Inhibitors”. It was used in the search builder (with the same above limits), and retrieved 252 papers. The majority of the papers were already found with the first search strategy.

INTRODUCTION

Most of the papers reviewed on the efficacy and safety of statins in the pediatric population are based on studies of statin use for cholesterol lowering in children with heterozygous familial hypercholesterolemia (FH). However, data on statin use in other groups of children, with different disease etiologies - such as obesity, hypertriglyceridemia, secondary hypercholesterolemia, etc. - are lacking [1].

While it may be possible to extrapolate some information from studies of statin use in children with FH, one should be very cautious in applying such statistics to determine efficacy and safety for children with other causes of dyslipidemia. Furthermore, children with secondary dyslipidemia may be of lower risk than those with FH and may benefit from other interventions such as diet and lifestyle changes, exercise, etc. [2]. A summary of the data is in Table 2.

A recent review has indicated that the side effect profiles will probably be similar in both groups [1].

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HEPATIC SIDE EFFECTS

1% to 5% of children treated with simvastatin or atorvastatin have been reported to have elevations in alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) [1,2], and also in a few children treated with lovastatin or pravastatin as well [3,4,5]. These elevations are usually asymptomatic and temporary – reversible after discontinuation of the drug [6,7,8].

No significant difference was found between the number of children within the statin and placebo treated groups who had elevated transaminases (greater than 3 times the upper normal limit) [9]. This was also concluded in other recent meta-analysis [10,11] and a Cochrane systemic review [12].

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MUSCULOSKELETAL SIDE EFFECTS

No cases of myositis, myopathy or rhabdomyolysis have been reported in children on statins in randomized clinical trials [1]. Only myalgia was reported, and it was not statistically significant between statin and placebo treated groups in a systematic review [1].

Elevations in creatine kinase (CK) levels were rare, but have been reported in children on statins [2-4]. However, a recent systematic review found no significant difference between the number of children within the statin or placebo treated groups with a clinically significant increase in CK values (greater than 10 times the upper normal limit) [5]. This was in agreement with the Cochrane review as well [6].

One trial reported a significant increase of blood CK levels by 17% in the lovastatin treated group compared to the placebo after 8 weeks of follow-up [7]. Another trial reported a subject on 10 mg of simvastatin who showed a very high CK increase (> 10 times the upper normal limit) but without any clinical symptoms [4]. That patient was also concomitantly on erythromycin, and after discontinuation of the antibiotic, the CK levels returned to normal [4]. Another study reported one case of a patient with an asymptomatic, extreme elevation in CK blood levels (16,400 U/l), but that patient was eventually found to be on the placebo [8].

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EFFECTS ON GROWTH

One meta-analysis found a statistically significant increase in height (0.35 cm; CI, 0.16–0.55 cm) and weight (0.23 kg; CI, 0.03–0.44 kg) among children on statins [1]. Another review also found a small increase in height (0.33 cm; 95% CI: 0.03 cm to 0.63 cm) in the statin treated groups as well [2].

Moreover, no statistical significant difference was found between mean changes in body mass index in the placebo and statin treated groups [3-11]. However, a meta-analysis reports a non-significant increase in body mass index (0.173 kg/m²; CI, -0.04 to 0.39 kg/m²) in statin treated children [1].

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EFFECTS ON SEXUAL MATURATION

Multiple reviews found no significant differences between statin and placebo treated groups in relation to their sexual maturation, which was measured by mean change in Tanner staging [1-4].

One review found that there was a non-significant slower Tanner stage change in statin treated males (RR 0.98; CI, 0.86–1.11) and no statistically significant difference in Tanner stage change in statin treated females (RR 0.94; CI, 0.80–1.11) [2]. A statistically significant increase in testes volume (1.69 cm³; CI, 1.34–2.04 cm³) in males treated with statins was also observed [2].

Two studies have found a significant, small increase in dehydroepiandrosterone (DHEA) levels in groups treated lovastatin (10-40 mg), as compared to placebo [5,6]. However, another study found a significant reduction in DHEA levels in group treated with simvastatin (40 mg), but there was no significant change from baseline [7]. Moreover, other studies found no significant difference in DHEA levels [8,9]. In all those trials, the changes in DHEA levels did not clinically affect sexual development though.

Of note was a randomized clinical trial that found a slightly decreased level of luteinizing hormone (LH) in the placebo group (vs. the lovastatin-treated group) after 24 weeks of therapy, which was statistically significant [8]. Nonetheless, other studies have shown that statins did not affect the levels of estradiol in girls or testosterone in boys nor the gonadotropic hormones LH and follicle-stimulating hormone (FSH) [7,9,10].

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EFFECTS ON OTHER HORMONES

No statistical significant difference was found in blood levels of testosterone, estradiol, cortisol, FSH, ACTH, or TSH in clinical trials, as assessed by two systematic reviews [1,2].

Yet one uncontrolled study reported a significant increase in plasma levels of cortisol in subjects on 10 mg of lovastatin [3]. The same study also reported a significant decrease in plasma cortisol levels in subjects on 40 mg of lovastatin [2]. Other trials, however, reported no changes in plasma cortisol levels [4-7].

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OTHER SIDE EFFECTS

Common side effects that were also experienced in the clinical trials included headaches, abdominal pain, infections and flu-like symptoms [1,2], which were temporary and similar across treatment and placebo groups in different randomized clinical trials [3]. When groups were compared within trials, these side effects did not vary by the type or dose of the statin drug. Very few children actually discontinued treatment due to side effects. They were also not statistically significant as compared to side effects reported by the placebo group in each individual trial [4,5].

Of interest was one randomized controlled trial that also found that school performance was not affected by children treated with statins [6].

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CASE REPORTS

Stein et al. reported one subject (on lovastatin) that developed bruising and purpura, but there were no abnormalities in the patient's hematological indices, and therefore it was not discontinued. It was not considered to be related to the statin therapy [1].

de Jongh et al reported one child that was discontinued from simvastatin (10 mg) because the child developed infectious mononucleosis that was unrelated to the statin therapy [2].

McCrinkle et al reported one subject on atorvastatin 20 mg that discontinued the drug because of mental depression (that later resulted in hospitalization). It was unclear whether it was related to statin therapy - but it was considered as a possibility [3].

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THE NEED FOR LONG-TERM STUDIES

The need for studies to assess long term safety of statins in children cannot be overemphasized. The available data is based on clinical trials that have ranged in duration from 6 months to 2 years [1]. While this data on short-term safety has been reassuring, there is no information on the potential for late side effects of taking statins at an early age. Also, not only were these studies rather short, but they were also relatively underpowered to reveal uncommon and rare adverse events [2-6]. Long term follow up needs to be addressed separately, and this information cannot be supplanted by data from adult studies.

Furthermore, the question of the large cumulative dose that these children will eventually receive (as they continue taking statins through adolescence and adulthood) needs to be raised, especially with recent studies in adults that have found increased incidence of diabetes mellitus with sustained statin use [7,8].

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RECOMMENDATIONS FROM PROFESSIONAL ORGANIZATIONS

The Food and Drug Administration (FDA) approves the use of pravastatin in children 8 years or older, and approves other statins in children 10 years or older (simvastatin, atorvastatin, fluvastatin, rosuvastatin, and lovastatin) [1].

The American Heart Association (AHA) and the American Academy of Pediatrics (AAP) have both recommended statin therapy for children with high-risk lipid abnormalities [2,3].

The National Cholesterol Education Program (NCEP) recommends that drugs should be administered only to patients above 10 years of age (ideally at pubertal Tanner stage II or higher, preferably after onset of menses in girls), and only after failure of an aggressive diet over a 6–12-month period [4,5].

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SPECIAL NOTES

→ Even though maximum adult doses of statins are not approved in pediatric patients, according to a recent Cochrane review there is a tendency to use adult statin doses for children with FH [1].

- [1] Vuorio A, Kuoppala J, Kovanen PT, Humphries SE, Strandberg T, Tonstad S, Gylling H. Statins for children with familial hypercholesterolemia. *Cochrane Database Syst Rev.* 2010 Jul 7;(7):CD006401.

→ There has been some debate on whether liver transaminases are the best method to detect liver toxicity, and it has been suggested that fractionated bilirubin may be an additional approach [1].

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→ The context of clinical and laboratory adverse events needs to be standardized to better compare studies, as that varied between clinical trials and prevented accurate review [1,2].

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→ All statins (except pravastatin and rosuvastatin) are metabolized by the cytochrome P450 3A4 system. Caution should be exercised when administering these statins with drugs that are also metabolized by the same pathway (such as cyclosporine, erythromycin, itraconazole, ketoconazole, nicotinic acid, and fibrates, especially gemfibrozil). This may potentially increase the risk of adverse events, such as myopathy, because it results in higher serum concentrations of these drugs [1].

- [1] Rodenburg J, Vissers MN, Trip MD, Wiegman A, Bakker HD, Kastelein JJ. The spectrum of statin therapy in hyperlipidemic children. *Semin Vasc Med.* 2004 Nov;4(4):313-20.

→ Animal studies and case series in humans have revealed that statins are potent teratogens [1-3]. Statins are thus not considered safe during pregnancy and breastfeeding, and physicians must be careful when prescribing statins to young women of child-bearing age. There is consensus on prescribing simultaneous contraception to these young women [4-6].

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TOXICITY IN ADULTS

The most serious adverse event is rhabdomyolysis – which occurs at a rare rate of 3.4 per 100,000 person-years of treatment, and leads to death in 10% of those cases [1,2]. Myopathy with elevated creatine kinase levels is described in patients using statins at a rate of 11 per 100,000 person-years [2]. Minor muscle aches and myalgias occur at an equal rate in both statin and placebo control groups in randomized clinical trials [2,3,4]. An observational study of 32,225 subjects taking statins found that 9% of statin users had myopathic events while only 4% of people not on statins had such events [5]. A variation of the gene SLCO1B1 (CC genotype) is an important risk factor for myopathy with 18% of patients taking 80 mg of simvastatin daily with this gene developed myopathy within 4 years of therapy [6]. There is also an immune mediated statin myopathy with antibodies to HMG Co A reductase, the target of statins which is up-regulated by statin therapy [7]. A randomized clinical trial found that statin-treated subjects had more loss of energy and more exertional fatigue than placebo treated subjects [8]. A possible mitochondrial mechanism has been suggested for these and other statin effects (9).

A temporary, common side effect of statins is raised amino-transaminases (identified as more than 3 times the upper normal limit on two successive measurements), which occurs in 1 to 3% of its users [10,11]. Elevated levels of alanine aminotransferase occur in greater than 70 per 100,000 person-years among statin users [2] - usually asymptomatic and happen more than 90 days after starting therapy [12,13]. It is more often observed with higher doses of drug [14]. The rate of liver failure in statin users is the same as that in the general population [15].

Furthermore, peripheral neuropathy has also been reported to happen in about 12 per 100,000 person-years [2]. Several meta-analyses and long-term follow-up (10 years) studies failed to reveal any increased incidence of cancers or cancer death rates in statin users [16-20]. Case-control studies did not show any increased incidence of depression and suicide amongst statin users either [21,22].

One meta-analysis discovered that there is an increased incidence of diabetes mellitus in statin users – more than 1 in 255 persons taking statins for 4 years [23]. Questions on the possible cumulative risk of many years of statin treatment may hence arise [24].

Equivocal data has been reported with respect to adverse effects of statins on cognitive functions. One randomized clinical trial did find a significant association [25], while two large, randomized clinical trials did not [26,27].

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Table 1

	authors	subject	treatment	duration	efficacy measure		safety
1	Wiegman et al. JAMA, 2004	214 children with familial hypercholesterolemia 8-18 yrs in Netherlands	paravastin	2 yrs	Mean change in carotid IMT LDL-C	0.014mm -24.1% vs. 0.3%	growth maturation hormone level measurement no sig. change in growth, muscle of liver enzymes, endocrine function, tanner staging process, onset of menstruation, testicular volume
2	Couture et al. Arterioscler Thromb Vasc Biol. 1998	57 children LDL receptor genotype separated less than 18yrs old in Canada	placebo vs. simvastin		LDL-C: (separated LDL-C by receptor genotype) total n=57 n=14, W66G: 31% n=23, deletion: 38% n=10, C46Y: 42%	-31% to -42%	well tolerated
3	Knipscheer et al. Pediatric Res. 1996	72 children with het. FH	paravastin 5-10-20mg/d	12 weeks (3months)	Total cholesterol LDL-C HDL-C B100 VLDL	-24.6% -32.9% 10.8% -26.8% -24.5%	
4	McCrinkle et al. J. Pediatr. 2003	187 children with familial or severe hypercholesterolemia	atorvastatin 10-20mg/d (4 week interval)	26weeks (6months and 2 weeks)	LDL-C (atorvastin vs. placebo) Total cholesterol triglycerides ApoB HDL-C	-40% vs.-0.4% -32% vs.-1.5% -12% vs. 1% 34% vs.0.7% 2.8% vs.-1.8%	well tolerated

5	Stein et al. JAMA 1999	132 children with het. FH 11-17 yrs male	lovastatin 10-20-40mg/d (8week interval)	48 weeks (1 year) 1990-1994	LDL-C	-25%	growth and sexual maturation by tanner staging testicular volume serum hormone levels biochemical parameters of nutrition ALL NOT SIGNIFICANT at 24 weeks and 48 weeks note: serum Vitamin E decreased
6	Lambert et al. Pediatrics 1996	69 male children with FH 12.9 +/- 2.4 yrs	lovastatin after 4-week placebo period 10-20-30- 40mg/d for 8 weeks dose response relationship up to 30mg/d	8 weeks plasma lipid protein measured every 2 weeks	Total cholesterol LDL-C apoB HDL-C ApoA1	-17% to - 29% -21% to - 36% -19% to - 28% 7% 4%	well tolerated (no clinical adverse experience reported) decreased aspartate aminotransferase concentration (no dose response) no change in alanine aminotransferase
7	Schanberg et al. Arthritis Rheum. 2012	221 children with systemic lupus erythematosus 10-21 yrs	atovastatin 10, 20mg depending on weight	3 years	Carotid intima- media thickening (CIMT) high-sensitivity C- reactive protein (hsCRP) Total cholesterol LDL-C	P=0.24 P=0.04 P<0.001 P<0.001	well tolerated

8	McCrimdiddle 2002	36 children with FH or familial combined hyperlipidemia	placebo vs. pravastatin vs. bile-acid binding protein (colestipol) vs. combined 10mg/d for for colestipol,5mg-10mg pravastatin	two 18 week regimen	LDL-C	-17 +/- 16% vs. -10 +/- -13% with combined therapy	free of adverse effects - more with colestipol only regimen
9	Ducobu et al. Lancet 1992	32 children with FH younger than 17 years total cholesterol above 300mg/dl after diet therapy for 6months	Simvastatin 5-10-20mg/d (4 week interval) for younger than 10 10-20mg/d (8 week interval) for older children	6-8months followed measured at 52 weeks and 104 weeks (1 and 2 years)	LDL/HDL LDL-C HDL-C Total Cholesterol Triglyceride	-43% -37.3% 22.5% -25.5% -8.8% (not significant)	At weeks 4, 12, 26, 52, 78, 104 transaminase aklaline phosphatase creatinine phosphokinase NO SIGNIFICANT CHANGE children remained growing
10	de Jongh et al Circulation 2002	173 children with het. FH (98 boys, 75 girls)	After 4 week diet/placebo run simvastatin 10-20-40mg/d (8 week intervals)	1 year	LDL-C Total cholesterol ApoB VLDL-C Triglyceride HDL-C ApoA-I	-41% -31% -34% -21% -9% 3.3% 10.4%	no sig. change in adrenal, pituitary, gonadal hormomone change small decreas in dehydroepiandrosterone sulfate

11	Claus Pediatrics 2005	54 children with het. FH 10-17yrs	lovastatin with diet 20mg/d for 4 weeks 40mg/d for 20weeks	6 months	LDL-C Total cholesterol ApoB	-23% to - 27% -27% to - 22% -20% to - 23%	blood pressure pulse rate follicle stimulating hormone dehydroepiandrosterone sulfate estrodiol cortisol menstrual cycle strength liver and muscle function
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Table 2

Year	Type	Author	Title	Patients/Method	Drug& Dose	Significance of adverse effects	Types of adverse effects	Follow Up
1992	Prospective Cohort Study	Ducobu et al. [1]	Simvastatin use in children	-32 patients (< 17 years old) with hyperlipidemia - <u>Inclusion Criteria:</u> Total Cholesterol > 300 mg/dl or after diet therapy for 6 months	<u>Simvastatin</u> : titrated up to 20 mg/dl in < 10 years old & up to 40 mg/dl in rest	no significant changes in CK or transaminase levels growth & development remained normal	-Only 1 patient showed an increase in liver trans-aminases -2 patients had transient elevations in CK levels.	24 -36 m
2002	Randomized, double-blind, placebo-controlled trial	De Jongh et al. [2]	Efficacy and safety of statin therapy in children with familial hypercholesterolemia	-173 children with familial hypercholesterolemia -Placebo run-in period >> patients were randomized to placebo or simvastatin -Entry criteria included children aged 10 to 17 years with LDL-C levels between 4.1 and 10.3 mmol/L and 1 parent with a confirmed diagnosis of heFH.	<u>Simvastatin</u> : initial dose 10 mg with titration up to 40 mg/d during a 24-week period	-Laboratory abnormalities slightly increased in the simvastatin group, although not statistically significantly. -Growth and maturation were not different from those on placebo. -Both boys & girls on simvastatin had sig. lesser degrees of increase in DHEA levels, although the magnitude of these differences was thought not to be clinically important.	-Abdominal & chest pain, constipation, flatulence, weight gain, myalgia, headache, sleep disorder -Only 3 patients had transient elevations of CK, one of whom had been also taking erythromycin.	48 wks
2004	Randomized, double-blind, placebo-	Wiegman et al. [3]	Efficacy and safety of statin therapy in	- 214 children with familial hypercholesterolemia (age 8 to 18	<u>Pravastatin:</u> a daily dose of 20 mg if <14 years	No differences were observed for growth, muscle or liver enzymes, endocrine	Transient elevations in CK & trans-aminases were infrequent & occurred equally in both groups	2 years

	controlled trial		children with familial hypercholesterolemia	years) – Randomized to placebo or pravastatin, 20 to 40 mg/dl.	old & 40 mg if older for a period of 2 years	function parameters, Tanner staging scores, onset of menses, or testicular volume between the 2 groups.		
2005	Prospective clinical follow-up study	Hedman et al. [4]	Efficacy and safety of pravastatin in children and adolescents with heterozygous familial hypercholesterolemia	30 patients with familial hypercholesterolemia (age 4.1-18.5 yr)	<u>Pravastatin:</u> started at 10 mg/d, with a forced titration by 10 mg at 2, 4, 6, and 12 months until the target cholesterol level [≤ 194 mg/dl] was reached	– No clinically significant elevations in ALT, CK, or creatinine were seen. – Growth and pubertal maturation remained normal in all subjects – Although a statistically significant decrease in vitamin E levels was seen, the fat-soluble vitamins remained at clinically satisfactory levels	The most common adverse experiences were headache and GI symptoms, affecting 13% & 37% of the patients, respectively, at 2 months. Sleep disorder occurred in 10%, but no other social or psychological adverse experiences.	2 years
1996	Randomized, double-blind, placebo-controlled trial	Knipscheer et al. [5]	Short-term efficacy and safety of pravastatin in 72 children with familial hypercholesterolemia	– 72 children with familial hypercholesterolemia (25 boys, 47 girls) who had LDL-C > 95th % despite diet therapy – After an 8 week placebo run-in period >>>	<u>Pravastatin:</u> 5, 10 and 20 mg/d administered over a 12-week period.	– Equally distributed among groups taking placebo & different dosage levels of pravastatin. – Plasma TSH, ACTH, cortisol, CPK & liver enzyme levels, did not show significant changes in any of the	– A total of 10 adverse clinical events were reported among the 54 children treated with pravastatin, including self-limited headache, nausea, vomiting, and abdominal pain. – The nature of adverse effects was similar in the	12 weeks

			sterolemia	stratified by age (8–10 y, 11–13 y, 13–16 y) & randomized to receive treatment with pravastatin or placebo		groups between the end of the treatment period & baseline – Rash, nose-bleeding, headache, nausea/vomiting, abdominal pain, myalgia	children randomized to receive placebo, except for one child who experienced a rash with pravastatin 5 mg/d. – Abnormal ALT, CPK, TSH & unbound cortisol were reported more often in the pravastatin- treated children, but did not attain statistical significance at the end of treatment when compared with baseline values.	
2000	Open-label dosage-titration study	Firth et al. [6]	Fluvastatin in heterozygous familial hypercholesterolemia	29 boys with heterozygous familial hypercholesterolemia	<u>Fluvastatin</u> : titrated up to 80 mg/d		– Transient asymptomatic increases in CK – Other lab abnormalities absent	2 years
1996	Randomized, double-blind trial	Lambert et al. [7]	Treatment of familial hypercholesterolemia in children and adolescents: effect of lovastatin: Canadian Lovastatin in Children Study	– 69 boys with heterozygous familial hypercholesterolemia (aged 9–17 y) with LDL-C > 95th % despite drug therapy with a bile acid sequestrant & diet. – Stopped all lipid-lowering agents	<u>Lovastatin</u> : 10, 20, 30, or 40 mg/d for a treatment period of 8 weeks	– No serious clinical adverse experience was reported. – Transient AST elevations were experienced by 3 children who received lovastatin 30 or 40 mg/d, but no evidence of a dose-response relationship. – No significant	– Transient increases in liver trans-aminases: but did not exceed twice ULN. – Asymptomatic increases in CK rare & resolved spontaneously – An increase in the mean morning cortisol & mean DHEA-S was detected in children receiving lovastatin 10 mg/d, while a decrease in the mean morning cortisol was	8 weeks

			Group.	<p>at least 8 weeks before entry into study</p> <ul style="list-style-type: none"> Enrolled in an initial 4-week placebo period, followed by randomization to drug dose 		<p>change in ALT.</p> <ul style="list-style-type: none"> Hormonal status was monitored, and increases in cortisol & DHEAs: clinical significance is questionable. 	<p>found in children receiving lovastatin 40 mg/d</p> <ul style="list-style-type: none"> 13 clinical adverse events were reported among the children while receiving lovastatin, including headache, fatigue, heartburn, jaundice, muscle cramps, chest pain, lymph node enlargement & cold- and flu-like symptoms 	
1999	Randomized, double blind, placebo-controlled trial	Stein et al. [8]	Efficacy and safety of lovastatin in adolescent males with heterozygous familial hypercholesterolemia	<ul style="list-style-type: none"> 132 boys with heterozygous familial hypercholesterolemia (aged 10–17 y) with LDL-C of 189–503 mg/dl despite at least 4 months of diet therapy Required to be prepubescent in Tanner I stage or pubescent in Tanner II–IV stages & weigh between 10th & 95th % for their ages Randomized to either placebo or 	<p><u>Lovastatin:</u> 10 mg/d followed by dose titration to 20 mg/d at week 8 and to 40 mg/d at week 16</p>	<ul style="list-style-type: none"> No differences between placebo & lovastatin dose groups were seen with regard to liver transaminases Infrequent & sporadic increases in CK occurred, not significantly different between groups. Growth & sexual maturation not affected. 	<ul style="list-style-type: none"> Biochemical nutritional parameters & serum hormones remained w/in normal range. 2 lovastatin-treated children experienced non-sustained elevations in CK to more than five times ULN that resolved without intervention; asymptomatic & associated with vigorous or unusual activity. DHEA-S tended to increase in children in lovastatin group more than in placebo group (18% vs. 5%; p = 0.03), but Tanner staging & physical assessment revealed that all of the 	48 weeks

				drug			boys experienced appropriate growth & sexual maturation throughout the study period. – The nature or frequency of adverse clinical or laboratory events was not reported	
2005	Randomized, placebo-controlled trial	Clauss et al. [9]	Efficacy and safety of lovastatin therapy in adolescent girls with heterozygous familial hypercholesterolemia	– 54 post-menarchal girls (10 – 17 years old) with familial hypercholesterolemia – Randomized to either placebo or drug after 4 week diet/placebo run-in period	<u>Lovastatin</u> : 20 mg/d for 4 wks; followed by 40 mg for 20 wks	– No differences from placebo were seen with regard to any safety parameter, including hormone levels – No differences in menstrual cycle length – abdominal pain, diarrhea, nausea, headache	No clinically significant alterations in vital signs (BP & HR), height, weight & BMI, hormone levels (LH, FSH, DHEAs, estradiol & cortisol), menstrual cycle length, or tests of liver & muscle function.	24 weeks
2003	Multicenter, randomized, placebo-controlled trial	McCrindle et al. [10]	Efficacy and safety of atorvastatin in children and adolescents with familial hypercholesterolemia or severe	– 187 male & female children with familial or severe hypercholesterolemia – 6-month phase comparing subjects taking placebo with drug	<u>Atorvastatin</u> : 10 to 20 mg	– Excellent safety & tolerance – A single withdrawal in the atorvastatin group, caused by increased depression, was judged to be possibly treatment related. – Among patients with normal liver function tests at baseline, 1% of those treated with	– Abdominal pain, fever, flu, headache, infection, pharyngitis, accidental injury, etc. – An open-label 6-month extension in which all subjects took 10 mg/d showed ongoing safety & tolerance with no effect on growth & development.	12 mon

			hyperlipidemia			atorvastatin had an AST elevation (>3.03ULN) and 1% had an ALT elevation (>33ULN), whereas no placebo-treated patients had such elevations. Atorvastatin had no significant effect on sexual development, as measured by Tanner staging.		
2004		Shepherd et al. [11]	Safety of rosuvastatin	children with familial hypercholesterolemia	<u>Rosuvastatin</u> :			
1992	Prospective clinical follow-up study	Sinzing et al. [12]	Treatment of hypercholesterolaemia in children	<ul style="list-style-type: none"> - 13 children with TC >300 mg/dL following diet therapy. - Lovastatin 20 mg/d (6 girls and 3 boys, aged 6–13 y) OR lovastatin 20 mg/d plus cholestyramine 8 g/d (2 girls and 2 boys, aged 7–10y) 	<u>Lovastatin</u> : 20 mg/d	All of the children remained in the same growth percentile as they had been before treatment with lovastatin.	The nature or frequency of adverse events was not reported.	208 weeks