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Review Article

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Statins Use in Children & Adolescents

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Cholesterol and statin therapy have fixed relationship. The use of pharmacologic therapy in children with dyslipidemia is a matter of controversy. There is growing evidence to suggest that the development of atherosclerotic cardiovascular disease (CVD) begins early in life, even in childhood [1].

Statins, or 3-Hydroxy-3-Methyl-Glutaryl Coenzyme-A (HMG-CoA) reductase inhibitors, are one of the most widely prescribed medication classes all over the world. Statins have been shown to be effective at reducing coronary morbidity and mortality in high-risk adults. Depending on the patient baseline values and the dose used, these medications result in cholesterol reductions of 20-50% below baseline [2].

Lipids in Children & Adolescents

Cholesterol Concentrations: At birth cholesterol levels shows Total Cholesterol (TC) 70 mg/dL, Low Density Lipoprotein cholesterol (LDL) 30 mg/dL, High Density Lipoprotein cholesterol (HDL) 35 mg/dL. Low birth LDL-c levels rise with breastfeeding & in adulthood with exposure to Western diet. In the first 2 years of life, cholesterol increases rapidly at least doubled. Between ages 9 and11 years, the mean TC peaks 170 mg/dL. During puberty cholesterol, levels decrease and increase thereafter. In young men during puberty, their HDL falls permanently [3]. Ethnic differences is present as black children have higher HDL and lower TG than white Hispanics or non-Hispanic [4].

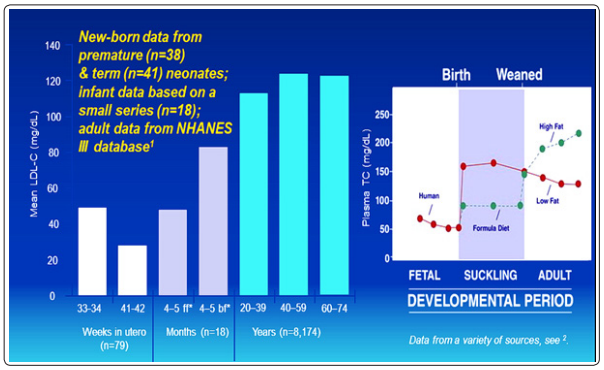

Figure 1: Low Birth Ldl-C Levels Rise With Breastfeeding & In Adulthood With Exposure To Western Diet

Cholesterol concentrations in youth; elevated concentrations of lipids and lipoproteins are quite common. In the Child & Adolescent Trial for Cardiovascular Health (grades 3-4) showed the prevalence of total cholesterol >200 mg/dL was 15.6% in girls and 11.1% in boys [5]. About 75% of children in the Muscatine Study and 70% of children in the Bogalusa Heart Study with elevated lipids tracked into adulthood [6].

Lipid Testing For Children [7]

- For children under the age 2 years, lipid screening is NOT recommended.
- From age 2 to 8 years, screening is recommended ONLY if other risk factors for cardiovascular disease are present as personal history of diabetes mellitus (DM), high Blood Pressure (BP), Body Mass Index (BMI) greater than the 95th percentile, smokes cigarettes or a family history of early Coronary Artery Disease (CAD) or lipid disorder, high BP, obesity, tobacco exposure, DM, or Chronic Kidney Disease (CKD).
- From age 9 to 11 years, universal screening is recommended with either a fasting or non-fasting lipid profile.
- From age 12 to 16 years, universal screening is NOT recommended because of changing lipid levels during puberty. If risks factors mentioned above are present, then screening may be recommended.
- From age 17 to 21 years, universal screening is recommended, as lipid levels are more stable after puberty.

What are statins available for use in pediatrics

The four statins currently approved for use by the US Food and Drug Agency (FDA) are lovastatin, simvastatin, pravastatin, and atorvastatin, based on randomized placebo-controlled trials of at least 24 weeks over more than 750 male and female children [8].

Now pravastatin and rosuvastatin, FDA approval for children age ≥ 8 years with Heterozygous Familial Hypercholesterolemia (HeFH). Lovastatin, simvastatin, fluvastatin, atorvastatin, and rosuvastatin approved for children ≥10 years with HeFH [9]. Still, the use of pitavastatin in children has not been studied yet.

The Evidence of Statins

LDL-c is closely related to Coronary Heart Disease (CHD) events

in statin trials

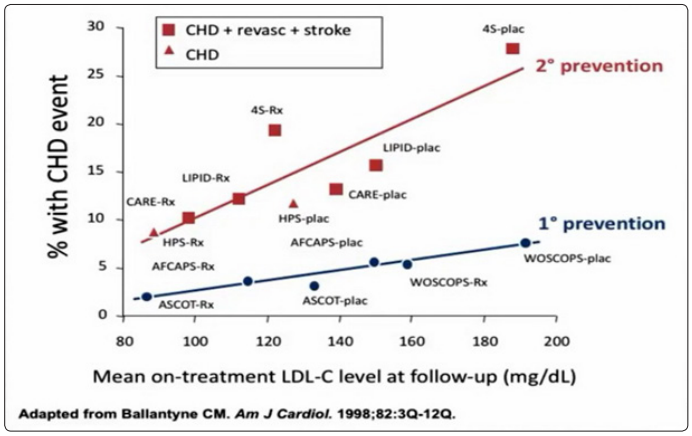

Figure 2: Ldl-C Is Closely Related To Chd Events in Statin Trials

Justification for the Use of Statin in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) [10].

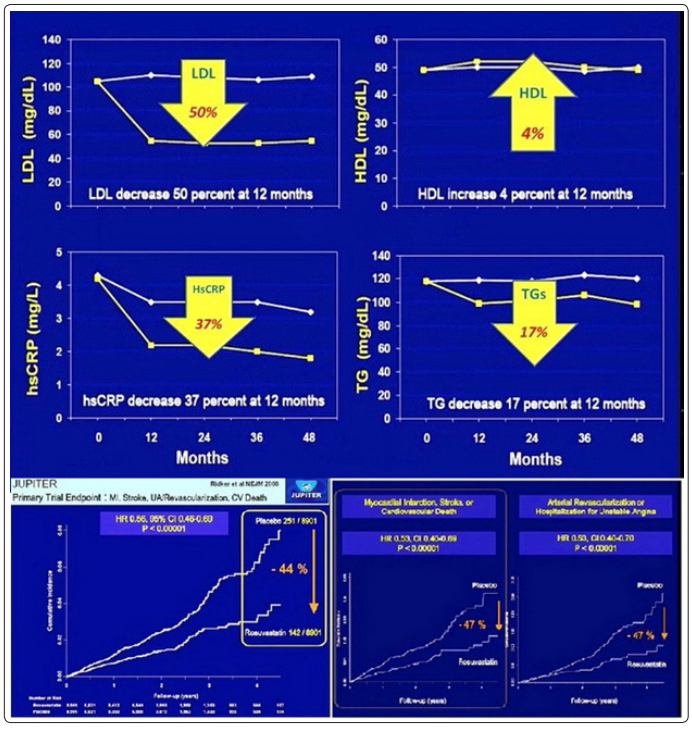

Figure 3: Jupiter Trial

Another study, Reduction in cardiovascular events with atorvastatin in 2,532 patients with type 2 diabetes: Anglo-Scandinavian Cardiac Outcomes Trial--lipid-lowering arm (ASCOT-LLA) [11].

What Do the Recent Guidelines Say?

2019 Normal & abnormal childhood lipid values New 2019 European Lipid Guidelines Take Aggressive Approach [12,13].

2019 Normal & abnormal childhood lipid values

Table 9: Normal and Abnormal Lipid Values in Childhood*†

	Acceptable, mg/dL	Borderline, mg/dL	Abnormal, mg/dL
TC	<170 (<4.3 mmol)	170-199 (4.3-5.1 mmol)	≥200 (≥5.1 mmol)
Triglycerides (0-9 y)	<75 (<0.8 mmol)	75-99 (0.8-1.1 mmol)	≥100 (≥1.1 mmol)
Triglycerides (10-19 y)	<90 (<1.0 mmol)	90-129 (1.0-1.5 mmol)	≥130 (≥1.4 mmol)
HDL-C	>45 (>1.2 mmol)	40-45 (1.0-1.2 mmol)	<40 (<1.0 mmol)
LDL-C	<110 (<2.8 mmol)	110-129 (2.8-3.3 mmol)	≥130 (≥3.4 mmol)
Non-HDL-C	<120 (<3.1 mmol)	120-144 (3.1-3.7 mmol)	≥145 (≥3.7 mmol)

*Vallues for plasma lipid and lipoprotein levels are from the NCEP Expert Panel on Cholesterol Levels in Children. Non-HDL-C Values from the Bogalusa Heart Study are equivalent to the NCEP Pediatric Panel cutpoints for LDL-C.

†The cutpoint for high and borderline high respect approximately the 95th and 75th percentiles, respectively.

Low cutpoint for HCL-C represent approximately the 10th percentile. Values given are in mg/dL. To convert to SI units, divide the results for TC, LDL-C, HDL-C, and non-HCL-C by 38.6; for triglycerides, divide by 88.6.

HDL-C indicates high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NCEP, National Cholesterol Education Program; *SI, System international d'unites* (International System of Units); and TC, total cholesterol.

Intensity of lipid lowering agents showed in

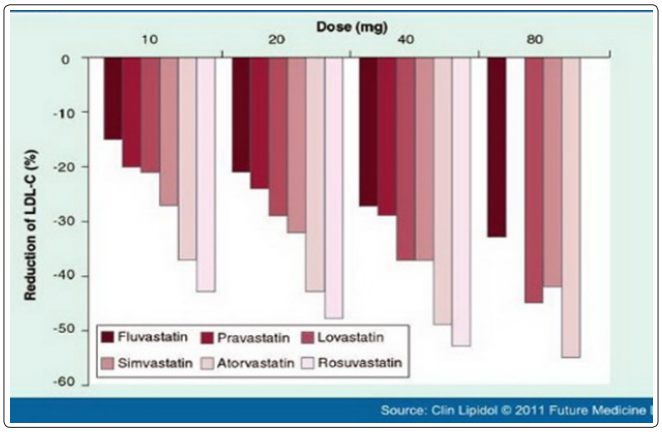

Figure 5: Ldl Reduction By Different Statins

In 2018 AHA/ACC & other societies, guidelines on the management of Blood cholesterol, shown when you should investigate dyslipidemia in children and adolescents?

In children and adolescents with family history of either early CVD or significant hypercholesterolemia, it is reasonable to measure a fasting or non-fasting lipoprotein profile as early as age 2 years to detect Familial Hypercholesterolemia (FH) or rare forms of hypercholesterolemia [14]. In children and adolescents without CV

risk factors or family history of either early CVD, it is reasonable to measure a fasting or non-fasting lipoprotein profile once between the age of 9 and 11 years, and again between the ages of 17 and 21 years, to detect moderate to severe lipid abnormalities.

In 2017 AACE/ACE guidelines for management of dyslipidemia & prevention of CVD for children & adolescents [15].

- Pharmacotherapy for those older than 10 years who do not respond sufficiently to lifestyle modification, particularly for those satisfying the following criteria: LDL-C ≥190 mg/dL, LDL-C ≥160 mg/dL + the presence of two or more CV risk factors, even after vigorous intervention, Family history of premature ASCVD (age < 55 y), or Having overweight, obesity, or other elements of the insulin resistance syndrome

Fasting or non-fasting lipid profile

Traditionally, blood sampling for lipid analyses has been recommended in the fasting state (12 hrs.). Recent systematic studies comparing fasting & non-fasting samples have suggested that the difference is small for most lipid parameters. Non-fasting sampling has been used in large population-based studies. In most studies, non-fasting samples display a higher TG level of 0.3 mmol/L (27 mg/ dL). On average, for most individuals, this increment will be of no clinical significance. Indeed, a number of guidelines recommend non-fasting sampling. For general risk screening, non-fasting samples seem to have at least the same prognostic value as fasting samples [16].

The practical advantages of non-fasting samples, including better patient acceptability, outweigh the potential imprecision in some patients. Even if non-fasting sampling can be used in most cases, in patients with metabolic syndrome (MetS), DM, or hypertriglyceridemia (HTG), calculated LDL-C should be interpreted with caution.

In addition to fasting/non-fasting state there are other factors (pre-analytical) which may affect lipid components [16-18].

1. A change from an upright to a supine position due to dilutional effect can reduce the cholesterol levels by 10% and triglycerides by 12%.
2. Prolonged tourniquet application (2–5 min) can increase cholesterol from 5 to 15%.
3. Cholesterol is slightly higher in winter than in summer and the opposite is true for triglycerides.
4. The disease conditions like nephrotic syndrome increase total cholesterol, LDL cholesterol and VLDL cholesterol and hypothyroidism increases LDL cholesterol and total cholesterol. Infection and inflammation may decrease total cholesterol and HDL cholesterol and increase triglycerides. Lipids alter following myocardial infarction and these changes may persist for several weeks [17,18]. That is why it is better to do lipid profile in such patients within 24 h of myocardial infarction.

LDL-c; How low should we go? Is it safe [19,20]

Although the present study did not, and was not designed to, address the question of what amount of LDL-c reduction was optimal or the parallel issue of the LDLc "goal" in children, we know from numerous adult trials that when it comes to reductions in LDL-c, "the lower, the better".

What are concerns about using statins in pediatrics?

1. Remember that all body cells can synthetize its own cholesterol, but we are talking about the excess circulating cholesterol mainly LDL-c and non-HDL cholesterol; which can be deposited in the intima of the arteries.
2. Cholesterol is an important factor for growth & development in children. Neurological safety data should not be extrapolated from adults and applied to children (mainly concerning lipophilic statins that can cross the blood brain barrier). Lovastatin & simvastatin are the most lipophilic readily translocating across membranes, whereas pravastatin & rosuvastatin are the most hydrophilic agents.
3. Cholesterol also synthesizes steroid hormones. Concerns exist utilizing statins for long term therapy when it is unknown if the child's CNS, energy function, growth & sexual hormones could be altered by statin use at such a young age.
4. The 4S study (1994) 10-years Follow-up; Simvastatin treatment for 5 years in a placebo-controlled trial, followed by open-label statin therapy, was associated with survival benefit over 10 years of follow-up compared with open-label statin therapy for the past 5 years only. No difference was noted in mortality from & incidence of cancer between the original simvastatin group & placebo group. Same result also with WOSCOPS trial 20-years Follow-up.

Tolerance of statins

Statin therapy is generally well tolerated and very effective in the prevention and treatment of cardiovascular disease, regardless of cholesterol levels; however, it can be associated with various adverse events (myalgia, myopathy, rhabdomyolysis, and diabetes mellitus, among others). Patients frequently discontinue statin therapy without medical advice because of perceived side effects and consequently increase their risk for cardiovascular events. In patients with statin intolerance, it may be advisable to change the dose, switch to a different statin, or try an alternate-day regimen. If intolerance is associated with all statins-even at the lowest dose-non-statin drugs and certain nutraceuticals can be considered. This review focuses on the definition of statin intolerance and on the development of clinical and therapeutic strategies for its management, including emerging alternative therapies. About 70-80% well tolerate statins, 20-30% may have suspected intolerance and only 5-6% have confirmed intolerance [21].

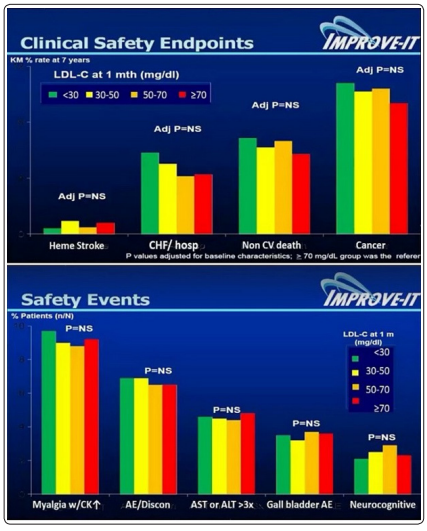

Figure 6

The Risk of Discontinuing Statin [22,23]

Is more risky than compared to non-users

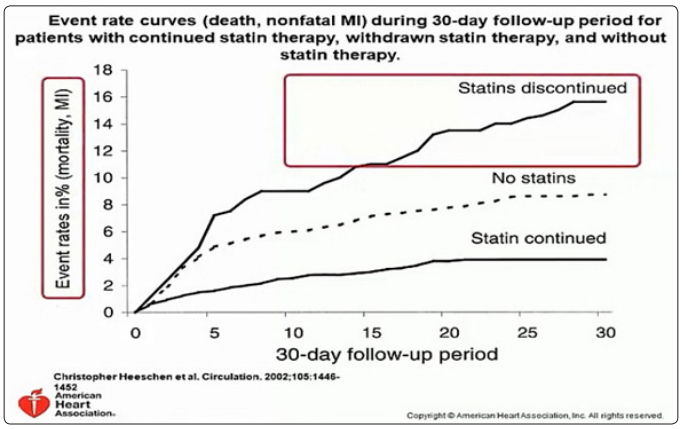

Figure 7: The Risk of Discontinuing Statin

What are steps applied in treatment of dyslipidemia in children [24]

Recommendations for Children and Adolescents

Referenced studies that support recommendations are summarized in Online Data Supplements 18, 19, 20, and 21.

COR	LOE	Recommendations
I	A	1. In children and adolescents with lipid disorders related to obesity, it is recommended to intensify lifestyle therapy, including moderate caloric restriction and regular aerobic physical activity (S4.4.4.2-1–S4.4.4.2-4).
I	B-NR	2. In children and adolescents with lipid abnormalities, lifestyle counseling is beneficial for lowering LDL-C (S4.4.4.2-1-3, S4.4.4.2-5–S4.4.4.2-12).
IIa	B-R	3. In children and adolescents 10 years of age or older with an LDL-C level persistently 190 mg/dL (≥4.9 mmol/L) or higher or 160 mg/dL (4.1 mmol/L) or higher with a clinical presentation consistent with FH (see Section 4.2) and who do not respond adequately with 3 to 6 months of lifestyle therapy, it is reasonable to initiate statin therapy (S4.4.4.2-13–S4.4.4.2-16).
IIa	B-NR	4. In children and adolescents with a family history of either early CVD* or significant hypercholesterolemia,† it is reasonable to measure a fasting or nonfasting lipoprotein profile as early as age 2 years to detect FH or rare forms of hypercholesterolemia (S4.4.4.2-17–S4.4.4.2-21).
IIa	B-NR	5. In children and adolescents found to have moderate or severe hypercholesterolemia, it is reasonable to carry out reverse-cascade screening of family members, which includes cholesterol testing for first-, second-, and when possible, third-degree biological relatives, for detection of familial forms of hypercholesterolemia (S4.4.4.2-22–S4.4.4.2-24).
IIa	C-LD	6. In children and adolescents with obesity or other metabolic risk factors, it is reasonable to measure a fasting lipid profile to detect lipid disorders as components of the metabolic syndrome (S4.4.4.2-25–S4.4.4.2-27).
IIb	B-NR	7. In children and adolescents without cardiovascular risk factors or family history of early CVD, it may be reasonable to measure a fasting lipid profile or nonfasting non HDL-C once between the ages of 9 and 11 years, and again between the ages of 17 and 21 years, to detect moderate to severe lipid abnormalities (S4.4.4.2-19, S4.4.4.2-21, S4.4.4.2-27–S4.4.4.2-29).

*Family history of early CVD is defined here as MI, documented angina, or atherosclerosis by angiography in parents, siblings, grandparents, aunts, or uncles (<55 years of age for men, <65 years of age for women).
†TC ≥240 mg/dL (≥6.2 mmol/L), LDL-C ≥190 mg/dL (≥4.9 mmol/L), non–HDL-C ≥220 mg/dL (≥5.7 mmol/L), or known primary hypercholesterolemia.
CVD indicates cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; and TC, total cholesterol.

Figure 8

1. Treatment of dyslipidemia in children is similar to treatment in adults in that it involves both lifestyle interventions as well as possible pharmacologic therapy.
2. The National Cholesterol Education Program (NCEP) of the National Heart, Lung, & Blood Institute recommends that diet therapy be utilized for 6 months to 1 year prior to the addition of pharmacological treatment
3. Weight management should be considered the primary treatment in children who are overweight or obese and those who have an elevated TG concentration or a low HDL concentration.

The American Academy of Pediatrics (AAP) states that pharmacologic intervention should be considered only in pediatric patients with substantially elevated LDL concentrations. The AAP recommends that:

1. Patients <8 years of age should be treated pharmacologically when they present with persistent LDL concentrations >500 mg/dL (which are generally present in patients with the homozygous form of familial hypercholesterolemia).
2. For patients ≥8 years old, the AAP recommendations state that in patients with a strong family history of CVD, particularly with the presence of other risk factors (e.g. obesity, diabetes mellitus, and metabolic syndrome, LDL targets of 130 mg/dL or even 110 mg/dL) may be reasonable.
3. In all other pediatric patients with elevated LDL-c concentrations, the initial goal is to lower LDL-c concentrations to <160 mg/dL.

The minimal LDL goal is <130 mg/dL with ideal goal being <110 mg/dL.

Treatment goal for LDL-c, shown by ESC guidelines 2019

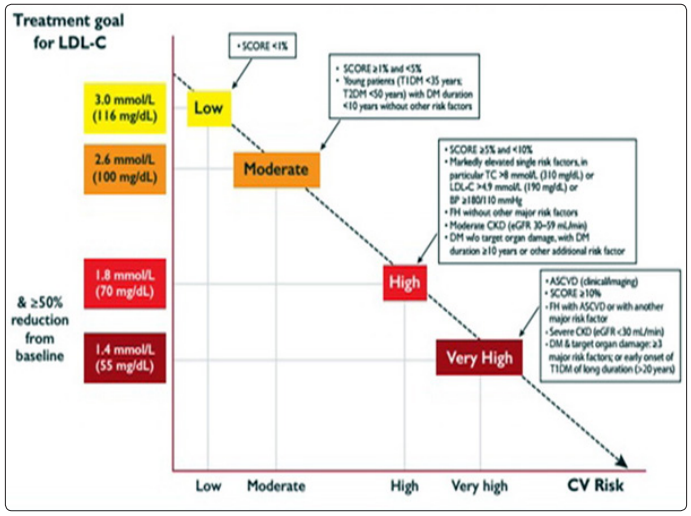

Figure 9: Treatment goal for LDL-c, shown by ESC guidelines 2019

Table 2: Pharmacological Treatment of Dyslipidemia in Childran >8 Years of Age with Elevated LDL

AAP[1]	AHA[2]
No CVD Risk Factors Treat when LDL > 190 mg/dL despite diet therapy	No CVD Risk Factors Treat when LDL > 190 mg/dL
Family history of premature heart disease or ≥2 additional CVD risk factors present Treat when LDL > 160 mg/dL despite diet therapy	Risk factors present (blood pressure elevation, diabetes, obesity, strong family history of premature CVD) Treat when LDL > 160 mg/dL
Diabetes Consider treatment when LDL > 130mg/dL	
*Diet therapy recommended for all high risk groups	*Lifestyle modifications recommended for all patients if LDL > goal

Data from, Daniels, et al., [1] and Newman, et al.,[2]

Conclusion

Atherosclerosis has its origins in childhood. For children under the age 2 years, lipid screening not recommended. Universal screening recommended for all children 9 - 11 years old regardless of general health or the presence/absence of risk factors for cardiovascular disease. Screening should be repeated again at 17 - 21 years of age. Children with genetic mutations that result in a markedly elevated LDL-c benefit from lipid-lowering medications. Children age 8 years and older meeting cut-points for pharmacological treatment - statins are the drug of first choice. Rosuvastatin should be your first choice in management of dyslipidemia. Recent data confirm safety of very low levels of LDL-c down to 15 mg/dl. Combination therapy should be initiated after reaching the highest tolerable doses of statin [25,26].

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