Childhood initiated statin therapy in familial hypercholesterolemia

Avis, H.J.
STATINS AND OTHER LIPID-LOWERING DRUGS IN CHILDREN AT INCREASED RISK FOR CARDIOVASCULAR DISEASE

H.J. Avis

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ABSTRACT

Atherosclerosis, the condition underlying cardiovascular disease (CVD), begins in childhood already. Therefore, strategies to prevent CVD should be implemented at an early age, especially in populations at high risk for CVD. An example of such a population, are patients with familial hypercholesterolemia. In addition to lifestyle interventions, strategies to prevent CVD include pharmacological treatment of dyslipidemia, a well-established risk factor for CVD in adults. Several lipid-lowering agents have been evaluated in children (mostly with FH), but long-term safety and efficacy data are lacking. As in adults, statins are the preferred pharmacological agents in paediatric practice due to excellent efficacy and tolerability, with few adverse safety outcomes observed to date. However, more studies are needed to confirm the lifelong benefit of lipid-lowering therapy initiated in childhood.
INTRODUCTION

Despite substantial therapeutic advances in the last few decades, atherosclerotic cardiovascular disease (CVD) remains the leading cause of death worldwide.\(^1\) Therefore, the prevention of CVD events has become a major goal in current clinical practice. Whereas interventions formerly concentrated on secondary prevention to avoid recurrent events in CVD patients, the focus is now shifting to primary prevention strategies in populations at increased risk for CVD. The process underlying CVD, atherosclerosis, commences in childhood. As early as in 1930, a study was published in which fatty streaks were identified in newborns.\(^2\) While some of these lesions regress over time, others may further evolve into advanced atherosclerotic lesions.\(^3\) In fact, such advanced lesions were observed in the coronary arteries of young American casualties from the Korean War (mean age of 22 years).\(^4\) Subsequent studies revealed that the extent of atherosclerotic plaques along the arterial vasculature was determined by the number of pre-existent classical CVD risk factors, such as hypercholesterolemia, smoking and obesity.\(^5\) These observations led to the hypothesis that modifications of risk factors during childhood will delay the process of atherosclerosis and thereby diminish the risk of CVD in later life.

Hypercholesterolemia has convincingly been identified as a risk factor for atherosclerosis and CVD.\(^6\) Moreover, it has been demonstrated that the treatment of hypercholesterolemia in adults significantly reduces the incidence of CVD.\(^7\) In addition, the initiation of drug treatment in children at an increased risk for developing CVD is hypothesized to further diminish the incidence of CVD events.\(^8\) To date, more than 40 studies have investigated the effects of several lipid-lowering agents in pediatric populations. Because cholesterol is crucial in human physiology, a considerable proportion of these studies have also focused on safety measures such as (sexual) development and growth.

Guidelines advocating the use of lipid-lowering agents in children at risk for CVD are becoming increasingly explicit. The use of lipid-lowering medication in pediatric practice is heavily debated in response to the release of guidelines from the American Academy of Pediatrics (AAP) on lipid screening and cardiovascular health in childhood.\(^8,9\) These guidelines discuss conditions predisposing individuals for atherosclerosis and CVD, lipid-lowering drugs, and treatment recommendations for children considered at an increased risk for developing CVD.
Atherosclerosis in childhood

The rationale for childhood initiation of lipid-lowering drugs is to delay atherosclerosis progression at an early stage that might be more amenable to change than later, more complex stages of the disease process. Atherosclerosis is a condition that results from the accumulation of lipids, inflammatory cells, necrotic tissue and calcification in the arterial wall. This process begins when leukocytes bind endothelial adhesion molecules to penetrate the vascular wall and become tissue macrophages. These macrophages subsequently instigate an inflammatory response that characterizes atherosclerosis. Atherogenic lipoproteins, such as LDL-cholesterol (LDL-C), are absorbed by the macrophages after they have been oxidized, thereby transforming these cells into foam cells. After apoptosis, these foam cells empty their contents into the inflamed vascular wall. T-cell infiltration into the vascular wall enhances the inflammatory process, as well as inducing smooth muscle cell proliferation. A further cascade of processes leads to the formation of an atherosclerotic plaque that is characterized by fibrosis, extracellular matrix and atheroma. Due to the continuing process of inflammation, such a plaque might rupture and its contents might be exposed to the arterial lumen, leading to acute occlusion, as occurs in myocardial infarction and ischemic stroke. It is generally assumed that atherosclerosis begins at a location where the endothelial layer is damaged by other factors, such as low shear stress, smoking, hyperglycemia, hypertension and age, which are, together with dyslipidemia, well-established risk factors for atherosclerosis and CVD.

In several conditions already present in childhood, the process of atherosclerosis is accelerated, and childhood-initiated treatment of dyslipidemia is hypothesized to prevent CVD. A scientific statement by an expert panel on cardiovascular risk reduction in high-risk pediatric patients, published in 2006, defines three categories of conditions increasing CVD risk: (i) those patients with clinical evidence of manifest coronary artery disease who are < 30 years of age (‘high risk’), (ii) those with pathophysiological evidence of accelerated atherosclerosis (‘moderate risk’), and (iii) those with epidemiological evidence of a high-risk setting for accelerated atherosclerosis (‘at risk’) (Table 1). In addition to lifestyle interventions and the treatment of other risk factors, the treatment of dyslipidemia is considered beneficial in these conditions.

Familial hypercholesterolemia

One of the best examples of a condition that predisposes an individual for atherosclerosis is familial hypercholesterolemia (FH). In fact, myocardial ischemia has been diagnosed in a 5-year-old patient homozygous for FH. Although homozygosity is rare, heterozygous FH is a relatively common condition, with a prevalence of 1:500 in Caucasians, expressing
Table 1. Tiers of cardiovascular disease risk during childhood according to the ‘American Heart Association’s Scientific Statement’.\(^{12}\)

<table>
<thead>
<tr>
<th>Tier</th>
<th>Category</th>
<th>Definition</th>
<th>Example of condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>High risk</td>
<td>Manifest coronary artery disease &lt;30 years of age: clinical evidence</td>
<td>Homozygous familial hypercholesterolaemia</td>
</tr>
<tr>
<td>II</td>
<td>Moderate risk</td>
<td>Accelerated atherosclerosis: pathophysiological evidence</td>
<td>Heterozygous familial hypercholesterolaemia</td>
</tr>
<tr>
<td>III</td>
<td>At risk</td>
<td>High-risk setting for accelerated atherosclerosis: epidemiological evidence</td>
<td>Post-cancer-treatment survivors</td>
</tr>
</tbody>
</table>

A milder phenotype of FH.\(^{14}\) Although children heterozygous for FH do not experience cardiovascular events, they do show abnormal arterial wall function and morphology. In order to investigate arterial wall function, flow mediated dilation was assessed in FH children by sonographically measuring the percentage of dilatation of the brachial artery to achieve hyperaemia, in response to suspension of temporarily induced hypoxia in the lower arm (Figure 1a).\(^{15}\)

![Functional (a) and morphological (b) changes of the vasculature in children with familial hypercholesterolemia.](http://example.com/fig1.png)
Morphological changes in children with FH were identified by measuring intima media thickness (IMT) using ultrasonography. Numerous studies have shown that the carotid IMT constitutes a validated predictor for cardiovascular events in adults. Therefore, carotid IMT is widely accepted as a surrogate marker for atherosclerotic CVD in adults.\textsuperscript{16} Increased IMT has been shown in children with FH, when compared to unaffected siblings (Figure 1b).\textsuperscript{17} In addition, as in adults with CVD, inflammatory markers are increased in children with FH.\textsuperscript{18} These observations do not only illustrate the established relationship between atherogenic lipoproteins and atherosclerosis, but also point to the increased susceptibility to atherosclerosis in FH children. Due to the enhanced risk for CVD and the prevalence of FH, most of the research in lipid-lowering interventions in children has been conducted in patients with FH.

**LIPID-LOWERING INTERVENTIONS**

Whatever the underlying condition, a healthy diet and lifestyle are the basis of every lipid-lowering intervention. However, in some populations, lifestyle changes may not be sufficiently effective. In these patient populations, cholesterol-lowering drugs should be considered.

**Cholesterol metabolism and lipid-lowering drugs in children**

Cholesterol metabolism comprises two major routes: the endogenous route and the exogenous route. Approximately 80\% of plasma cholesterol is acquired through the endogenous route, in which cholesterol is synthesized by the liver and subsequently packed into very low-density lipoprotein (VLDL) particles that are excreted into the circulation. Parts of the circulating VLDL particles, mainly triglycerides, are separated and metabolized in peripheral tissues until a cholesterol-rich particle, LDL-C, remains. LDL-C is finally taken up by specific LDL-C receptors in the liver. In the exogenous route, cholesterol is absorbed in the small intestine and, together with triglycerides, is transported to the liver in chylomicrons. In the liver, cholesterol is further metabolized or excreted with bile into the intestines. Cholesterol in bile, together with bile acids, is again absorbed by the intestines, completing the enterohepatic cycle.\textsuperscript{19}

Since the second half of the 20th century, drugs targeting both routes of cholesterol metabolism have gradually become available and, over the past decade, experience with these agents in children has progressively been acquired, although long-term data are limited to several years follow up. Therefore, more long-term follow up of children
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Currently treated with lipid-lowering drugs is essential to gather more data, allowing conclusions with respect to lifelong safety and efficacy of these drugs.

**Statins**

Statins – or HMG-CoA reductase inhibitors – are currently considered the preferred lipid-lowering agents in children due to their excellent efficacy and tolerability in clinical studies and their ease of use. The mechanism of action is by inhibition of hydroxyl methylguanyl-coenzyme A reductase, the rate-limiting enzyme in cholesterol synthesis in hepatocytes. Due to decreased intracellular cholesterol levels, a feedback mechanism that enhances LDL-C receptor activity on the surface of the hepatocytes is triggered. This subsequently leads to increased clearance of LDL-C from the circulation and lower plasma LDL-C levels (Figure 2).\(^{20}\) In adults, statins are regarded as well tolerated and safe agents that reduce CVD morbidity and mortality.\(^{21}\) In children, almost 30 clinical studies have been conducted that, taken together, constitute a total of approximately 1700 treatment years in over 1000 patients with FH, cardiac and renal transplantation, and the nephrotic syndrome.\(^{22-40}\) An overview of these studies is provided in Table 2. The studies have demonstrated that statins are effective and well tolerated in children and do not produce untoward adverse effects, albeit with a maximum follow up of 5 years.

**Figure 2. Mechanism of action of statins.**

Statins lower HMG-CoA reductase levels, thereby reducing intracellular cholesterol production in hepatocytes. This leads to increased LDL-cholesterol (LDL-C) receptor synthesis and increased LDL-C clearance from the plasma. Acetyl CoA means acetyl coenzyme A, VLDL-C VLDL-cholesterol.

In terms of lipid-lowering potency, statins are equally effective in children and adults, with LDL-C reductions ranging from 21 to 39%, depending on the dose and type of
statin administered. In a placebo-controlled study in children (n = 50; 9 to 18 years old) with FH receiving simvastatin (10 to 40 mg/day) for 28 weeks, absolute LDL-C reductions (-2.13 ± 0.99 mmol/l; 39.8%) restored impaired FMD compared with healthy controls without FH (15.6 ± 6.8% versus 15.5 ± 5.4%, respectively; p = 0.958). Another placebo-controlled study in children (n = 214; 8 to 18 years old) with FH investigated the treatment effects of pravastatin (20 to 40 mg/day) on IMT, and demonstrated that 2 years of therapy reduced IMT, whereas placebo-treated children demonstrated IMT progression (mean change: -0.010 ± 0.048 mm versus +0.005 ± 0.044 mm, respectively). Following this study, placebo-treated children were able to receive statin treatment, and children treated with pravastatin continued to receive statin therapy. After an average follow up of 4.5 years, IMT was again assessed. The age of initiation of statin therapy was an independent predictor of IMT measured at this time. This study suggests that an earlier initiation of statin treatment in children with FH hinders IMT progression to a greater extent.

With respect to safety, none of the controlled studies conducted thus far have revealed a difference in the occurrence of clinical adverse events of any kind between statin- and placebo-treated children. A meta-analysis of six randomized, placebo-controlled studies of statins in children with FH revealed no clinically significant differences between statin- and placebo-treated children with respect to adverse events, growth or sexual development nor elevations of liver transaminases or creatinine kinase (CK), which could indicate liver or muscle toxicity respectively. A minimal, clinically non-relevant, but statistically significant, difference of +0.33 cm (95% CI 0.03 to 0.63) in height change between statin- and placebo-treated children in favor of the statin group was observed during four studies with a duration ranging from 6 to 26 months. Furthermore, several studies evaluated steroid and sex hormones, with important limitations being that the levels of these hormones vary over time and the naturally skewed distribution restricts statistical approaches. Contradictory results were reported; small but significant differences, both positive and negative, were observed for dehydroepiandrosterone, adrenocorticotropic hormone and luteinizing hormone. However, these differences did not affect clinical outcomes, such as growth and sexual development. Muscle toxicity of statins is described in adult patients, but no significant differences in clinical muscle-related events or CK levels were identified in pediatric studies. There has been one published case of rhabdomyolysis attributed to statin therapy in a child with the nephrotic syndrome treated with atorvastatin. Temporary and mild elevations of CK are frequently observed in statin-treated children, but are often preceded by intense physical activity and resolve spontaneously within a short time. None of the pediatric studies have reported permanently impaired liver function or liver cell damage due to
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statin therapy; however, monitoring of CK and liver transaminases is advised at baseline and every 3 to 6 months during statin therapy.52

Hitherto, two studies investigated the pharmacokinetics of pravastatin in children with FH.26,27 In the first study, 20 children with FH (4.9 to 15.6 years old) were administered pravastatin (10 mg/day) for 8 weeks, and in the second study, 24 children (12 prepubertal, 12 pubertal; 8 to 16 years old) with FH were given pravastatin (20 mg/day) for 2 weeks. The pharmacological profiles in both studies were largely similar to that of adults, although the first study demonstrated a significant inverse correlation between maximum plasma pravastatin concentration and age, weight and body mass index.27 In the second study, although the difference was not significant, the maximum plasma pravastatin concentration was also inversely correlated with age, and tended to be higher in prepubertal patients when compared with pubertal individuals (52.1 ± 27.0 μg/l versus 31.7 ± 29.2 μg/l, respectively; p = 0.09). However, no correlation between the maximum plasma pravastatin concentration and LDL-C reduction was demonstrated, which suggests that plasma levels are not representative of the response to pravastatin in terms of LDL-C reduction. These studies do not indicate that pravastatin should be prescribed in a dosage according to body weight or age, or that different dosage regimens from those in adults should be applied for children; however, for prepubertal children, half the starting dose for adults may be sufficient.26 This is in line with the registration of pravastatin by the European Medicines Agency, in which a dose of 10 to 20 mg pravastatin is authorized for use in children from 8 year of age onwards.53 It is unknown to what extent the pharmacological profile of pravastatin in children can be extrapolated to other statins.

Finally, the psychological impact of statin therapy was investigated in a study in children with FH. Of children (n = 69, aged to 10 to 18 years) treated with simvastatin, 62% of patients felt safer by taking the medication, and 81% expressed that they had no difficulties with the knowledge that they would have to take the medication for the rest of their life.54

Altogether, these data suggest that, as in adults, statins are suitable agents for the treatment of dyslipidemia in children, with the limitations that most studies have been conducted in children with FH and that long-term data are lacking.
Table 2. Overview of clinical studies on statin therapy in children.

<table>
<thead>
<tr>
<th>Characteristics of studies</th>
<th>Safety outcomes</th>
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<tbody>
<tr>
<td><strong>Study, year</strong></td>
<td><strong>Design</strong></td>
</tr>
<tr>
<td>Hedman, 2005</td>
<td>Prospective cohort study</td>
</tr>
<tr>
<td>Clauss, 2005</td>
<td>RCT</td>
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<tr>
<td>Wiegman, 2004</td>
<td>RCT</td>
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<tr>
<td>McCrindle, 2003</td>
<td>RCT</td>
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<tr>
<td>Wiersma, 2004</td>
<td>Prospective cohort study</td>
</tr>
<tr>
<td>Hedman, 2003</td>
<td>Prospective cohort study</td>
</tr>
<tr>
<td>Dirisamer, 2003</td>
<td>Prospective cohort study</td>
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<tr>
<td>Author</td>
<td>Type</td>
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<tr>
<td>De Jongh, 2002</td>
<td>RCT</td>
</tr>
<tr>
<td>Vohl, 2002</td>
<td>RCT</td>
</tr>
<tr>
<td>Athyros, 2002</td>
<td>Prospective cohort study</td>
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<tr>
<td>McCrindle, 2002</td>
<td>Rand. crossover trial</td>
</tr>
<tr>
<td>Stein, 1999</td>
<td>RCT</td>
</tr>
<tr>
<td>Stefanutti, 1999</td>
<td>Non-rand. parallel matched trial</td>
</tr>
<tr>
<td>Couture, 1998</td>
<td>RCT</td>
</tr>
<tr>
<td>Knipscheer, 1996</td>
<td>RCT</td>
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<tr>
<td>Study, year</td>
<td>Design</td>
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</table>
| Lambert, 1996 | RCT      | FH         | n=17 (♂): lovastatin 10 mg  
n=18 (♂): lovastatin 20 mg  
n=19 (♂): lovastatin 30 mg  
n=15 (♂): lovastatin 40 mg | 2 mo     | 10 subjects with ≥1 AE’s reported | Not reported | Not reported | No difference FSH, LH, test., androstenedione, progest. Significant difference DHEAS between groups (↑↓) | n=3 elevations ≥3xULN | Small but significant increase | No significant increase |
<p>| Ducobu, 1992 | Prospective cohort study | Hyp. chol. | n=32: 5-20 mg | 24-26 mo | Not reported | 'Remained in same percentile' | Not reported | Not reported | No significant change | No significant change | No significant change |
| Sinzinger, 1992 | Prospective cohort study | Severe hyp. chol. | n=13: lovastatin 20 mg or lovastatin 20 mg and 8 g cholestyramine | 52 mo | 'No sign. change in any of the safety parameters’ | 'Remained in same percentile’ | Not reported | Not reported | No significant change | No significant change | No significant change |
| Mahle, 2005 | Retrospect. cohort study | Card. trans. | n=90: pravastatin 0.1-0.3 mg/kg (+immunosuppression) | Mean follow-up 6.1±3.7 years | 2 patients discontinued: n=1 legpain n=1 headache | Not reported | Not reported | No significant increase | No significant change | No significant increase |
| Hedman, 2004 | Prospective cohort study | Card. trans. | n=19: pravastatin 0.1-0.3 mg/kg (+immunosuppression) | 2 mo | Not reported | Not reported | Not reported | No significant increase | No significant increase | No significant increase |
| Seipelt, 2004 | Retrospect. chart review | Card. trans. | n=20: pravastatin 5-20 mg (+immunosuppression) | 6-62 mo | 'No unusual conditions reported’ | Not reported | Not reported | n=1 ‘asympt. CK increase’ | No elevations | No elevations |</p>
<table>
<thead>
<tr>
<th>Reference</th>
<th>Type of Study</th>
<th>Study Design</th>
<th>Treatment Details</th>
<th>Follow-up Duration</th>
<th>Adverse Events</th>
<th>Laboratory Changes</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chin, 2002&lt;sup&gt;43&lt;/sup&gt;</td>
<td>Retrospect. cohort study Card. trans.</td>
<td>n=38: atorvastatin 0.2±0.1 mg/kg (+immunosuppression)</td>
<td>13.3±0.3 mo n=2 muscle pain Not reported Not reported Not reported</td>
<td>n=2 asympt. elevations ≥10xULN, n=2 'mild elevations'</td>
<td>No significant difference</td>
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<tr>
<td>Penson, 2001&lt;sup&gt;44&lt;/sup&gt;</td>
<td>Retrospect. cohort study Card. trans.</td>
<td>n=20: pravastatin 10-20 mg (+immunosuppression)</td>
<td>Not reported 'No clinical evidence of myositis' Not reported Not reported</td>
<td>No significant changes</td>
<td>No significant changes</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td>Butani, 2003&lt;sup&gt;45&lt;/sup&gt;</td>
<td>Retrospect. case-control study Renal trans.</td>
<td>n=7: pravastatin 10-20 mg n=9: renal trans. recipients who did not receive pravastatin (+immunosuppression)</td>
<td>12 mo 'No adverse reactions' 'No noticeable change in growth velocity' Not reported Not reported</td>
<td>No elevations</td>
<td>No significant changes</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td>Argent, 2003&lt;sup&gt;46&lt;/sup&gt;</td>
<td>Prospective cohort study Renal trans.</td>
<td>n=9: hypercholesterolemic subjects treated with atorvastatin 5-30 mg (+immunosuppression)</td>
<td>7-11 mo 'No myalgia, n=1 mild nausea with spontaneous recovery' Not reported Not reported</td>
<td>No significant change</td>
<td>No significant change</td>
<td>No significant change</td>
<td></td>
</tr>
<tr>
<td>Sanjad, 1997&lt;sup&gt;47&lt;/sup&gt;</td>
<td>Prospective cohort study Ster. res. nephr. syndr.</td>
<td>n=12: lovastatin ≤40 mg or simvastatin ≤20 mg</td>
<td>12-60 mo 'Well tolerated' Not reported Not reported</td>
<td>Remained normal</td>
<td>Remained normal</td>
<td>Remained normal</td>
<td></td>
</tr>
<tr>
<td>Coleman, 1996&lt;sup&gt;48&lt;/sup&gt;</td>
<td>Prospective cohort study Ster. res. nephr. syndr.</td>
<td>n=7: simvastatin 5-40 mg</td>
<td>10 mo Not reported 'Growth parameters maintained' Not reported Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
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Ezetimibe
Ezetimibe prevents the intestinal absorption of cholesterol originating from both dietary intake and bile at the level of enterocytes in the jejunum, most likely by blocking the cholesterol transporter Niemann-Pick C1-like 1 (Figure 3). The efficacy of ezetimibe is modest, with an approximately 15 to 20% LDL-C reduction whether administered in addition to a statin or not. Results from a recent trial of ezetimibe in adults have been controversial because, despite a significant lipid-lowering effect, no improvement in IMT was observed. Whether this was caused by a failure of ezetimibe to inhibit atherosclerosis or a consequence of the fact that patients had already been administered lipid-lowering treatment before inclusion in the trial remains to be clarified.

A multicenter, randomized, double-blind, placebo-controlled trial in children (n = 248; between 10 and 17 years old) with FH treated with ezetimibe (10 mg/day) added to simvastatin (10, 20 or 40 mg/day) for a total duration of 53 weeks demonstrated an approximately 15% additional LDL-C-lowering with excellent tolerability, without adverse safety outcomes.

![Figure 3. Mechanism of action of ezetimibe in the jejunum. Ezetimibe inhibits cholesterol uptake in the jejunum, where cholesterol is stored in micelles, most likely by blocking the Niemann-Pick C1-like 1 (NPC1L1) protein that mediates cholesterol absorption. The transport of cholesterol as chylomicrons to the liver is subsequently decreased, instigating a feedback mechanism that results in increased LDL-cholesterol (LDL-C) receptor expression on the surface of hepatocytes and enhanced LDL-C clearance.](image)

Ezetimibe is registered for pediatric use by the US FDA and the EMEA. According to current guidelines for use in pediatric patients, ezetimibe could be considered for additional lipid-lowering in combination with a statin. The doubts about the efficacy of ezetimibe on surrogate clinical endpoints should be resolved with further clinical studies before a definitive position can be advocated in guidelines.

Bile acid-binding resins
Bile acid-binding resins interrupt the enterohepatic cycle by binding to bile acids in the small intestine, thereby preventing reabsorption by enterocytes in the ileum. The diminished return of bile acids to the liver results in increased bile acid synthesis from
cholesterol. This decreases cholesterol levels in hepatocytes, triggering increased LDL-C receptor activity on the surface of hepatocytes that results in increased LDL-C clearance from plasma and, consequently, reduced LDL-C levels. Because bile acid-binding sequestrants act in the intestinal lumen and are not systemically absorbed, they are generally considered safe for administration in children, although interference with the uptake of fat-soluble vitamins and some medications has been suggested. These agents have long been considered the only suitable lipid-lowering drugs for children with hypercholesterolemia, and were advised in the 1992 National Cholesterol Education Program (NCEP) guidelines.57

The efficacy and tolerability of these agents have been studied in several pediatric trials. Lipid-lowering efficacy ranged from 13 to 20% for LDL-C, without safety concerns, although supplementation with folate and vitamin D is recommended.52 However, long-term compliance and tolerability of the classical bile acid sequestrants is poor, mainly due to gastrointestinal side effects. A new formula, colesevelam, can be administered in tablet form and is better tolerated than the classical bile acid-binding sequestrants.

**Fibric acid derivates**

Fibric acid derivates have a complex and largely unknown mechanism of action that results in a decreased production of VLDL particles and an increased clearance of triglycerides. These compounds lower total cholesterol and LDL-C levels, as well as triglyceride levels, and elevate HDL-C levels, albeit very modestly. The main side effect is gastrointestinal upset. Risks of myopathy and rhabdomyolysis are increased if these agents are combined with a statin or in patients with renal insufficiency. A 1-month, randomized, crossover trial with bezafibrate (10 to 20 mg/kg/day bid) in children (n = 14; 4 to 15 years old) with FH demonstrated a significant 22% reduction in total cholesterol. One transient elevation in liver transaminases and one in alkaline phosphatases was also observed. Medication was well tolerated, with no impact on growth or development. Fibric acids are preferentially used for children with severe elevations in triglycerides with an associated risk for pancreatitis, and are usually not prescribed for the prevention of CVD. Also, there is little evidence that these agents prevent CVD in adults.

**Nicotinic acid**

The mechanism of action of nicotinic acid is complex and largely unknown. This agent results in a decrease in both total cholesterol and LDL-C levels, and an increase in HDL-C levels, which is thought to protect patients from CVD. The compound is known for its side effects, which is the reason that nicotinic acid is very rarely administered to children.
One observational study in children (n = 21) treated with niacin (500 to 2250 mg/day) for an average duration of 8.1 days demonstrated a 30% decrease in LDL-C levels, with 76% of patients reporting reversible adverse effects, including flushing, abdominal complaints, headache and elevated serum aminotransferase levels.60

Guidelines
Since 1983, several guidelines regarding cholesterol in childhood and CVD risk in later life have been published; however, it was not until 1992 that drug therapy for children with hypercholesterolemia was mentioned. In the NCEP guidelines published in 1992, bile acid-binding sequestrants were the only recommended drugs for children with LDL-C levels above 190 mg/dl, or 160 mg/dl in the presence of other risk factors not responding to a healthy diet.57 With an increasing amount of data on the effects of statins in children emerging, recommendations have been updated regularly by several institutions, such as the NCEP, AAP and the American Heart Association. In 2008, the AAP released new guidelines, 'Lipid screening and cardiovascular health in childhood'.8 These guidelines state that drug therapy should be considered for children from 8 years of age onwards when LDL-C is greater than 190 mg/dl, or 160 mg/dl when other risk factors are present, with a treatment target as low as 110 mg/dl in patients with a strong family history for CVD, especially when there are additional risk factors present. In these guidelines, statins were for the first time suggested as first-line drug therapy in children.8

CONCLUSION
Although indirect, a plethora of evidence suggests that childhood initiation of lipid-lowering drugs in populations at an increased risk of developing CVD could hinder the process of atherosclerosis and therefore lower the risk for CVD later in life. In fact, widely accepted guidelines have been published suggesting threshold and target levels of LDL-C. Future clinical studies should challenge the hypothesized benefit of childhood-initiated lipid-lowering therapy in terms of CVD reduction. Furthermore, these studies should investigate lifelong tolerability and safety of these drugs. Until definite conclusions can be drawn from these studies, clinicians will have to rely on their own appraisal of current evidence, and a balance of benefit and risk based on individual risk profiles in treatment decisions regarding lipid-lowering therapy in pediatric patients.

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REFERENCES


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