Familial hypercholesterolemia in childhood: diagnostics, therapeutical options and risk stratification
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The spectrum of statin therapy in hyperlipidemic children

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Abstract

The recommended therapy of hypercholesterolemia in children consists of dietary modification and bile acid-binding resins. Unfortunately, the lipid-lowering efficacy of bile acid-binding resins is modest and, moreover, long-term compliance is poor due to side effects. In contrast, HMG-CoA reductase inhibitors (statins) are widely used in adults and are considered a first choice in the treatment of hypercholesterolemia in that age category. In the last few years, several randomized trials have been conducted to evaluate the efficacy, safety, and tolerability of statin therapy in both children and adolescents. In this article we review statin therapy in hypercholesterolemic children in terms of efficacy, safety, pharmacokinetics and psychosocial functioning.

Statins are not only effective in reducing LDL cholesterol levels in children with familial hypercholesterolemia, but also improve endothelial function and reduce the progressive thickening of the intima media complex of the carotid arteries. Statins seem safe at the longer term in children in terms of plasma levels of liver enzymes and liver function, creatine kinase levels and muscle function as well as growth and sexual development. Long-term follow-up studies are needed to assess whether statin treatment started early in children with FH can prevent future cardiovascular events.
Introduction

In the last decade, treatment of elevated lipid concentrations has been fundamentally changed by the introduction of the hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors or statins. As the use of these agents has been proven to be effective and safe in adults, they might also be beneficial for hypercholesterolemic children.

The most important target paediatric population for lipid reduction includes children with homozygous or heterozygous familial hypercholesterolemia (FH). FH is an autosomal dominantly inherited metabolic disease, due to mutations in the LDL receptor (LDLR) gene. FH is clinically characterized by elevated levels of low-density lipoprotein cholesterol (LDL-C) and total cholesterol (TC) from birth onwards resulting in early atherogenesis and premature cardiovascular disease (CVD).

The urgent need for early therapy in children with heterozygous FH has been substantiated by studies using surrogate markers which are able to assess subclinical atherosclerosis and thereby predict cardiovascular disease. As the early stages of the process of atherosclerosis are characterized by endothelial dysfunction and intima media thickening, widely used surrogate markers to assess preclinical atherosclerosis are flow-mediated dilatation (FMD), which measures endothelial function of the brachial artery, and B-mode ultrasound, which measures the intima-media thickness (IMT) of the carotids and the femoral arteries. In recent years, several studies have unequivocally shown that endothelial function measured as FMD of the brachial artery is impaired and carotid IMT is increased in FH children when they are compared to healthy controls. This underscores the very early onset of atherogenesis in FH children and the need for early and aggressive treatment.

Currently, the recommended therapy for hypercholesterolemic children only consists of dietary and life-style modifications. The National Cholesterol Education Program (NCEP) recommends considering drug therapy in children aged 10 years and older if, after an adequate Step II diet, they still have LDL-C levels ≥190 mg/dl (4.9 mmol/L) or ≥160 mg/dl (4.1 mmol/L) in the presence of a positive family history for premature CVD (before 55 years of age). The consequent and recommended treatment of hypercholesterolemic FH children consists of bile acid-binding resins. Unfortunately, trials using resins for the treatment of hypercholesterolemia in childhood show poor compliance and a high frequency of discontinuation due to side effects.
Treatment with statins would be expected to result in a better therapeutic response. Recently, several trials have demonstrated the efficacy and short and longer term safety of early initiation of statin therapy in children and adolescents with heterozygous FH. Currently, six drugs are available within this therapeutic class: lovastatin, fluvastatin, pravastatin, simvastatin, atorvastatin, and recently rosuvastatin. In the USA, the Food and Drug Administration (FDA) has approved lovastatin in February 2002 for heterozygous FH adolescent boys and girls, who are at least one year postmenarche. The FDA also approved pravastatin since October 2002 for the management of FH in children aged 8 years or older. However, statin therapy is not yet approved by the European Agency for the Evaluation of Medicinal Products (EMEA) for use in children.

In this article we describe the spectrum of statin therapy in children with hypercholesterolemia in terms of efficacy, safety, pharmacokinetics and psychosocial functioning.

### Efficacy

**Effects of various statins on lipids and lipoproteins in FH children**

Table 1 presents an overview of studies that have been conducted with statins in children and adolescents. All trials demonstrated significant reductions in the levels of LDL-C, TC, and apolipoprotein B100 (apoB). The reduction of LDL-C levels varied between 17 and 45%, for TC between 13 and 37%, and for apoB between 18 and 34%, depending on dose and statin used in the trial.\(^{17-27}\) Most studies demonstrated mean elevations of HDL-cholesterol (HDL-C) levels between 1 and 11% and of apoAI between 2 and 10% in the statin treated children, but these differences were not statistically significant as compared to either placebo or baseline. One study showed a significant increase in HDL-C of 22.5% after treatment with atorvastatin, but this study was not controlled.\(^{27}\) Table 2 gives an overview of the efficacy of various statins in children. Overall, all studies demonstrated that statins are efficacious in terms of lowering LDL-C levels in children who are at high risk for premature CVD.
### Table 1. Overview of trials with statins in children

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment</th>
<th>Randomized Subjects</th>
<th>Mean Age</th>
<th>Follow-up (week)</th>
<th>Mean LDL-C Reduction (%)</th>
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</thead>
<tbody>
<tr>
<td>(year published)</td>
<td></td>
<td>Placebo (n)</td>
<td>Statin (n)</td>
<td>y (range)</td>
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<tr>
<td></td>
<td>5-10-20 mg</td>
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<td>20 mg</td>
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<tr>
<td></td>
<td>10-20-40 mg</td>
<td>(male)</td>
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<tr>
<td>Stefanutti et al (1999)</td>
<td>Simvastatin</td>
<td>8</td>
<td>8</td>
<td>9</td>
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</tr>
<tr>
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<td>10 mg</td>
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<tr>
<td></td>
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<td>(10-17)</td>
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<tr>
<td></td>
<td>20-40 mg</td>
<td>(8-18)</td>
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</table>

### Efficacy on surrogate markers for atherosclerotic disease

Impaired FMD and increased IMT are predictive for future CVD and improvement in these markers upon lipid lowering correlates with attenuation of the atherosclerotic process. In adults, several studies have shown that aggressive statin therapy not only reduces LDL C but also improves FMD and reduces the progression of carotid IMT. Also in children, FMD and IMT are improved by statins. De Jongh et al demonstrated that statin therapy restored endothelial dysfunction towards normal after 28 weeks of 40 mg simvastatin therapy in children aged 10-17 years. In the simvastatin group, FMD increased to a level similar to that of healthy controls. In the placebo group, FMD did not change during the 28 weeks treatment. Wiegman et al demonstrated that the mean combined carotid IMT exhibited less progression after two years of treatment with pravastatin compared to the mean carotid IMT in the placebo group. Improvement or even normalization of the pre-atherosclerotic...
Table 2. Efficacy of statin therapy on lipids and lipoproteins in FH children

<table>
<thead>
<tr>
<th>Statin</th>
<th>Dosage</th>
<th>TC</th>
<th>LDL-C</th>
<th>HDL-C</th>
<th>Apo B100</th>
<th>Apo A1</th>
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<td>Lovastatin</td>
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<td>8&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>30</td>
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<td>-27&lt;sup&gt;a&lt;/sup&gt;</td>
<td>11&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-22&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5&lt;sup&gt;a&lt;/sup&gt;</td>
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<td></td>
<td>40</td>
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<td>-31&lt;sup&gt;ab&lt;/sup&gt;</td>
<td>3&lt;sup&gt;ab&lt;/sup&gt;</td>
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<td>2&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>Pravastatin</td>
<td>5</td>
<td>-18</td>
<td>-23</td>
<td>3.8</td>
<td>-18.0</td>
<td>2.5</td>
<td>Knipscheer et al&lt;sup&gt;19&lt;/sup&gt;, Stein et al&lt;sup&gt;17&lt;/sup&gt;</td>
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<tr>
<td></td>
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<td>-24</td>
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<td>-40</td>
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<td>-34.1</td>
<td>8.8</td>
<td>Dirisamer et al&lt;sup&gt;22&lt;/sup&gt;, De Jongh et al&lt;sup&gt;21&lt;/sup&gt;, Couture et al&lt;sup&gt;20&lt;/sup&gt;</td>
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<td>Atorvastatin&lt;sup&gt;‡&lt;/sup&gt;</td>
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<td>5</td>
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<td>Athyros et al&lt;sup&gt;25&lt;/sup&gt;, Athyros et al&lt;sup&gt;26&lt;/sup&gt;, De Jongh et al&lt;sup&gt;21&lt;/sup&gt;</td>
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<td>-49&lt;sup&gt;ghi&lt;/sup&gt;</td>
<td>4&lt;sup&gt;ghi&lt;/sup&gt;</td>
<td>-32&lt;sup&gt;ghi&lt;/sup&gt;</td>
<td>2.9&lt;sup&gt;ghi&lt;/sup&gt;</td>
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</table>

*a The changes are the means of the changes of the various studies, per statin.
‡ children younger than 14 years received 20 mg and those 14 years and older received 40 mg pravastatin.
§ The study of Ducobu et al<sup>26</sup> was not included as the lipid changes of the three dosages could not be disentangled.
§‡ We did not include atorvastatin 40 mg<sup>24</sup> because only two children were treated with this medication.
** The reductions are presented as the percentage reduction as compared to the diet intervention.
‡§ 55% of the patients in the atorvastatin treatment group received 20 mg and 45% received 10 mg atorvastatin.

Abnormalities of the arterial wall after the use of statins highlights the importance of early initiation of such therapy in children with rapidly progressive atherosclerosis such as FH heterozygotes.
Safety

Clinical adverse effects
Statins are well tolerated by the majority of patients. The most common adverse effects, albeit in adults, are: gastro-intestinal symptoms like constipation, diarrhea, flatulence, dyspepsia and abdominal pain. Other adverse effects include: myalgia, rash, headache, pruritus, fatigue, and sleep and mood disorders. For most patients, those symptoms resolve within the first month of treatment without altering or discontinuing the therapy. However, myalgia without changes in creatine phosphokinase (CK) is often a reason to change statin therapy in adults.

All above-mentioned side effects have also been reported in the statin studies with children, but adverse events, whether or not judged to be related to therapy, did not differ between treatment and placebo groups. However, some adverse effects resulted in discontinuation of the study subjects. Stein et al reported one lovastatin-treated subject with increased bruising and purpura, but no abnormal results were found in the haematological indices. The investigators did not consider the reason for discontinuation clinically significant or definitely related to study drug. De Jongh et al reported the discontinuation of a child on simvastatin 10 mg; the child developed infectious mononucleosis that was considered not drug related. Finally, McCrindle et al reported one patient on atorvastatin 20 mg that discontinued the trial due to mental depression. The depression resulted in hospitalization and the investigators judged this adverse event as possibly treatment related. Other reported adverse events during the treatment periods with statins were mild or moderate and resolved spontaneously without interrupting the study medication.

Laboratory safety parameters
Statins have been extensively evaluated for laboratory abnormalities in adults. Most clinical trials in adults show that statin therapy is associated with an elevation of liver transaminases or CK levels in some cases. Clinically relevant hepatotoxicity has never been observed, but rare cases of myositis and myopathy have been reported. Clinically important rhabdomyolysis with statins is rare, with an overall incidence of fatal rhabdomyolysis of approximately 0.15 per 1 million prescriptions. Rhabdomyolysis is a clinical and biochemical defined syndrome resulting from skeletal muscle injury.
and defined as clinical muscle symptoms with severely elevated CK (> 10 x ULN) levels in conjunction with myoglobinuria. The risk of myopathy or rhabdomyolysis is increased when statins are given together with medication that is metabolised by the same pathway via cytochrome P450 3A4 such as cyclosporine, erythromycin, itraconazol, ketoconazol, nicotinic acid and fibrates, especially gemfibrozil. Except for pravastatin and rosuvastatin, all statins are metabolized by cytochrome P450 3A4. Elevations of CK levels were also seen in children participating in statin trials. Such CK elevations fluctuated between 3x ULN and 5x ULN, without any clinical symptoms of myalgia, myositis or rhabdomyolysis. The investigators of the studies in question could not find a relationship with the study medication, and mostly attributed the CK elevation to excessive exercise and sports. All these laboratory abnormalities returned to normal without interruption of the study drug. Wiegman et al reported one child with an asymptomatic but extreme CK elevation of 16,400 U/L after 168 days of study therapy, being either pravastatin or placebo. Within one week after cessation of the study drug, CK fell to normal values and, thereafter, the study drug was reintroduced. At the end of the trial, the medication turned out to be placebo. One child on simvastatin, who received concomitant administration of erythromycin, showed a CK increase of more than 10x ULN without muscle symptoms. The levels returned to normal after discontinuation of the antibiotic. None of the investigators reported any clinical symptoms of myositis, myopathy or rhabdomyolysis in children.

With respect to the liver enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST), some trials showed increased levels in the active treatment group as compared to the placebo group. In the simvastatin study of de Jongh et al, one child experienced several elevations <3x ULN as well as one elevation >3x ULN. Those elevations were considered drug related but not clinically significant. Therapy was interrupted for ten days, and levels returned to normal. In the study of McCrindle et al, two children treated with atorvastatin (10-20 mg) had an AST elevation of >3x ULN and one had an ALT elevation of >3x ULN, whereas no placebo-treated patients had such elevations. However, none of the children discontinued the study medication. In an uncontrolled study of Lambert et al, statistically significant but minor and clinically unimportant increases of 2 and 3x U/L from baseline were observed in AST levels during treatment with 30- and 40 mg lovastatin, respectively. ALT levels were not changed. In other controlled studies, there were no differences between the statin and the placebo group with respect to liver enzyme changes.
In summary, discontinuation of statin treatment due to hepatic transaminase or CK elevation was rare in the total number of 665 paediatric patients who received statins for 6 to 156 weeks. In most cases, such elevations decreased to normal spontaneously without changing or interrupting the study medication.

Hormone levels, growth and sexual maturation

Since cholesterol is the precursor of adrenal and gonadal steroids, inhibition of cholesterol synthesis by HMG-CoA reductase inhibitors may affect steroidogenesis, which in turn may affect growth and/or sexual maturation of treated children. Most statin trials in children evaluated steroid hormones. However, results were not unequivocal. One uncontrolled study showed that lovastatin 10 mg significantly increased plasma levels of cortisol and that lovastatin 40 mg significantly reduced cortisol levels whereas other trials did not observe any changes in the levels of plasma cortisol. Similarly, for dehydroepiandrosterone sulphate (DHEAS), lovastatin treated children showed significantly increased plasma levels of DHEAS whereas simvastatin 40 mg significantly reduced levels of DHEAS in treated children. In view of the fact that statins inhibit cholesterol synthesis, an increase of steroid hormones levels was totally unexpected and could not be explained by the investigators. In the case of simvastatin, the decrease of DHEAS was small and investigators did not observe a deviation in growth nor sexual development. Therefore, no clinical significance was attributed to the effects on DHEAS. In contrast, in the pravastatin trial no changes were found in the levels of DHEAS. Furthermore, statins did neither affect the gonadal hormone estradiol in girls or testosterone in boys, nor the gonadotropic hormones lutropin and follicle-stimulating hormone (FSH). Besides a slight progression to more advanced Tanner staging and larger testicular volume in the lovastatin group at rates not significantly different from those of the placebo group, no deviations were observed for sexual maturation or growth in any other study. In conclusion, statins do not appear to have clinically meaningful effects on hormone levels, growth or sexual maturation in children.
Pharmacokinetics of statin therapy in children

The pharmacokinetics of statins have been widely studied in adults\textsuperscript{37}. In order to formulate a rational dosing regimen for children, such studies have to be conducted in children as well. In fact, two trials have described the single-dose pharmacokinetics of pravastatin in children; one with a single dose of 10 mg pravastatin in 20 children with FH, aged 5-16 y\textsuperscript{38}, and another with a daily dose of 20 mg pravastatin in 24 children with FH, aged 8-16 y\textsuperscript{39}. Pravastatin 10 mg was absorbed rapidly and the mean maximum concentration was 15.7 ng/mL. The mean half-life of pravastatin was 1.6 h and the plasma levels were below the detection limit 10 hours after dosing\textsuperscript{38}. Pravastatin 20 mg showed a mean maximum concentration of 52.1 ng/mL in 8-10 y old children and 31.7 ng/mL in 11-16 y old children. The mean half-life was 2.5 h in both groups\textsuperscript{39}. The investigators of both studies concluded that the pharmacokinetic profile of pravastatin in children was similar to that reported in adults\textsuperscript{38,39}. Yet, the pharmacokinetics of other statins have not been studied in children specifically.

Psychosocial aspects

Considering the fact that lowering LDL-C requires life-long therapy with statins, we have to be aware of the long-term effects of such therapy on the quality of life, anxiety and concerns of children with familial hypercholesterolemia. Several studies showed that the emotional impact of premature death of an affected parent is much greater than having FH per se\textsuperscript{40-42}. One study evaluated the influence of simvastatin on psychosocial functioning in 69 children with FH (mean age 15.3 years). De Jongh et al demonstrated that 46% of the children with FH suffer from the fact that they have FH, but 62% felt safer by taking medication and 81% did not mind taking the medication their whole life\textsuperscript{43}. The investigators of this study concluded that statin treatment did not negatively influence the psychosocial functioning of the children.
Discussion and conclusion

The NCEP recommends considering drug therapy in children aged 10 years and older, only if after an adequate AHA step II diet they still have LDL-C levels ≥190 mg/dl (4.9 mmol/L) or ≥160 mg/dl (4.1 mmol/L) in the presence of a positive family history for premature CVD. As a consequence, the question arises which drug therapy is preferred in children and adolescents suffering from hypercholesterolemia. At the moment the recommended drug therapy for FH children above 10 years consist of bile-acid resins. However, the lipid lowering efficacy is modest (10-15%), and long-term compliance is very poor. Although statin therapy for FH children has not been approved, except for lovastatin and pravastatin in the USA only recently, several studies over the past few years have demonstrated both good efficacy as well as reassuring safety of this therapy in prepubertal and pubertal FH children. LDL-C reductions were dependent on the dosage and statin itself but more importantly, the reductions were larger than those obtained with bile-acid resins, which reduced LDL-C by 15-20% at best. Furthermore, statins not only decreased LDL-C, they also improved the endothelial function and the regression of the intima-media thickness in children with FH, who are already characterized by functional changes of the arterial wall from early age onwards.

In view of the lack of adverse effects of statins in children with FH, we must conclude that statin therapy seems safe. All studies reported some adverse effects, but these were equally distributed between the placebo and statin groups. The investigators reported no cases of myositis, myopathy or rhabdomyolysis. Besides one hospitalization for a child with worsening of depression during atorvastatin administration, none of the investigators reported any serious adverse event or death with the use of statins in children. With respect to routine laboratory parameters some studies reported increased liver enzymes and CK levels without clinical symptoms. These laboratory abnormalities returned to normal without removal of the study drug. No serious adverse effects, in terms of laboratory abnormalities were reported in these children. Even though several trials demonstrated significantly increases or decreases in DHEAS during statin use in the pubertal children, those changes were not clinically relevant. Taken together, statins seem safe not only for adults, but also for hypercholesterolemic children.

We need to point out that children were not followed for more than 2 years of statin
treatment. Therefore, no guarantee can be given that statins are safe for life-long use. Follow-up studies are required to assess this. Long-term follow-up studies are also required to investigate whether statin therapy at a young age prevents premature CVD at an older age.

It is still unclear at what age statin therapy should be considered. The age of the youngest patients in the studies varied from 4-10 years (table 1), which indicates that patients can be safely treated at an age of 10 years. However, further research is needed to determine if statin therapy should be initiated at a younger age.

If children have started with statin therapy, they should be seen by a lipid specialist or pediatrician at regular intervals. Growth, sexual development, and liver enzymes levels should be checked frequently. Because statins increase the risk for myopathy or rhabdomyolysis, CK levels should be evaluated as well. Patients and their families should be instructed to immediately report symptom of muscle pain, myalgia, weakness, or the appearance of dark urine. In such case, CK levels should be assessed, and if levels are more than 5 times of normal, therapy should be discontinued. If CK levels have returned to normal, therapy may be continued at a lower dose. Furthermore, limited evidence from animal and human studies indicates that statins should not be taken during pregnancy. Adolescent girls and young women taking statins should be counseled about the need for contraception.

In conclusion, statins seem safe and are proven to be effective to lower cholesterol concentrations in prepubertal and post-pubertal children. Early initiation of statin therapy seems to be the proper therapeutic option with regards to improvement of endothelial dysfunction, regression of intima-media thickening, and prevention of future cardiovascular events.

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