Statin and Its Use in Children: A Review Brief

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ABSTRACT
Atherosclerotic cardiovascular disease (ASCVD) is a disease that occurs causes death among adult patients who previously had a history of familial hypercholesterolemia (FH) in childhood. The main cause of FH is gene mutation in the low-density lipoprotein (LDL) receptor from birth because the mother inherits it. The form of FH consists of two types, namely heterozygous and homozygous. Heterozygous FH is the most usual form of gene abnormalities in children with FH with a prevalence of 1 per 137-250 of the general population. Lipid-lowering drugs are often used adults in hyperlipidemia but rarely used in children. It can be given as a preventative agent so that it does not develop into ASCVD. For FH, statins have been recommended as a first-line treatment for hyperlipidemia, because it has a significant LDL reduction effect. One of the statins that have the most prominent reduction in LDL is with the use of atorvastatin and rosuvastatin. When viewed from various studies on statin use in the long term, pravastatin used for 20 years has a significant reduction in LDL of 32% and is proven to have no side effects. Most statin has mild side effects that commonly report in adults, rhabdomyolysis, but in children is rarely. In other words, statins well tolerated in children.

Keywords: ASCVD, Children, Familial Hypercholesterolemia, Hyperlipidemia, Statin

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INTRODUCTION
Atherosclerotic cardiovascular disease (ASCVD) is one of the main causes of morbidity and mortality in adults. Familial hypercholesterolemia (FH) is known to be prominent risk factors that can cause ASCVD, especially in children. ASCVD occurs infrequently throughout childhood, but they can develop and appear as adults1.

FH is defined as a genetic abnormalities in metabolism of cholesterol signified by elevating LDL-C levels since birth2,3,4. The main cause of FH is gene mutation in the LDL receptor5,6. Typically, patients with FH will inherit one defective gene and make their children born with phenotypic abnormalities. Heterozygous FH (HeFH) is the most usual gene abnormality and occurs in 1 per 137-250 of the general population, estimated to be about twice as high as previously thought1. Homozygous form of FH (HoFH) is a rare disorder with an estimated prevalence of 1 per 160,000-300,000 population, especially in Europe6.

Heterozygous FH often appears in children without symptoms and has LDL-C levels of 150 to 500 mg/dL7. The increase in LDL-C in homozygous FH is often higher than 500 mg/dL in severe cases8. Homozygous and heterozygous forms of FH result in a decrease in the capacity of the liver to clean low-density lipoprotein (LDL) cholesterol-rich atherogenic from circulation, with the consequence of an accumulation of LDL cholesterol (LDL-C). Starting in the fetus, continued exposure of the arterial wall with increasing LDL-C levels expedites cholesterol accumulation and inflammation of the arteries, develops into atherosclerosis, mainly in the aorta and coronary arteries, and causes coronary heart disease9 (Figure 1). Changes in lipoprotein levels in FH may also involve increased levels of triglyceride-rich lipoprotein remnants, together with decreasing high-density lipoprotein (HDL) and lipoprotein (a) [Lp (a)], which can collectively contribute to expediting ASCVD10,11. Sixty baby is born with FH every hour in the world. If children is diagnosed with hyperlipidemia and treated early, they can have a healthy life prospect. Lipid-lowering drugs can be given as a preventative agent in children with hyperlipidemia so that it does not develop into ASCVD. Treatment strategies for hyperlipidemia in children produced by administering statins, sequestrant bile acids, fibrates, nicotinic acid, and ezetimibe. Statins recommended as first-line treatment for hyperlipidemia, especially for FH and well-tolerated in children12,13. The aim of this review is to offer an illustration of statin use in children especially with hyperlipidemia and areas for further research.


SCREENING AND MANAGEMENT GUIDELINES

Screening for Pediatric Hyperlipidemia

According to National Heart, Lung, and Blood Institute (NHLBI) and National Lipid Association (NLA), routine screening checks are conducted for all children especially aged 9 to 11 years to recognize children with increased LDL-C levels before they get puberty. Throughout puberty, LDL-C levels can decline by around 10-20%, and thus screening at that time can lead to underdiagnosis. Universal screening is the primary and most recommended screening for measuring lipid profiles for all children aged 9-11 years by measuring lipid profiles during fasting and non-fasting. In non-fasting lipid profiles, if the measurement results from non-HDL-C ≥145 mg/dL ± HDL-C <40 mg/dL, it is necessary to check two lipid profiles during fasting and the average results. Fasting lipid profile was measured in children with LDL-C results ≥130 mg/dL ± non-HDL-C ≥145 mg/dL ± HDL-C <40 mg/dL ± TG >100 mg/dL if <10 years or 30 130 mg/dL. If children are ≥ ten years old, it is necessary to repeat the measurement of fasting lipid profile and average results.

In addition to universal screening, a method that recommended to identify people who are at risk of genetic conditions through a systematic family search is cascade screening. Cascade screening relies on identifying patients for cholesterol testing, genetic testing, or both for all potentially affected relatives. All children aged two years or older with first or second-degree relatives with a history of ASCVD recorded before age 55 in men and 65 years in women must have at least a fasting lipid profile to determine the status of hyperlipidemia. Some countries have guidelines that recommend universal screening of children if there is a family history. The Familial Hypercholesterolemia Foundation recommends a cascade screening to identify families at risk.

Ideal Lipid Profile

According to NLA and NHLBI, they recommend that ideally, non-HDL-C levels should be <120 mg/dL and LDL-C levels be <110 mg/dL, and (Table 1). It should note that non-HDL-C may be more predictive of persistent hyperlipidemia than LDL-C. As a result, non-HDL-C can be a more suitable lipid target, mainly because non-fasting blood samples used to determine non-HDL-C. Besides, the NLA Expert Panel shows that LDL-C findings ≥160 mg/dL in children should be considered suspicious of potential genetic disorders and should be further evaluated.

Lipid screening is recommended to help recognize children with high lipid levels who are at risk of ASCVD, as outlined in Table 1. Lipid levels represent to be examined until children become adults so that early treatment of hyperlipidemia can help decline the risk of lifelong ASCVD.

Table 1: Profile of lipids in children

<table>
<thead>
<tr>
<th>Category</th>
<th>Low (mg/dL)</th>
<th>Acceptable (mg/dL)</th>
<th>Borderline (mg/dL)</th>
<th>High (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>-</td>
<td>&lt;170</td>
<td>170-199</td>
<td>≥200</td>
</tr>
<tr>
<td>LDL-C</td>
<td>-</td>
<td>&lt;110</td>
<td>110-129</td>
<td>≥130</td>
</tr>
<tr>
<td>TG (0-9 y)</td>
<td>-</td>
<td>&lt;75</td>
<td>75-99</td>
<td>≥100</td>
</tr>
<tr>
<td>TG (10-19 y)</td>
<td>-</td>
<td>&lt;90</td>
<td>90-129</td>
<td>≥130</td>
</tr>
<tr>
<td>Non-HDL-C</td>
<td>-</td>
<td>&lt;120</td>
<td>120-144</td>
<td>≥145</td>
</tr>
<tr>
<td>HDL-C</td>
<td>&lt;40</td>
<td>&gt;45</td>
<td>40-45</td>
<td>-</td>
</tr>
</tbody>
</table>
Management Hyperlipidemia for Pediatric

The first recommendation for the evaluation and treatment of hyperlipidemia is to start with lifestyle modification for six months. In individuals with additional risk, if LDL-C shows $\geq 130$ mg/dL constantly after lifestyle modification, pharmacological therapy is considered. A continuous increase of LDL-C level $\geq 190$ mg/dL indicates genetic etiology, and statin therapy is recommended.

Non-Pharmacological Therapy

Lifestyle modification is recommended for children who have LDL-C values of 130 mg/dL or more. Lifestyle modifications such as diet and recommended physical activity that avoid obesity will also have a positive impact on the prevention of hyperlipidemia.

Diet therapy begins with the Integrated Health Cardiovascular Health-1 (CHILD-1) Diet for 3-6 months, which includes total fat less than 30% of daily calorie intake, 8-10% saturated fat, trans fat avoidance, and intake cholesterol less than 300 mg/day. This safe and effective diet is associated with average growth and development in children from the age of 6-7 months. Besides, physical activity is one of the lifestyle changes that are also important from hyperlipidemia. It includes 60 minutes of exercise a day, layer time $\leq$ 2 hours a day.

Pharmacological Therapy

One of lipid-lowering agents which can increase LDL-C levels prominently is 3-hydroxy-3-methyl-glutaryl coenzyme A reductase inhibitors (as known as statin). Statins produce upregulation of LDL receptor and reduce LDL-C values. The initiation of statins results in a primary reduction in ASCVD risk. Six of the seven commercially available statins (not including pitavastatin) indicate for children at various ages and doses. The US FDA approved using rosuvastatin and pravastatin in children aged eight years. While atorvastatin, lovastatin, simvastatin, and fluvastatin use at the age of 10 years.

The primary goal of FH treatment is to get LDL-C level of 130 mg/dL or lower, ideally 110 mg/dL or smaller, or LDL-C reduction of 50% or higher. If the initial target not achieved with maximum doses, consideration gives to doubling the statin dose. However, increasing the statin dose will decline LDL-C by only about 6%.

If combination of lifestyle modification and maximal dose statin provides insufficient reduction of LDL-C, other lipid-lowering therapies have considered. Cholestyramine, one of bile acid sequestrants (BAS), can be given from the age of 6 years. Children aged more than ten years with FH, BAS, colesevelam, ezetimibe, and cholesterol absorption blockers (such as acarbose), can be administrated with statin to reduce LDL-C levels. It binds bile salt in the digestive tract and prevents reuptake, which causes an elevate in the conversion of cholesterol into bile in the liver, elevated regulation of LDL receptors, and elevated cleansing of LDL-C from the circulation.

OVERVIEW OF STATINS

Pharmacology

The action mechanism of statins is to diminish hepatic cholesterol biosynthesis by blocking 3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase enzymes competitively, thereby blocking the conversion L-mevalonate from HMG-CoA (Figure 2). Decrease in intracellular cholesterol, the expression of genes that encode LDL receptors on the cell surface becomes regulated. In turn, it will increase liver LDL absorption and reduce circulating LDL levels in serum.
Statins also have pleiotropic effects by blocking the synthesis of essential isoprenoids, such as isopentenyl-pyrophosphate, dimethylallyl-pyrophosphate, geranyl-pyrophosphate, farnesyl pyrophosphate, squalene, geranylgeranylated proteins, and other isoprenoids (such as ubiquitin, heme, dolichol). This isoprenoid transition needed for activation of intracellular proteins or Ras signaling proteins of bound guanosine phosphate and proteins such as Ras (Rab, Rac, Ral, Rap, and Rho) which play an indispensable role in several cellular processes (Figure 3).

Figure 3 Pleiotropic effects on statins

Decreased isoprenoid intermediates in circulation as an outcome of blocking HMG CoA reductase by statins prevent the activation of signaling proteins. Therefore, statins cause several effects such as antioxidant, anti-inflammation, plaque stability, antiproliferative and immunomodulatory effects, and prevention of platelet aggregation. Table 2 summarizes some of the pleiotropic effects of statins from various studies.

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Antioxidant</th>
<th>Anti-inflammation</th>
<th>Antiproliferative Immunomodulator</th>
<th>Plaque Stability</th>
<th>Prevention of platelet aggregation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simvastatin</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Pitavastatin</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>+</td>
<td>+</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

Statins divided into two types based on lipophilicity, namely hydrophilic compounds such as pravastatin and rosuvastatin and others, including lipophilic compounds. Permeability of lipophilic statin membranes is higher than hydrophilic statins. Pravastatin can trigger peroxisome proliferator-activated receptor-γ (PPARγ) in macrophages by inactivating Rho, thereby reducing ROS. However, the action needs a concentration 100 times higher than the type of lipophilic statin to be active. Lipophilic statins have a high ability to activate PPAR-γ, which acts to reduce ROS and ROS activity induced by statins was 58%, 31%, 29%, and 15% respectively for fluvastatin, pitavastatin, simvastatin, and atorvastatin. A study by Landmesser et al. (2005) found that simvastatin can significantly increase the activity of superoxide dismutase (SOD), which acts as a natural antioxidant for the body. Lovastatin can increase the activity of antioxidant enzymes in the body, such as catalase and glutathione peroxidase. Rosuvastatin reported having activity in reducing malondialdehyde (MDA) and oxidized LDL (oxLDL) in patients who have atherosclerotic strokes.
Besides, rosuvastatin also found to increase SOD activity and decrease acylhydrazines (oxidants) in patients with pulmonary disease.

Statins have anti-inflammatory activity by inactivating necrosis factor kappa-B (NF-κB) transcription factors. Atorvastatin, lovastatin, and simvastatin are reporting have the effect of reducing the production of ROS mediated by Rac1 and involving activity on NF-κB transcription factors, thereby decreasing oxidation-sensitive inflammation. Besides, the statin also reduce the production of activator protein 1 (AP-1), which is one of transcription factors in cellular gene expressions such as transformation, proliferation, and cell apoptosis. Pravastatin also have the ability to inhibit activity of Rac1, which plays a role in ROS in healthy humans. Lovastatin and simvastatin also reduce pro-inflammatory cytokines, monocyte-1 chemotactic proteins, interleukin-6 (IL-6), and interleukin (IL-8) involved in the inflammatory process. Atorvastatin, simvastatin, pravastatin, or fluvastatin reduce IL-6 production by 50%, 53%, 60%, and 64%, prominently. Pitavastatin also has a significant activity inhibiting the production of IL-6 and IL-8, thus showing anti-inflammatory effects and reducing atherosclerosis. However, a study conducted by Karmau et al. (2019) in humans showed that there was no significant for decreasing IL-6.

Statins also have antiproliferation activity from increased interleukin-18 (IL-18). Pleiotropic proinflammatory cytokines, interleukin-18 (IL-18), are reported to show prominent antitumor activity through activation of cytotoxic T lymphocytes and natural killer cells and inhibition of angiogenesis. Simvastatin, pravastatin, and fluvastatin can trigger IL-18 production in human monocytes, thereby decreasing smooth muscle cell proliferation and playing an essential role in the action of statins in cancer. Another case with pitavastatin reduces IL-18 production in humans. A new report also found that rosuvastatin inclined to have higher plasma IL-18 levels.

Statins can increase plaque stability through decreased lipids and compounds involved in plaque formation. Simvastatin, lovastatin, fluvastatin, and atorvastatin can inhibit the secretion of several metalloproteinases (MMP) in macrophages and smooth muscle cells, which can cause to plaque stabilization. Pravastatin and rosuvastatin reported having the ability to reduce the concentration of malondialdehyde (MDA), which plays a role in lipid peroxidation and plaque instability. Pitavastatin can weaken the expression of osteopontin, which has the function of promoting calcification in plaque so that it can reduce some plaque due to calcification.

Increased platelet reactivity in hypercholesterolemia and platelets is one of the factors in the formation of an acute coronary syndrome. Statins also have platelet aggregation prevention activities. Pravastatin can normalize platelet reactivity and thrombin generation by reducing it.

Atorvastatin increases endothelial nitrite oxide synthase (eNOS) by reducing the regulation of β-thrombomodulin and platelet factor 4 in platelets. In other studies, atorvastatin inhibits platelet recruitment, decreases thromboxane A2 and Rac1, and increases levels of nitrite oxide (NO). β-thrombomodulin and platelet factor-4 are both released by trombosit when activated and are chemostats for inflammatory cells. Arachidonic acid increases platelet aggregation, which is inhibited by simvastatin and fluvastatin. According to a multicentre randomized-controlled trial, rosuvastatin significantly reduced the incidence of symptomatic venous thromboembolism.

### Structural Characteristics and Pharmacokinetic

Statins consist of two types including, type I, fungal derived statins (lovastatin, pravastatin, simvastatin), and type II, fully synthetic statins (atorvastatin, fluvastatin, pitavastatin, rosuvastatin). Type I statins preserve a structural homology close to mevastatin, as known as the first statin developed, maintaining lactone/open acid moiety in addition to the substituted decalin ring framework (Table 3). While statin type II maintains lactone groups such as HMG-CoA for binding, these compounds are synthetic HMG-CoA reductase inhibitors entirely and indicate pharmacokinetic properties, including differences in metabolism, bioavailability, lipophilicity dose (lipophilicity), half-life, excretion, and time of availability.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Simvastatin</th>
<th>Lovastatin</th>
<th>Pravastatin</th>
<th>Fluvastatin</th>
<th>Pitavastatin</th>
<th>Atorvastatin</th>
<th>Rosuvastatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular Structure</td>
<td><img src="image1.png" alt="Simvastatin" /></td>
<td><img src="image2.png" alt="Lovastatin" /></td>
<td><img src="image3.png" alt="Pravastatin" /></td>
<td><img src="image4.png" alt="Fluvastatin" /></td>
<td><img src="image5.png" alt="Pitavastatin" /></td>
<td><img src="image6.png" alt="Atorvastatin" /></td>
<td><img src="image7.png" alt="Rosuvastatin" /></td>
</tr>
<tr>
<td>Type</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>II</td>
<td>II</td>
<td>II</td>
<td>II</td>
</tr>
</tbody>
</table>
Efficacy and Safety of Statins in Children

Several studies have examined the efficacy and safety of statins in children. A Cochrane study in 2014 that analyzed eight RCTs published between 1996 and 2010 compared the efficacy of statins with placebo in 1074 children with hypercholesterolemia aged 4-18 years. Eight studies revealed that statins prominently reduced LDL-C levels compared with placebo, with a reduction in LDL-C levels at six months by 35% (95% CI: −38 to −32) and at twelve months by 27% (95% CI: −32 to −22). Statins have also shown to have positive effects on other critical atherogenic lipids, specifically apoB, VLDL, apoA1, HDL-C, TC, and TG.[10,11] Although all statins have the same mechanism of action, each statin has different effects on the lipid profile. Table 4 summarizes outcomes in LDL-C (%) reduction observed in all statin studies in children with heterozygous FH and homozygous FH.

### Table 4: Summary of the use of statins in pediatric studies

<table>
<thead>
<tr>
<th>Agent (reference)</th>
<th>Population</th>
<th>Statin Dosing</th>
<th>Treatment Duration (month[s])</th>
<th>LDL Reduction (%)</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simvastatin (Couture et al., 1998)</td>
<td>n = 63: 8-17 yr H eFH</td>
<td>20 mg/day x 6 wks</td>
<td>1.5</td>
<td>38</td>
<td>No difference vs. placebo</td>
</tr>
<tr>
<td>Statin</td>
<td>Study Details</td>
<td>Participants</td>
<td>Intervention</td>
<td>Duration</td>
<td>Outcomes</td>
</tr>
<tr>
<td>--------------------------</td>
<td>--------------------------------------------------------</td>
<td>--------------</td>
<td>------------------------------------------------------------------------------</td>
<td>----------</td>
<td>---------------------------</td>
</tr>
<tr>
<td><strong>Simvastatin</strong></td>
<td>(Stefanutti et al, 1999)</td>
<td>n = 16; 4-12 yr HeFH</td>
<td>10 mg/day × 52 wks 12 wks</td>
<td>29</td>
<td>No difference vs. placebo</td>
</tr>
<tr>
<td><strong>Simvastatin</strong></td>
<td>(de Jongh et al, 2002a)</td>
<td>n = 173; 14.4 ± 2.1 yr HeFH</td>
<td>10 mg/day × 8 wks 20 mg/day × 8 wks 40 mg/day × 8 wks 40 mg/day × 24 wks</td>
<td>31 at wk 8 35 at wk 16 38 at wk 24 41 at wk 48</td>
<td>No SAE, slight decrease in DHEA-S</td>
</tr>
<tr>
<td><strong>Simvastatin</strong></td>
<td>(de Jongh et al, 2002b)</td>
<td>n = 50; 14.2 ± 3.1 yr HeFH</td>
<td>10 mg/day × 8 wks 20 mg/day × 8 wks 40 mg/day × 12 wks</td>
<td>40</td>
<td>No difference vs. placebo</td>
</tr>
<tr>
<td><strong>Simvastatin</strong></td>
<td>(Dirisamer et al, 2003)</td>
<td>n = 20; 13 ± 2.4 yr FH</td>
<td>5 or 10 mg/day (LDL &lt; 220 vs. ≥ 220) step-wise titration up to 20 mg × 52 wks</td>
<td>25 (5 mg) 30 (10 mg) 36 (20 mg)</td>
<td>No differences between groups</td>
</tr>
<tr>
<td><strong>Simvastatin</strong></td>
<td>(Ferreira et al, 2007)</td>
<td>n = 36; 10.3 ± 4 yr HC</td>
<td>10 mg/day × 4 wks</td>
<td>37</td>
<td>No difference vs. placebo</td>
</tr>
<tr>
<td><strong>Simvastatin</strong></td>
<td>(Garcia-de-la-Puente et al, 2009)</td>
<td>n = 25; 4-17 yr renal disease with hyperlipidemia</td>
<td>5 or 10 mg/day (LDL ≤ 30 vs. &gt; 30) × 4 wks 10 or 20 mg titration (at wk 4) × 8 wks</td>
<td>34</td>
<td>No difference vs. placebo</td>
</tr>
<tr>
<td><strong>Lovastatin</strong></td>
<td>(Lambert et al, 1996)</td>
<td>n = 69; 13.3 ± 2.7 yr HeFH</td>
<td>10 mg qd × 8 wks 20 mg/day × 8 wks 30 mg/day × 8 wks 40 mg/day × 24 wk</td>
<td>21</td>
<td>No SAE, increase in CK</td>
</tr>
<tr>
<td><strong>Lovastatin</strong></td>
<td>(Stein et al, 1999)</td>
<td>n = 132 (65 placebo); 13.3 ± 2.5 yr (males only) HeFH</td>
<td>10 mg/day × 8 wks 20 mg/day × 8 wks 40 mg/day × 8 wks 40 mg/day × 24 wks</td>
<td>17</td>
<td>No difference vs. placebo</td>
</tr>
<tr>
<td><strong>Lovastatin</strong></td>
<td>(Clauss et al, 2005)</td>
<td>n = 54; 11-18 yr (females only) HeFH</td>
<td>20 mg/day × 4 wks</td>
<td>23 at wk 4 27 at wk 24</td>
<td>No difference vs. placebo</td>
</tr>
<tr>
<td>Drug</td>
<td>n</td>
<td>Age Range</td>
<td>Treatment Details</td>
<td>Weeks</td>
<td>Result</td>
</tr>
<tr>
<td>-------------</td>
<td>-----</td>
<td>-----------</td>
<td>----------------------------------------------------------------------------------</td>
<td>-------</td>
<td>-------------------------</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>72</td>
<td>8-16 yr</td>
<td>40 mg/day × 20 wks</td>
<td>20</td>
<td>No difference between groups</td>
</tr>
<tr>
<td>(Knipscheer et al, 1996)</td>
<td></td>
<td></td>
<td>5 mg/day × 12 wks, 10 mg/day × 12 wks, 20 mg/day × 12 wks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pravastatin</td>
<td>20</td>
<td>4.9-15.6 yr</td>
<td>10 mg/day × 8 wks</td>
<td>2</td>
<td>No SAE</td>
</tr>
<tr>
<td>(Hedman, 2003)</td>
<td></td>
<td></td>
<td>Titration by 10 mg at 8, 16, 24, 104 wks per LDL goal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pravastatin</td>
<td>19</td>
<td>4.4-18.9 yr</td>
<td>10 mg/day × 8 wks</td>
<td>2</td>
<td>No SAE, mild increase in CK</td>
</tr>
<tr>
<td>(Hedman, 2004)</td>
<td></td>
<td></td>
<td>Titration to 40 or 80 mg intervals per LDL × 96 wks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pravastatin</td>
<td>214</td>
<td>13 ± 3 yr HeFH</td>
<td>20 or 40 mg/day (&lt;14 vs. ≥14 yr) × 104 wks</td>
<td>24</td>
<td>No difference vs. placebo</td>
</tr>
<tr>
<td>(Wiegman et al, 2004)</td>
<td></td>
<td></td>
<td>Titration to 40 or 80 mg intervals per LDL × 96 wks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pravastatin</td>
<td>35</td>
<td>4.1-18.5 yr HeFH</td>
<td>10 mg/day Titration by 10 mg at 8, 16, 24, 104 wks per LDL goal</td>
<td>24</td>
<td>No SAE</td>
</tr>
<tr>
<td>(Hedman, 2005)</td>
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<td>Titration to 40 or 80 mg intervals per LDL × 96 wks</td>
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<tr>
<td>Pravastatin</td>
<td>20</td>
<td>4.9-15.6 yr HeFH</td>
<td>10 mg/day × 8 wks</td>
<td>20(TT)</td>
<td>No SAE</td>
</tr>
<tr>
<td>(Hedman, 2006)</td>
<td></td>
<td></td>
<td>Titration to 40 or 80 mg intervals per LDL × 96 wks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pravastatin</td>
<td>184</td>
<td>8-18 yr HeFH</td>
<td>20 or 40 mg/day (&lt;14 vs. ≥14 yr) × 104 wks</td>
<td>240</td>
<td>No SAE</td>
</tr>
<tr>
<td>(Luirink et al, 2019)</td>
<td></td>
<td></td>
<td>Titration to 40 or 80 mg intervals per LDL × 96 wks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>84</td>
<td>12.6 ± 2.1 yr HeFH</td>
<td>20 mg/day for 6 wks Titration to 40 or 80 mg intervals per LDL × 96 wks</td>
<td>24</td>
<td>N/A, no placebo arm</td>
</tr>
<tr>
<td>(van der Graaf et al, 2006)</td>
<td></td>
<td></td>
<td>Titration to 40 or 80 mg intervals per LDL × 96 wks</td>
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</tr>
<tr>
<td>Pitavastatin</td>
<td>106</td>
<td>6-17 yr hyperlipidemia</td>
<td>1 mg/day × 12 wks, 2 mg/day × 12 wks, 4 mg/day × 12 wks</td>
<td>23.5</td>
<td>DHEA-S significantly decreased (4 mg group)</td>
</tr>
<tr>
<td>(Braamskamp et al, 2015)</td>
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<td>Titration to 20 mg at wk 4 based on LDL continuing over 26 wks</td>
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<tr>
<td>Atorvastatin</td>
<td>187</td>
<td>14.1 ± 2.0 yr HeFH</td>
<td>10 mg/day Titration to 20 mg at wk 4 based on LDL continuing over 26 wks</td>
<td>6.5</td>
<td>No difference vs. placebo</td>
</tr>
<tr>
<td>(McCrendle et al, 2003)</td>
<td></td>
<td></td>
<td>Titration to 20 mg at wk 4 based on LDL continuing over 26 wks</td>
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<tr>
<td>Atorvastatin</td>
<td>18</td>
<td>13 ± 4 renal transplant with hyperlipidemia</td>
<td>5 or 10 mg/day (&lt;40 kg vs. ≥40 kg) × 36 wks</td>
<td>9</td>
<td>No difference vs. untreated</td>
</tr>
<tr>
<td>(Argent et al, 2003)</td>
<td></td>
<td></td>
<td>Titration to 20 mg at wk 4 based on LDL continuing over 26 wks</td>
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</tbody>
</table>
In general, one of which concerns side effects in children and adolescents who receive statin treatment that is reported similar to those who receive a placebo.\textsuperscript{1,70} The risk ratio of statin side effects compared with placebo for 1 month was 0.86 (95% CI: 0.65-1.13), for 6 months it was 1.02 (95% CI: 0.82-1.27), and for 1 year 1.01 (95% CI: 0.81 to 1.26).\textsuperscript{70} Common side effects that often occur in muscles and liver are investigating from statin use, so it needs to be observed along with other side effects. Statin use rarely causes serious liver disorders. Muscle aches and weakness, rhabdomyolysis, have also been reported. Changes in liver transaminase and creatinine kinase values appear to be similar to those reported in adults.\textsuperscript{1,25,70} Drug interactions that are widely involved together with statins are drugs that inhibit cytochrome P450 3A4, such as macrolides, HIV-protease blockers, calcium channel blockers, antifungal agents, and cyclosporine. As a result of these interactions lead to an increase in statin levels in the blood and increase the risk of toxicity from statins.\textsuperscript{25,98} Some studies inform that statin administration restricted to children with the highest risk of ASCVD. However, the use of this statin has been approved for use as pravastatin at the age of 8 years while atorvastatin, fluvastatin, lovastatin, rosuvastatin, and simvastatin at the age of 10 years.\textsuperscript{99-101}

**SUMMARY**

Lipid-lowering drugs is recommended in children with familial hypercholesterolemia, especially statin drugs. Statins are the right drug choice because they have good efficacy in reducing LDL-C compared to other anti hyperlipidemia. The most significant reduction in LDL in children with atorvastatin and rosuvastatin. When viewed from various studies on statin use in the long term, pravastatin used for 20 years has a significant reduction in LDL and is proven safe. However, substantial and long-term randomized controlled trials are still needed on several other types of statins to establish the efficacy and safety for long term. Besides, pleiotropic effects on statins need to tested in adults.

**ABBREVIATIONS**

ASCVD, atherosclerotic cardiovascular disease; CYP, cytochrome p450; HDL, high-density lipoprotein; HMG-CoA, 3-hydroxy-3-methylglutaryl-coenzyme A; LDL, low-density lipoprotein; TC, total cholesterol; TG, triglyceride

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CONFLICT OF INTEREST
The authors declare no conflict of interest.

REFERENCES


