

Statin and Its Use in Children: A Review Brief

Marizki Pondawinata¹, Yulistiani^{2*}

¹Master of Clinical Pharmacy Programme, Faculty of Pharmacy, Airlangga University, Surabaya, Indonesia

²Department of Clinical Pharmacy, Faculty of Pharmacy, Airlangga University, Surabaya, Indonesia

*Corresponding Author E-mail: yulist_r@yahoo.co.id

Article History:

Submitted: 25.01.2020

Revised: 16.02.2020

Accepted: 17.03.2020

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

Correspondence:

Yulistiani

Department of Clinical Pharmacy, Faculty of Pharmacy, Airlangga University, Surabaya, Indonesia

E-mail: yulist_r@yahoo.co.id

DOI: [10.5530/srp.2020.3.46](https://doi.org/10.5530/srp.2020.3.46)

@Advanced Scientific Research. All rights reserved

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 birth^{2,3,4}. The main cause of FH is gene mutation in the LDL receptor^{5,6}. 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 thought⁷. Homozygous form of FH (HoFH) is a rare disorder with an estimated prevalence of 1 per 160,000-300,000 population, especially in Europe⁸.

Heterozygous FH often appears in children without symptoms and has LDL-C levels of 150 to 500 mg/dL⁹. The increase in LDL-C in homozygous FH is often higher than 500 mg/dL in severe cases¹⁰. 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 disease¹¹ (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 ASCVD¹².

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 children^{13,14}. The aim of this review is to offer an illustration of statin use in children especially with hyperlipidemia and areas for further research.

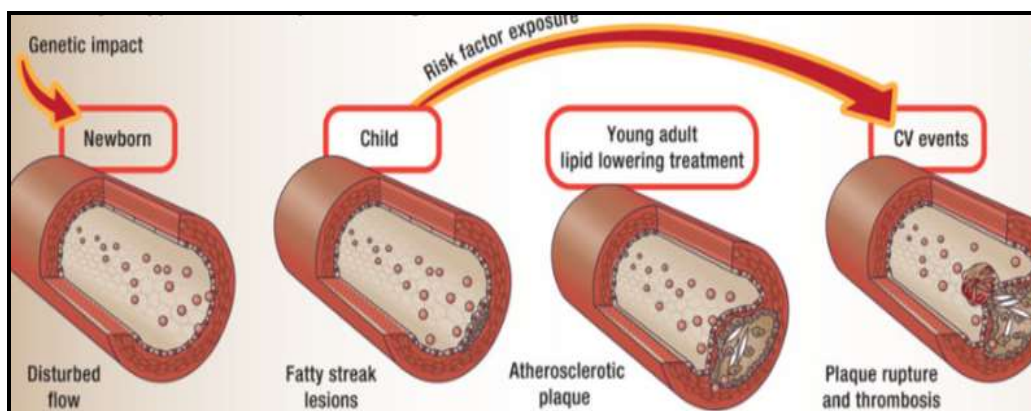


Figure 1: Early development of ASCVD in children with familial hypercholesterolemia (Wiegman et al., 2015).

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 underdiagnosis¹⁵.

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 \pm 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 \pm non-HDL-C ≥ 145 mg/dL \pm HDL-C < 40 mg/dL \pm TG ≥ 100 mg/dL if < 10 years or 30 130 mg/dL. If children are \geq ten years old, it is necessary to repeat the measurement of fasting lipid profile and average results^{1,15}.

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 relatives¹⁶. 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 hyperlipidemia¹⁷. 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 risk¹⁸.

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^{1,15}. 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 evaluated¹.

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^{1,8}.

Table 1: Profile of lipids in children¹⁵

Category	Low (mg/dL)	Acceptable (mg/dL)	Borderline (mg/dL)	High (mg/dL)
TC	-	< 170	170-199	≥ 200
LDL-C	-	< 110	110-129	≥ 130
TG (0-9 y)	-	< 75	75-99	≥ 100
TG (10-19 y)	-	< 90	90-129	≥ 130
Non-HDL-C	-	< 120	120-144	≥ 145
HDL-C	< 40	> 45	40-45	-

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 ≥ 130 mg/dL constantly after lifestyle modification, pharmacological therapy is considered. A continuous increase of LDL-C level ≥ 190 mg/dL indicates genetic etiology, and statin therapy is recommended¹⁵.

Non-Pharmacological Therapy

Lifestyle modification is recommended for children who have LDL-C values of 130 mg/dL or more¹⁹. Lifestyle modifications such as diet and recommended physical activity that avoid obesity will also have a positive impact on the prevention of hyperlipidemia¹⁴.

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 ≤ 2 hours a day¹⁵.

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 risk²⁰. 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 years²¹.

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 higher²². 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 considered²¹. 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, colessevelam, ezetimibe, and cholesterol absorption blockers (such as acarbose), can be administered 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 circulation²³.

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^{24,25}.

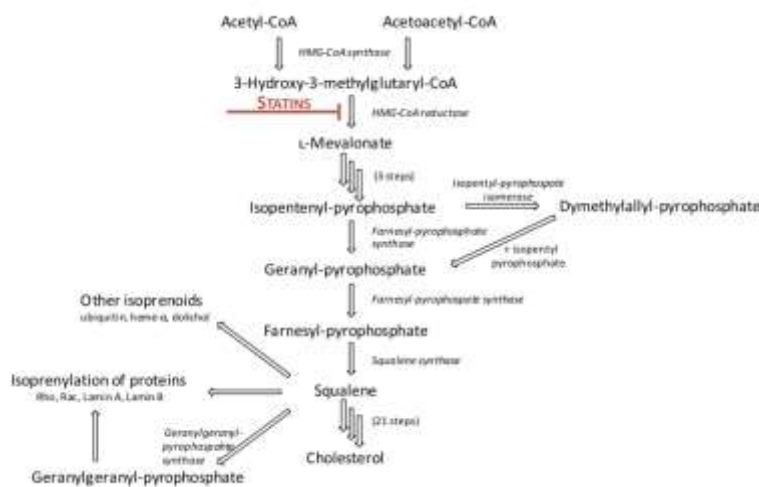


Figure 2: Action mechanism of statins in reducing cholesterol biosynthesis²⁴

Statins also have pleiotropic effects by blocking the synthesis of essential isoprenoids, such as isopentenyl-pyrophosphate, dimethylallyl-pyrophosphate, geranyl-pyrophosphate, farnesyl pyrophosphate, squalene, geranylgeranyl pyrophosphate, isoprenylation of 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 processes²⁶ (Figure 3).

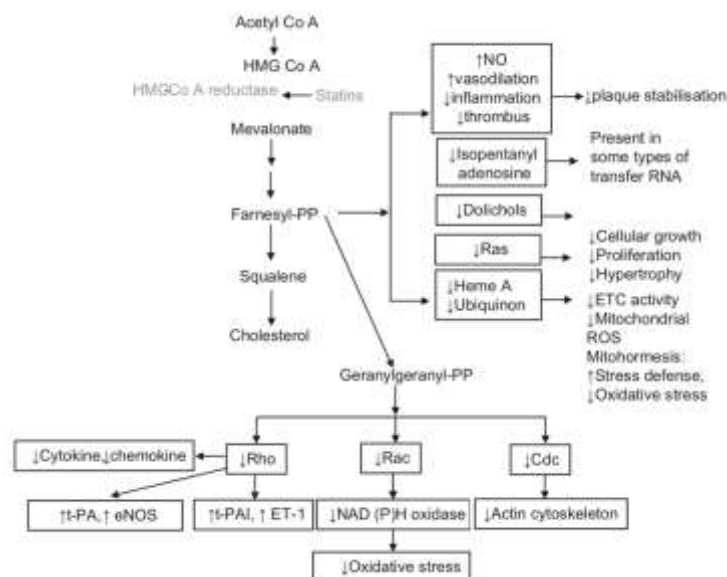


Figure 3 Pleiotropic effects on statins²⁶

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 aggregation²⁷. Table 2 summarizes some of the pleiotropic effects of statins from various studies.

Table 2: Summary of pleiotropic effects in several statins²⁶⁻²⁹

Drugs	Antioxidant	Antiinflammation	Antiproliferative dan Immunomodulator	Plaque Stability	Prevention of platelet aggregation
Simvastatin	+	+	+	+	+
Lovastatin	+	+	+	+	+
Pravastatin	+	+	+	+	+
Fluvastatin	++	+	+	+	+
Pitavastatin	+	+	-	+	+
Atorvastatin	+	+	+	+	+
Rosuvastatin	+	+	+/-	+	+

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 (PPAR γ) in macrophages by inactivating Rho, thereby reducing ROS²⁸. 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^{28,30}. PPAR γ

activity induced by statins was 58%, 31%, 29%, and 15% respectively for fluvastatin, pitavastatin, simvastatin, and atorvastatin²⁸. 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 body³¹. Lovastatin can increase the activity of antioxidant enzymes in the body, such as catalase and glutathione peroxidase³². Rosuvastatin reported having activity in reducing malondialdehyde (MDA) and oxidized LDL (oxLDL) in patients who have atherosclerotic strokes³³.

Besides, rosuvastatin also found to increase SOD activity and decrease acylhydrazines (oxidants) in patients with pulmonary disease³⁴.

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^{35,36}. Pravastatin also have the ability to inhibit activity of Rac1, which plays a role in ROS in healthy humans³⁷. 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^{38,39}. Atorvastatin, simvastatin, pravastatin, or fluvastatin reduce IL-6 production by 50%, 53%, 60%, and 64%, prominently²⁹. Pitavastatin also has a significant activity inhibiting the production of IL-6 and IL-8⁴⁰. Rosuvastatin reported inhibiting the production of IL-6 and IL-8, thus showing anti-inflammatory effects and reducing atherosclerosis⁴¹. However, a study conducted by Karmaus et al. (2019) in humans showed that there was no significant for decreasing IL-6⁴².

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 cancer⁴³⁻⁴⁶. Another case with pitavastatin reduces IL-18 production in humans⁴⁷. A new report also found that rosuvastatin inclined to have higher plasma IL-18 levels^{42,48}.

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

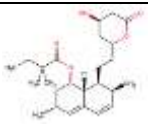
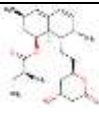
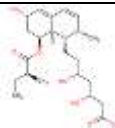
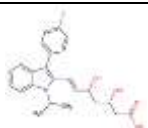
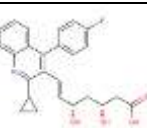
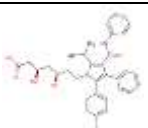
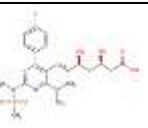
macrophages and smooth muscle cells, which can cause to plaque stabilization^{39,49-50}. Pravastatin and rosuvastatin reported having the ability to reduce the concentration of malondialdehyde (MDA), which plays a role in lipid peroxidation and plaque instability^{33,51}. Pitavastatin can weaken the expression of osteopontin, which has the function of promoting calcification in plaque so that it can reduce some plaque due to calcification⁵².

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 it⁵³. Atorvastatin increases endothelial nitrite oxide synthase (eNOS) by reducing the regulation of β-thrombomodulin and platelet factor 4 in platelets⁵⁴. In other studies, atorvastatin inhibits platelet recruitment, decreases thromboxane A2 and Rac1, and increases levels of nitrite oxide (NO)⁵⁵. 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 fluvastatin⁵⁶⁻⁵⁹. According to a multicentre randomized-controlled trial, rosuvastatin significantly reduced the incidence of symptomatic venous thromboembolism⁶⁰.

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)⁶¹. 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 availability⁶².

Table 3: Pharmacokinetic characteristics of statins^{24,67-69}

Parameter	Simvastatin	Lovastatin	Pravastatin	Fluvastatin	Pitavastatin	Atorvastatin	Rosuvastatin
Molecular Structure							
Type	I	I	I	II	II	II	II

Log D *	4.40 (lactone)/1.80 (acid)	3.91 (lactone)/1.51 (acid)	-0.47	1.75	1.50	1.53	-0,25 to -0,50
Lipophilicity	Lipophilic	Lipophilic	Hydrophilic	Lipophilic	Lipophilic	Lipophilic	Hydrophilic
Bioavailability	<5%	5%	18%	9%-50%	51%	12%	20%
Onset	>3 days	3 days	2 weeks	3-4 weeks	2-4 weeks	3-5 days	(not available)
Duration	(not available)	4-6 weeks	4 weeks	(not available)	(not available)	48-72 hr	(not available)
Peak Serum Time	1.3-2.4 hr	2-4 hr	1-1,5 hr	0,5-1 hr	1 hr	1-2 hr	3-5 hr
Volume of Distribution	(not available)	(not available)	35 L	330 L	148 L	381 L	134 L
Protein Binding	95%	95%	50%	98%	96%	98%	90%
Prodrug	Yes	Yes	No	No	No	No	No
Active	Yes	Yes	Yes	No	Yes	Yes	Yes
Metabolites							
CYP	3A4	3A4	3A4	2C9	2C8, 2C9	3A4	2C9
Substrate							
Half-Life	3 h	3 h	1.3-2.7 h	2.3 h	12 h	14 h	19 h
Excretion (Renal)	13%	10%	20%	6%	2%	<2%	10%
Excretion (Faecal)	60%	83%	70%	93%	79%	>98%	90%
Dialyzable	(not available)	(not available)	(not available)	(not available)	(not available)	No (HD)	(not available)

* Logarithms of octanol-water distribution coefficients (log D) presented at pH 7.0 for rosuvastatin and pH 7.4 for all other drugs.

For oral administration, statins have low bioavailability (5-50%) due to extensive first metabolic pathways in the liver, so they well absorbed from the intestine⁶³. Most statins have β -hydroxy-acid except for simvastatin and lovastatin, which are pro-drug and require liver metabolism for the active β -hydroxy-acid acid state⁶⁴⁻⁶⁵. Statins can bind to albumin in systemic circulation and also differ essentially to volume of distribution and half-life. The major metabolic routes of most statins are via cytochrome P450 (CYP), with atorvastatin, lovastatin, pravastatin and simvastatin, which are metabolism via the CYP3A4 isoform. Fluvastatin, pravastatin, and rosuvastatin which are metabolism through the CYP2C9 isoform⁶⁶. In contrast, pravastatin is metabolized mostly via sulfation, while rosuvastatin is eliminated up to 90% through biliary excretion. Differences in published studies about adverse effect profiles and pleiotropic effects between statins may be a direct result of their highly variable pharmacokinetic parameters⁶³.

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 TG⁷⁰⁻⁷¹. 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 the use of statins in pediatric studies⁷²⁻⁹⁷

Agent (reference)	Population	Statin Dosing	Treatment Duration (month[s])	LDL Reduction (%)	Safety
Simvastatin (Couture et al., 1998)	n = 63; HeFH	8-17 yr 20 mg/day x 6 wks	1.5	38	No difference vs. placebo

Simvastatin (Stefanutti et al, 1999)	n = 16; 4-12 yr HeFH	10 mg/day × 52 wks	12	29	No difference vs. placebo
Simvastatin (de Jongh et al, 2002a)	n = 173; 14.4 ± 2.1 yr HeFH	10 mg/day × 8 wks 20 mg/day × 8 wks 40 mg/day × 8 wks 40 mg/day × 24 wks	12	31 at wk 8 35 at wk 16 38 at wk 24 41 at wk 48	No SAE, A Slight decrease in DHEA-S
Simvastatin (de Jongh et al, 2002b)	n = 50; 14.2 ± 3.1 yr HeFH	10 mg/day × 8 wks 20 mg/day × 8 wks 40 mg/day × 12 wks	7	40	No difference vs. placebo
Simvastatin (Dirisamer et al, 2003)	n = 20; 13 ± 2.4 yr FH	5 or 10 mg/day (LDL < 220 vs. ≥ 220) step-wise titration up to 20 mg × 52 wks	12	25 (5 mg) 30 (10 mg) 36 (20 mg)	No differences between groups
Simvastatin (Ferreira et al, 2007)	n = 36; 10.3 ± 4 yr HC	10 mg/day × 4 wks	1	37	No difference vs. placebo
Simvastatin (Garcia-de-la-Puente et al, 2009)	n = 25; 4-17 yr renal disease with hyperlipidemia	5 or 10 mg/day (LDL ≤ 30 vs. > 30) × 4 wks 10 or 20 mg titration (at wk 4) × 8 wks	12	34	No difference vs. placebo
Lovastatin (Lambert et al, 1996)	n = 69; 13.3 ± 2.7 yr (males only) HeFH	10 mg qd × 8 wks 20 mg/day × 8 wks 30 mg/day × 8 wks 40 mg/day × 24 wk	2	21 24 27 36	No SAE, increase in CK
Lovastatin (Stein et al, 1999)	n = 132 (65 placebo); 13.3 ± 2.5 yr (males only) HeFH	10 mg/day × 8 wks 20 mg/day × 8 wks 40 mg/day × 8 wks 40 mg/day × 24 wks	12	17 24 27 25	No difference vs. placebo
Lovastatin (Clauss et al, 2005)	n = 54; 11-18 yr (females only) HeFH	20 mg/day × 4 wks	6	23 at wk 4 27 at wk 24	No difference vs. placebo

			40 mg/day × 20 wks			
Pravastatin (Knipscheer et al, 1996)	n = 72; 8-16 yr HeFH	5 mg/day × 12 wks 10 mg/day × 12 wks 20 mg/day × 12 wks	3	23 24 33		No difference between groups
Pravastatin (Hedman, 2003)	n = 20; 4.9-15.6 yr HeFH	10 mg/day × 8 wks	2	21		No SAE
Pravastatin (Hedman, 2004)	n = 19; 4.4-18.9 yr cardiac transplant with HeFH	10 mg/day × 8 wks	2	27		No SAE, mild increase in CK
Pravastatin (Wiegman et al, 2004)	n = 214; 13 ± 3 yr HeFH	20 or 40 mg/day (< 14 vs. ≥ 14 yr) × 104 wks)	24	24		No difference vs. placebo
Pravastatin (Hedman, 2005)	n = 35; 4.1-18.5 yr HeFH	10 mg/day Titration by 10 mg at 8, 16, 24, 104 wks per LDL goal	24	25 at wk 8 27 at wk 16 29 at wk 24 33 at wk 52 32 at wk 104		No SAE
Pravastatin (Hedman, 2006)	n = 20; 4.9-15.6 yr HeFH	10 mg/day × 8 wks	2	20 (TT) 23 (TC)		No SAE
Pravastatin (Luirink et al, 2019)	n = 184; 8-18 yr HeFH	20 or 40 mg/day (< 14 vs. ≥ 14 yr) × 104 wks)	240	32		No SAE
Fluvastatin (van der Graaf et al, 2006)	n = 84; 12.6 ± 2.1 yr HeFH	20 mg/day for 6 wks Titration to 40 or 80 mg intervals per LDL × 96 wks	24	34		N/A, no placebo arm
Pitavastatin (Braamskamp et al, 2015)	n = 106; 6-17 yr hyperlipidemia	1 mg/day × 12 wks 2 mg/day × 12 wks 4 mg/day × 12 wks	3	23.5 30.1 39.3		DHEA-S significantly decreased (4 mg group)
Atorvastatin (McCrinkle et al, 2003)	n = 187; 14.1 ± 2.0 yr HeFH	10 mg/day Titration to 20 mg at wk 4 based on LDL continuing over 26 wks	6.5	40		No difference vs. placebo
Atorvastatin (Argent et al, 2003)	n = 18; 13 ± 4 renal transplant with hyperlipidemia	5 or 10 mg/day (< 40 kg vs. ≥ 40 kg) × 36 wks	9	57		No difference vs. untreated

Atorvastatin (Gandelman et al, 2011)	n = 39; 6 to < 18 yr HeFH	5 or 10 mg/day × 2 8 wks (< 10 vs 10 yr) Titration per LDL at wk 4		37 (5 mg) 43 (5 mg to 10 mg) 38 (10 mg) 41 (10 mg to 20 mg)	No difference between groups
Atorvastatin (Langslet et al, 2016)	n = 272; 6-15 yr HeFH	5 or 10 mg/day × 36 8 wks (< 10 vs 10 yr) Titration per LDL at wk 4		43,8 (TS1 – 5 mg) 39,9 (TS≥2 – 10 mg)	No difference between groups
Rosuvastatin (Marais et al, 2008)	n = 44; 8-63 yr HoFH	20 mg/day × 6 4.5 wks 40 mg/day × 6 wks 80 mg/day × 6 wks		19 23 21.4	No SAE
Rosuvastatin (Avis et al, 2010)	n = 177; 13.8 ± 1.7 HeFH	5, 10, 20 mg/day 3 Titration at wk 12 per LDL × 40 wk		38 45 50	No difference vs. placebo
Rosuvastatin (Stein et al, 2017)	n = 13; 6 to < 18 yr HoFH	10 mg/day x 4 wks 3 20 mg/day x 6 wks Maintenance phase with 20 mg/day x 12 wks		22,3 (cross- over phase) 19,3 (maintenance)	No difference vs. placebo

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^{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)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^{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^{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 years⁹⁹⁻¹⁰¹.

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

ACKNOWLEDGMENT

The authors are grateful to the authorities of the Faculty of Pharmacy, Airlangga University, Surabaya, Indonesia for the facilities.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

- Jacobson TA, Maki KC, Orringer CE, Jones PH, Kris-Etherton P, Sikand G, et al. National Lipid Association Recommendations for Patient-Centered Management of Dyslipidemia: Part 2. *Journal of Clinical Lipidology*. 2015; 9(6): 1-122.
- Cuchel M, Bruckert E, Ginsberg HN, Raal FJ, Santos RD, Hegele RA. Homozygous Familial Hypercholesterolaemia: New Insights and Guidance for Clinicians to Improve Detection and Clinical Management. A Position Paper from The Consensus Panel on Familial Hypercholesterolaemia of The European Atherosclerosis Society. *European Heart Journal*. 2014; 35(32): 2146-2157.
- Bouhairie VE, and Goldberg C. Familial Hypercholesterolemia. *Clinical Cardiology*. 2015; 33: 169-179.
- Kliegman RM, Stanton BF, St Geme III JW, Schor NF. Editors. *Nelson Textbook of Pediatrics*. Canada: Elsevier. 2016; 20th Ed: pp. 692-694.
- Hovingh GK, Davidson MH, Kastelein JJ, O'Connor AM. Diagnosis and Treatment of Familial Hypercholesterolaemia. *European Heart Journal*. 2013; 34(13): 962-971.
- Sniderman AD, Tsimikas S, Fazio S. The Severe Hypercholesterolemia Phenotype: Clinical Diagnosis, Management, and Emerging Therapies, *Journal of The American College of Cardiology*. 2014; 63(19): 1935-1947.
- Vallejo-Vaz AJ, and Ray KK. Epidemiology of Familial Hypercholesterolaemia: Community and Clinical. *Atherosclerosis*. 2018; 277: 289-297.
- Wiegman A, Gidding SS, Watts GF, Chapman J, Ginsberg HN, Cuchel M, et al. Familial Hypercholesterolaemia in Children and Adolescents: Gaining Decades of Life by Optimizing Detection and Treatment. *European Heart Journal*. 2015; 36: 2425-2437.
- Nordestgaard BG, Chapman MJ, Humphries SE, Ginsberg HN, Masana L, Descamps OS, et al. Familial Hypercholesterolemia is Underdiagnosed and Undertreated in The General Population: Guidance for Clinicians to Prevent Coronary Heart Disease: Consensus Statement of The European Atherosclerosis Society. *European Heart Journal*. 2013; 34: 3478-3490.
- Sjouke B, Kusters DM, Kindt I, Besseling J, Defesche JC, Sijbrands EJ, et al. Homozygous Autosomal Dominant Hypercholesterolaemia in The Netherlands: Prevalence, Genotype-Phenotype Relationship, and Clinical Outcome. *European Heart Journal*. 2015; 36: 560-565.
- Van Wijk DF, Sjouke B, Figueroa A, Emami H, van der Valk FM, MacNabb MH, et al. Nonpharmacological Lipoprotein Apheresis Reduces Arterial Inflammation in Familial Hypercholesterolemia. *Journal of The American College of Cardiology*. 2014; 64: 1418-1426.
- Bellanger N, Orsoni A, Julia Z, Fournier N, Frisdal E, Duchene E, et al. Atheroprotective Reverse Cholesterol Transport Pathway is Defective in Familial Hypercholesterolemia. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2011; 31: 1675-1681.
- Wagner J, and Abdel-Rahman SM. Pediatric Statin Administration: Navigating A Frontier with Limited Data. *Journal of Pediatric Pharmacology Therapeutics*. 2016; 21(5): 380-403.
- Elkins C, Fruh S, Jones L, Bydalek K. Clinical Practice Recommendations for Pediatric Dyslipidemia. *Journal of Pediatric Health Care*. 2019; 33: 494-504.
- Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents, National Heart, Lung, and Blood Institute. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: Summary Report. *Pediatrics*. 2011; 128(5): 213-256.
- Knowles JW, Rader DJ, Khoury MJ. Cascade Screening for Familial Hypercholesterolemia and The Use of Genetic Testing. *JAMA*. 2017; 318: 381-382.
- de Ferranti SD. Familial Hypercholesterolemia in Children and Adolescents: A Clinical Perspective. *Journal of Clinical Lipidology*. 2015; 9(5): 11-19.
- O'Brien EC, Roe MT, Fraulo ES, Peterson ED, Ballantyne CM, Genest J. Rationale and Design of The Familial Hypercholesterolemia Foundation Cascade Screening for Awareness and Detection of Familial Hypercholesterolemia Registry. *American Heart Journal*. 2014; 167: 342-349.
- Wells BG, Schwinghammer TL, DiPiro JT, DiPiro CV. Editors. *Pharmacotherapy Handbook*. United States: McGraw-Hill Education. 2017; 10th Ed: pp. 108-109.
- Elkins JC, and Friedrich DA. Hypertriglyceridemia: A Review of The Evidence. *Nurse Practitioner Journal*. 2018; 43: 22-29.
- Bays HE, Jones PH, Orringer CE, Brown WV, Jacobson TA. National Lipid Association Annual Summary of Clinical Lipidology 2016. *Journal of Clinical Lipidology*. 2016; 10(1): 1-43.
- Wilson DP, McNeal C, Blackett P. Pediatric Dyslipidemia: Recommendations for Clinical Management. *Southern Medical Journal*. 2015; 108: 7-14.
- Yoon JM. Dyslipidemia in Children and Adolescents: When and How to Diagnose and Treat. *Pediatric Gastroenterology, Hepatology, and Nutrition*. 2014; 17: 85-92.
- McFarland AJ, Anoopkumar-Dukie S, Arora DS, Grant GD, McDermott CM, Perkins AV, Davey AK. Molecular Mechanisms Underlying The Effects of Statins in The Central Nervous System. *International Journal Molecular Sciences*. 2014; 15: 20607-20637.
- Katzung BG, Kruidering-Hall M, Trevor AJ. Editors. *Katzung & Trevor's Pharmacology Examination & Board*

- Review. United States: McGraw-Hill Education. 2019; 12th Ed: pp. 297-299.
26. Kavalipati N, Shah J, Ramakrishan A, Vasawala H. 2015. Pleiotropic Effects of Statins. *Indian Journal of Endocrinology and Metabolism*. 2015; 19(5): 554-562.
 27. Oesterle A, and Liao JK. The Pleiotropic Effects of Statins – From Coronary Artery Disease and Stroke to Atrial Fibrillation and Ventricular Tachyarrhythmia. *Current Vascular Pharmacology*. 2019; 17(3): 222-232.
 28. Yano M, Matsumura T, Senokuchi T, et al. Statins Activate Peroxisome Proliferator-Activated Receptor Gamma through Extracellular Signal-Regulated Kinase 1/2 and p38 Mitogen-Activated Protein Kinase-Dependent Cyclooxygenase-2 Expression in Macrophages. *Circ Res*. 2007; 100(10): 1442-1451.
 29. Lopnow H, Zhang L, Buerke M, Lautenschlage M, Chen L, Frister A, et al. Statins Potently Reduce the Cytokine-Mediated IL-6 Release in SMC/MNC Cocultures. *J Cell Mol Med*. 2011; 15(4): 994-1004.
 30. Chen M, Li H, Wang G, Shen X, Zhao S, Su W. Atorvastatin Prevents Advanced Glycation End Products (AGEs)-Induced Cardiac Fibrosis via Activating Peroxisome Proliferator-Activated Receptor Gamma (PPAR-Gamma). *Metabolism*. 2016; 65(4): 441-453.
 31. Landmesser U, Bahlmann F, Mueller M, Spiekermann S, Kirchhoff N, Schulz S, et al. Simvastatin versus Ezetimibe: Pleiotropic and Lipid-Lowering Effects on Endothelial Function in Humans. *Circulation*. 2005; 111: 2356-2363.
 32. Kumar S, Srivastava N, Gomes J. The Effect of Lovastatin on Oxidative Stress and Antioxidant Enzymes in Hydrogen Peroxide Intoxicated Rat. *Food and Chemical Toxicology*. 2011; 49(4): 898-902.
 33. Moon GJ, Kim SJ, Cho YH, Ryoo S, Bang OY. Antioxidant Effects of Statins in Patients with Atherosclerotic Cerebrovascular Disease. *J Clin Neurol*. 2014; 10(2): 140-147.
 34. Samorukova E, Adasheva T, Zadionchenko V, Malyavin A. Rosuvastatin Effects on Systemic Inflammation, Oxidative Stress and Antioxidants in Patients with Chronic Obstructive Pulmonary Disease. *European Respiratory Journal*. 2016; 48(60): PA3685
 35. Chen Z, Fukutomi T, Zago AC, et al. Simvastatin Reduces Neointimal Thickening in Low-Density Lipoprotein Receptor-Deficient Mice after Experimental Angioplasty without Changing Plasma Lipids. *Circulation*. 2002; 106(1): 20-23.
 36. Dichtl W, Dulak J, Frick M, et al. HMG-CoA Reductase Inhibitors Regulate Inflammatory Transcription Factors in Human Endothelial and Vascular Smooth Muscle Cells. *Arterioscler Thromb Vasc Biol*. 2003; 23(1): 58-63.
 37. Rashid M, Tawara S, Fukumoto Y, Seto M, Yano K, Shimokawa H. Importance of Rac1 Signaling Pathway Inhibition in The Pleiotropic Effects of HMG-CoA Reductase Inhibitors. *Circ J*. 2009; 73: 361-370.
 38. Rezaie-Majd A, Maca T, Bucek RA, et al. Simvastatin Reduces Expression of Cytokines Interleukin-6, Interleukin-8, and Monocyte Chemoattractant Protein-1 in Circulating Monocytes from Hypercholesterolemic Patients. *Arterioscler Thromb Vasc Biol*. 2002; 22(7): 1194-1199.
 39. Luan Z, Chase AJ, Newby AC. Statins Inhibit Secretion of Metalloproteinases-1,-2,-3, and-9 from Vascular Smooth Muscle Cells and Macrophages. *Arterioscler Thromb Vasc Biol*. 2003; 23(5): 769-775.
 40. Iwata A, Shirai R, Ishii H, Kushima H, Hashinaga K, Umeki K, et al. Inhibitory Effect of Statins on Inflammatory Cytokine Production from Human Bronchial Epithelial Cells. *Clin Exp Immunol*. 2012; 168(2): 234-240.
 41. Gualtero DF, Viafara-Garcia SM, Morantes SJ, Buitrago DM, Gonzalez OA, Lafaurie GI. Rosuvastatin Inhibits Interleukin (IL)-8 and IL-6 Production in Human Coronary Artery Endothelial Cells Stimulated With Aggregatibacter Actinomycetemcomitans Serotype b. *J Periodontol*. 2017; 88(2): 225-235.
 42. Karmaus PWF, Shi M, Perl S, Biancotto A, Candia J, Cheung F, et al. Effects of Rosuvastatin on The Immune System in Healthy Volunteers with Normal Serum Cholesterol. *Journal of Clinical Investigatio Insight*. 2019; 4(21): 1-13.
 43. Montero MT, Hernandez O, Suarez Y, Matilla J, Ferruelo AJ, Martinez-Botas J, et al. A. Hydroxymethylglutaryl-Coenzyme A Reductase Inhibition Stimulates Caspase-1 Activity and Th1-Cytokine Release in Peripheral Blood Mononuclear Cells. *Atherosclerosis*. 2000; 153: 303-313.
 44. Takahashi HK, Mori S, Weitz-Schmidt G, Iwagaki H, Yoshino T, Tanaka N, Nishibori M. Differential Effect of LFA703, Pravastatin, and Fluvastatin on Production of IL-18 and Expression of ICAM-1 and CD40 in Human Monocytes. *Journal of Leukocyte Biology*. 2005; 77: 400-407.
 45. Takahashi HK, Mori S, Iwagaki H, Yoshino T, Tanaka N, Nishibori M. Simvastatin Induces Interleukin-18 Production in Human Peripheral Blood Mononuclear Cells. *Clin. Immunol*. 2005; 116: 211-216.
 46. Xu JF, et al. Statins and Pulmonary Fibrosis: The Potential Role of NLRP3 Inflammasome Activation. *Am J Respir Crit Care Med*. 2012; 185(5): 547-556.
 47. Fujioka Y, Fukuda A, Ishida T, Kagimoto S, Nakamura Y, Iwakura A, et al. Pitavastatin Reduces Elevated IL-18 Levels in Japanese Subjects with Hypercholesterolemia: Sub-Analysis of Kansai Investigation of Statin for Hyperlipidemic Intervention in Metabolism and Endocrinology (KISHIMEN). *J Atheroscler Thromb*. 2011; 18(1): 8-15.
 48. Rogers AJ, et al. Association of Elevated Plasma Interleukin-18 Level with Increased Mortality in A Clinical Trial of Statin Treatment for Acute Respiratory Distress Syndrome. *Crit Care Med*. 2019; 47(8): 1089-1096.

49. Chandrasekar B, Mummidi S, Mahimainathan L, et al. Interleukin-18-Induced Human Coronary Artery Smooth Muscle Cell Migration is Dependent on NF-kappaB- and AP-1-Mediated Matrix Metalloproteinase-9 Expression and is Inhibited by Atorvastatin. *J Biol Chem*. 2006; 281(22): 15099-15109.
50. Jougasaki M, Ichiki T, Takenoshita Y, Setoguchi M. Statins Suppress Interleukin-6-Induced Monocyte Chemo-Attractant Protein-1 by Inhibiting Janus Kinase/Signal Transducers and Activators of Transcription Pathways in Human Vascular Endothelial Cells. *Br J Pharmacol*. 2010; 159(6): 1294-1303.
51. Karatzis S, Lekakis J, Papamichael C, Andreadou I, Cimponerlu A, Aznaouridis K, et al. Rapid Effect of Pravastatin on Endothelial Function and Lipid Peroxidation in Unstable Angina. *International Journal of Cardiology*. 2005; 101(1): 65-70.
52. Shibasaki M, Wang JG, Figueiredo JL, New SEP, Quillard T, Goettsch C, et al. Pitavastatin Reduces Inflammation in Atherosclerotic Plaques in Apolipoprotein E-Deficient Mice with Late Stage Renal Disease. *PLoS One*. 2015; 10(9): 1-17.
53. Aoki I, Aoki N, Kawano K, et al. Platelet-Dependent Thrombin Generation in Patients with Hyperlipidemia. *J Am Coll Cardiol*. 1997; 30(1): 91-96.
54. Laufs U, Gertz K, Huang P, et al. Atorvastatin Upregulates Type III Nitric Oxide Synthase in Thrombocytes, Decreases Platelet Activation, and Protects from Cerebral Ischemia in Normocholesterolemic Mice. *Stroke*. 2000; 31(10): 2442-2449.
55. Pignatelli P, Carnevale R, Pastori D, et al. Immediate Antioxidant and Antiplatelet Effect of Atorvastatin via Inhibition of Nox2. *Circulation*. 2012; 126(1): 92-103.
56. Haramaki N, Ikeda H, Takenaka K, et al. Fluvastatin Alters Platelet Aggregability in Patients with Hypercholesterolemia: Possible Improvement of Intraplatelet Redox Imbalance via HMG-CoA Reductase. *Arterioscler Thromb Vasc Biol*. 2007; 27(6): 1471-1477.
57. Armstrong PC, Truss NJ, Ali FY, Dhanji AA, Vojnovic I, Zain ZN, et al. Aspirin and The In Vitro Linear Relationship between Thromboxane A(2) Mediated Platelet Aggregation and Platelet Production of Thromboxane A(2). *J Thromb Haemost*. 2008; 6: 1933-1943.
58. Chou TC, Lin YF, Wu WC, Chu KM. Enhanced Nitric Oxide and Cyclic GMP Formation Plays A Role in The Anti-platelet Activity of Simvastatin. *Br J Pharmacol*. 2008; 153: 1281-1287.
59. Ali FY, Armstrong PC, Dhanji AR, et al. Antiplatelet Actions of Statins and Fibrates are Mediated by PPARs. *Arterioscler Thromb Vasc Biol*. 2009; 29(5): 706-711.
60. Glynn RJ, Danielson E, Fonseca FA, et al. A Randomized Trial of Rosuvastatin in The Prevention of Venous Thromboembolism. *N Engl J Med*. 2009; 360(18): 1851-1861.
61. Shuhaili MF, Samsudin, IN, Stanslas J, Hasan S, Thambiah SC. Effects of Different Types of Statins on Lipid Profile: A Perspective on Asians. *International Journal of Endocrinology Metabolism*. 2017; 15(2): 1-9.
62. Greenwood J, Steinman L, Zamvil SS. Statin Therapy and Autoimmune Disease: From Protein Prenylation to Immunomodulation. *Nature Reviews Immunology*. 2006; 6: 358-370.
63. Gazzero P, Proto MC, Gangemi G, Malfitano AM, Ciaglia E, Pisanti S, et al. Pharmacological Actions of Statins: A Critical Appraisal in The Management of Cancer. *Pharmacological Reviews*. 2012; 64: 102-146.
64. Tiwari V, and Khokhar M. Mechanism of Action of Anti-Hypercholesterolemia Drugs and Their Resistance. *European Journal of Pharmacology*. 2014; 741: 156-170.
65. Whalen K, Finkel R, Panavelil TA. Editors. *Illustrated Reviews: Pharmacology*. Philadelphia: Wolters Kluwer. 2015; 6th Ed: pp. 314-315.
66. Whittlesea C. and Hodson K. Editors. *Clinical Pharmacy and Therapeutics*. China: Elsevier. 2019; 6th Ed: pp. 56-59.
67. Goard CA, Mather RG, Vinepal B, Clendening JW, Martirosyan A, Boutros PC, et al. Differential Interactions between Statins and P-glycoprotein: Implications for Exploiting Statins as Anticancer Agents. *International Journal of Cancer*. 2010; 127: 2936-2948.
68. Niemi M. Transporter Pharmacogenetics and Statin Toxicity. *Clinical Pharmacology and Therapeutics*. 2010; 87: 130-133.
69. Ramkumar S, Raghunath A, Raghunath S. Statin Therapy: Review of Safety and Potential Side Effects. *Acta Cardiologica Sinica*. 2016; 32: 631-639.
70. Vuorio A, Kuoppala J, Kovanen PT, Humphries SE, Tonstad S, Wiegman A, et al. Statins for Children with Familial Hypercholesterolemia. *Cochrane Database of Systematic Reviews*. 2014; 7: CD006401.
71. Eiland LS, and Luttrell PK. Use of Statins for Dyslipidemia in The Pediatric Population. *Journal of Pediatric Pharmacology Therapeutics*. 2010; 15: 160-172.
72. Couture P, Brun LD, Szots F, Lelievre M, Gaudet D, Despres JP, Gagne C. Association of Specific LDL Receptor Gene Mutations with Differential Plasma Lipoprotein Response to Simvastatin in Young French Canadians with Heterozygous Familial Hypercholesterolemia. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 1998; 18: 1007-1012.
73. Stefanutti C, Lucani G, Vivenzio A, Di Gia-come S. Diet Only and Diet plus Simvastatin in The Treatment of Heterozygous Familial Hypercholesterolemia in Childhood. *Drugs under Experimental Clinical Research*. 1999; 25(1): 23-28.
74. de Jongh S, Ose L, Szamosi T, et al. Efficacy and Safety of Statin Therapy in Children with Familial Hypercholesterolemia: A Randomized, Double-blind, Placebo-Controlled Trial with Simvastatin. *Circulation*. 2002; 106(17): 2231-2237.

75. de Jongh S, Lilien MR, Op't Roodt J, et al. Early Statin Therapy Restores Endothelial Function in Children with Familial Hypercholesterolemia. *Journal of The American College of Cardiology*. 2002; 40(12): 2117-2121.
76. Dirisamer A, Hachemian N, Bucek RA, et al. The Effect of Low-Dose Simvastatin in Children with Familial Hypercholesterolaemia: A 1-Year Observation. *European Journal of Pediatrics*. 2003; 162(6): 421-425.
77. Ferreira WP, Bertolami MC, Santos SN, et al. One-Month Therapy with Simvastatin Restores Endothelial Function in Hypercholesterolemic Children and Adolescents. *Pediatric Cardiology*. 2007; 28(1): 8-13.
78. Garcia-de-la-Puente S, Arredondo-Garcia JL, Gutierrez-Castrellon P, et al. Efficacy of Simvastatin in Children with Hyperlipidemia Secondary to Kidney Disorders. *Pediatric Nephrology*. 2009; 24(6): 1205-1210.
79. Lambert M, Lupien PJ, Gagne C, et al. Treatment of Familial Hypercholesterolemia in Children and Adolescents: Effect of Lovastatin. *Canadian Lovastatin in Children Study Group. Pediatrics*. 1996; 97(5): 619-628.
80. Stein EA, Illingworth DR, Kwiterovich PO Jr, et al. Efficacy and Safety of Lovastatin in Adolescent Males with Heterozygous Familial Hypercholesterolemia: A Randomized Controlled Trial. *JAMA*. 1999; 281(2): 137-144.
81. Clauss SB, Holmes KW, Hopkins P, et al. Efficacy and Safety of Lovastatin Therapy in Adolescent Girls with heterozygous familial Hypercholesterolemia. *Pediatrics*. 2005; 116(3): 682-688.
82. Knipscheer HC, Boelen CC, Kastelein JJ, et al. Short-term Efficacy and Safety of Pravastatin in 72 Children with Familial Hypercholesterolemia. *Pediatric Research*. 1996; 39(5): 867-871.
83. Hedman M, Neuvonen PJ, Neuvonen M, Antikainen M. Pharmacokinetics and Pharmacodynamics of Pravastatin in Children with Familial Hypercholesterolemia. *Clinical Pharmacology and Therapeutics*. 2003; 74(2): 178-185.
84. Hedman M, Neuvonen PJ, Neuvonen M, et al. Pharmacokinetics and Pharmacodynamics of pravastatin in Pediatric and Adolescent Cardiac Transplant Recipients on A Regimen of Triple Immunosuppression. *Clinical Pharmacology and Therapeutics*. 2004; 75(1): 101-109.
85. Wiegman A, Hutten BA, de Groot E, et al. Efficacy and Safety of Statin Therapy in Children with Familial Hypercholesterolemia: A Randomized Controlled Trial. *JAMA*. 2004; 292(3): 331-337.
86. Hedman M, Matikainen T, Fohr A, et al. Efficacy and Safety of Pravastatin in Children and Adolescents with Heterozygous Familial Hypercholesterolemia: A Prospective Clinical Follow-up Study. *The Journal of Clinical Endocrinology and Metabolism*. 2005; 90(4): 1942-1952.
87. Hedman M, Antikainen M, Holmberg C, et al. Pharmacokinetics and Response to Pravastatin in Paediatric Patients with Familial Hypercholesterolaemia and in Paediatric Cardiac Transplant Recipients in Relation to Polymorphisms of The SLCO1B1 and ABCB1 Genes. *British Journal of Clinical Pharmacology*. 2006; 61(6): 706-715.
88. Luirink IK, Wiegman A, Kusters DM, Hof MH, Groothoff JW, de Groot E, et al. 20-year Follow-up of Statins in Children with Familial Hypercholesterolemia. *The New England Journal of Medicine*. 2019; 381: 1547-1556.
89. Van der Graaf A, Nierman MC, Firth JC, et al. Efficacy and Safety of Fluvastatin in Children and Adolescents with Heterozygous Familial Hypercholesterolaemia. *Acta Paediatrica*. 2006; 95(11): 1461-1466.
90. Braamskamp MJ, Stefanutti C, Langslet G, et al. Efficacy and Safety of Pitavastatin in Children and Adolescents at High Future Cardiovascular Risk. *The Journal of Pediatrics*. 2015; 167(2): 338-343.
91. McCrindle BW, Ose L, Marais AD. Efficacy and Safety of Atorvastatin in Children and Adolescents with Familial Hypercholesterolemia or Severe Hyperlipidemia: A Multicenter, Randomized, Placebo-Controlled Trial. *The Journal of Pediatrics*. 2003; 143(1): 74-80.
92. Argent E, Kainer G, Aitken M, et al. Atorvastatin Treatment for Hyperlipidemia in Pediatric Renal Transplant Recipients. *Pediatric Transplantation*. 2003; 7(1): 38-42.
93. Gandelman K, Glue P, Laskey R, et al. An Eight-Week Trial Investigating the Efficacy and Tolerability of Atorvastatin for Children and Adolescents with Heterozygous Familial Hypercholesterolemia. *Pediatric Cardiology*. 2011; 32(4): 433-441.
94. Langslet G, Breazna A, Drogari W. A 3-Year Study of Atorvastatin in Children and Adolescents with Heterozygous Familial Hypercholesterolemia. *Journal of Clinical Lipidology*. 2016; 10: 1153-1162.
95. Marais AD, Raal FJ, Stein EA, et al. A Dose-Titration and Comparative Study of Rosuvastatin and Atorvastatin in Patients with Homozygous Familial Hypercholesterolaemia. *Atherosclerosis*. 2008; 197(1): 400-406.
96. Avis HJ, Hutten BA, Gagne C, et al. Efficacy and Safety of Rosuvastatin Therapy for Children with Familial Hypercholesterolemia. *Journal of The American College of Cardiology*. 2010; 55(11): 1121-1126.
97. Stein EA, Dann EJ, Wiegman A, Skovby F, Gaudet D, Sokal E, et al. Efficacy of Rosuvastatin in Children with Homozygous Familial Hypercholesterolemia and Association with Underlying Genetic Mutations. *Journal of The American College of Cardiology*. 2017; 70: 1162-1170.

98. Belay B, Belamarich PF, Tom-Revson C. The Use of Statins in Pediatrics: Knowledge Base, Limitations, and Future Directions. *Pediatrics*. 2007; 119(2): 370-380.
99. Wagner J, and Leeder JS. Pediatric Pharmacogenomics: A Systematic Assessment of Ontogeny and Genetic Variation to Guide The Design of Statin Studies in Children. *Pediatric Clinics of North America*. 2012; 59(5): 1017–1037.
100. Zachariah JP, and Johnson PK. Pediatric Lipid Management: An Earlier Approach. *Endocrinology and Metabolism Clinics of North America*. 2014; 43(4): 981–992.
101. Gidding SS, Champagne MA, de Ferranti SD, et al. The Agenda for Familial Hypercholesterolemia: A Scientific Statement from The American Heart Association. *Circulation*. 2015; 132(22): 2167–2192.
102. Abulaiti, A., Aini, R., Xu, H., Song, Z. A special case of Wellens' syndrome (2013) *Journal of Cardiovascular Disease Research*, 4 (1), pp. 51-54. DOI: 10.1016/j.jcdr.2013.02.016