Published in WWW.ENDOTEXT.ORG © 2016

USE OF LIPID LOWERING MEDICATIONS IN YOUTH

Melissa L Miller, PharmD. Pharmacy Clinical Manager; Presbyterian/St. Luke's Medical Center and Rocky Mountain Hospital for Children at P/SL, Denver, CO 80218
Chanin C Wright, PharmD. Director of Pharmacy; McLane Children's Hospital, Baylor Scott & White Health, Temple, TX 76502
Barry Browne, PharmD. Retired

Received 5 June 2016

ABSTRACT

The treatment of youth with lipid lowering medications presents some unique challenges and consideration. As demonstrated by the 2011 NHLBI's guidelines, available information regarding the treatment of youth with lipid disorders has greatly expanded. HMG-CoA reductase inhibitors, or statins, are now considered first-line pharmacologic treatment for children and adolescents with severe dyslipidemia who fail treatment with diet and exercise alone, although statins are only FDA approved for youth with familial hypercholesterolemia. Despite their ability to effectively reduced cholesterol levels, use of bile acid sequestrants continue to pose challenges for pediatric patients due to their unpalatability and are typically utilized as adjunctive therapy or for patients not able to tolerate statins. Fibric acid derivatives, as a class of medications, not only lack an FDA approved agent, but also continue to lack significant pediatric safety and efficacy data. Niacin lacks FDA approval for pediatric patients and is plagued by significant adverse effects, making it an unlikely therapeutic option for youth. Ezetimibe provides clinicians with an alternative adjunct therapy option when synergistically paired with an HMG-CoA reductase inhibitor or used as monotherapy for patients intolerant to statins and bile acid sequestrants. Despite several marketed formulations, omega-3 fish oils currently lack FDA approval in pediatric patients and have failed to demonstrate statistically significant lipid lowering in pediatric and adolescent patients. Finally, PCSK9 inhibitors present an emerging adjunctive treatment option with more studies in the pediatric and adolescent population expected. Regular monitoring for adverse events and side effects of therapy is essential as youth will have a greater lifetime exposure compared to adults and long-term data is generally limited. For complete coverage of all related aeas of Endocrinology, please visit our on-line FREE web-text, WWW.ENDOTEXT.ORG.

INTRODUCTION

The diagnosis, treatment, and monitoring of dyslipidemia in youth has undergone significant transformations in recent years. As detailed by the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) and Bogalusa Heart studies, dyslipidemia plays a vital role in both the initiation, as well as the progression of atherosclerotic lesions in children and adolescents.(1-3) Because of their causative role in arterial disease progression of elevated apolipoprotein B containing lipoproteins, their control in various dyslipidemias provides clinicians with a targetable venue for potentially reducing morbidity and mortality. Observational data from individuals with genetic mutations that lower atherogenic cholesterol, low-density lipoprotein cholesterol (LDL-C) and non-high-density lipoprotein cholesterol (non-HDL-C), over a lifetime are associated with fewer events and longer life expectancy.(4,5) While these observations are very encouraging, it is not known if achieving the same level of lipid lowering with medications over decades will offer the same protective effects as observed in individuals with life-long lower cholesterol secondary to a genetic mutation.(6)

The first comprehensive pediatric dyslipidemia guidelines were published by the National Cholesterol Education Program's Expert Panel on Blood Cholesterol Levels in Children and Adolescents in 1992 and were updated by the American Academy of Pediatrics (AAP) in 1998.(7,8) In 2008 the AAP issued an updated clinical report detailing recommendations for screening and evaluation of cholesterol levels in children and adolescents as well as prevention and treatment strategies.(9) Following the publication of the first guidelines, the prevalence of obesity has significantly increased, producing an increasing and altered landscape of pediatric patients with dyslipidemias.(10) Recently, options for pharmacotherapeutic interventions in pediatric patients have expanded with new FDA approved indications of several lipid lowering medications, as well as additional safety and efficacy data.(11) In 2011, The National Heart Lung and Blood Institute (NHLBI) published its comprehensive report Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents.(12) As with previous guidelines, lifestyle modifications with an emphasis on a heart-healthy diet and daily moderate to vigorous exercise remain an integral part of treatment for pediatric lipid disorders; however, the recommendations for patients requiring management with pharmacotherapy have changed, and will be the focus of this discussion. Table 1 provides a comparison across the evolution of guideline recommendations for the initiation of pharmacologic intervention with the goal of balancing risk and benefit.(7,8,9,12) Table 2 details the risk factors and risk conditions described in the NHLBI guidelines.(12)

Table 1: Comparison of Recommendations for Treatment

Guidelines	**NCEP, AAP – 1992 & 1998** [7,8]	**AAP – 2008** [9]	**NHLBI, AAP – 2011** [12]
Pharmacologic Treatment Initiation	• Age > 10 years with LDL-C o ≥ 190 mg/dL	• Age ≥ 8 years with LDL-C o ≥ 190 mg/dL	• Ages 10-21 years with LDL-C o ≥ 190 mg/dL

Parameters* *After an adequate trial of diet and lifestyle management.	o > 160 mg/dL in addition to a positive family history of premature CVD or presence of at least 2 CVD risk factors in the child/adolescent	o ≥ 160 mg/dL in addition to a positive family history of premature CVD or presence of risk factors o ≥ 130 mg/dL in addition to presence of diabetes mellitus • Age < 8 years with LDL-C: o ≥ 500 mg/dL	o 160-189 mg/dL in addition to a positive family history of premature CVD or presence of 1 high level risk factor/condition or presence of 2 moderate level risk factors/conditions o 130-159 mg/dL in addition to the presence of 2 high level risk factors/conditions or 1 high level and at least 2 moderate level risk factors/conditions • Age < 10 years with severe hyperlipidemia or high-risk conditions associated with serious morbidity • Ages 8-9 years with LDL-C levels consistently ≥ 190 mg/dL in addition to a positive family history OR presence of risk factors
Pharmacologic Medication Recommendations	• Bile acid sequestrants	• Bile acid sequestrants • Cholesterol absorption inhibitors • Statins	• Statins

Table 2: NHLBI Risk Factors and Risk Conditions[12]

NHLBI,AAP 2011 Guidelines: Risk Factors and Risk Conditions	
High Level Risk Factors	• Hypertension requiring drug therapy • Tobacco use • BMI ≥ 97th percentile • High risk conditions
Moderate Level Risk Factors	• Hypertension not requiring drug therapy • BMI ≥ 95th percentile, < 97th percentile • HDL < 40 mg/dL • Moderate risk conditions
High Risk Conditions	• T1DM and T2DM • CKD, ESRD, post-renal transplant • Post-orthotopic heart transplant • Kawasaki disease with current aneurysms
Moderate Risk Conditions	• Kawasaki disease with regressed aneurysms • Chronic inflammatory disease • HIV infection • Nephrotic syndrome

PHARMACOTHERAPEUTIC TREATMENT IN YOUTH

The treatment of youth with lipid lowering medications presents some unique challenges and consideration. As patients progress into adolescence it is particularly important for the patient to understand not only the need for their lipid lowering therapies, but also the consequences of non-compliance. Counseling regarding pharmacotherapy should begin at an early age with developmentally appropriate explanations and expand as patients mature. During adolescence counseling that addresses how to integrate therapy into the patient's social norms is important for achieving compliance to both pharmacotherapy as well as lifestyle modifications. It is also critical to continually readdress the correct use of medications as patients are likely to be on multiple therapies and adolescents will begin some their own medication management as they mature. Regular monitoring for adverse events and side effects of therapy is essential as youth will have a greater lifetime exposure compared to adults and long-term data is generally limited. As with all pharmacotherapy careful consideration should be given to potential drug interactions including those that may increase lipid levels. It is not uncommon for adolescent patients to be prescribed medications which have the potential to negatively impact lipid levels such as systemic steroids or oral contraceptive pills. Each patient case must be evaluated on an individual basis to determine the risks and benefits of prescribing medications which negatively alter lipid levels for patients also utilizing lipid lowering therapies. It should be noted there is significant risk for adolescent females should they become pregnant while taking lipid lowering medications as most have demonstrated a negative impact on fetal development. Adolescent females should be counselled regarding pregnancy and methods of contraception should be discussed. The US Medical Eligibility Criteria for Contraceptive Use compiled by the CDC details several contraceptive options where the benefits generally outweigh any theoretical or proven risk for patients with hyperlipidemias.(13) Despite several expanded FDA approvals for

the use of lipid lowering medications by youth, off-label medication use remains a reality in the treatment of youth dyslipidemia and has the potential to impact cost. The cost of therapy can significantly impact compliance and should be factored into therapy decisions especially as youth transition into adulthood and may be faced with changes in insurance coverage.

HMG-CoA REDUCTASE INHIBITORS

HMG-CoA reductase inhibitors, or statins, are recommended as first line treatment of youth with severe dyslipidemia who fail non-pharmacologic interventions such as diet and lifestyle modification.(11-15) Statins first debuted in clinical practice in 1987 with the FDA's approval of lovastatin. At present, there are six HMG-CoA reductase inhibitors with FDA approval for youth with heterozygous familial hypercholesterolemia (8 years and older for pravastatin, all others 10 years of age and older).(16-21) Table 3 provides a summary of HMG-CoA reductase inhibitors, pediatric approval and indications, recommended dosing ranges, comments on dosing, and supporting clinical trials.

Table 3: HMG-CoA Reductase Inhibitors[16-21, 45]

Medication	Pediatric Approvals & Indications	Dosing	Comments	Supporting Clinical Trials
Atorvastatin	Age 10-17 Heterozygous familial hypercholesterolemia	10-20 mg/day	May be titrated at ≥ 4 week intervals	McCrindle, et al[23]
Fluvastatin	Age 10-16 Heterozygous familial hypercholesterolemia	20-80 mg/day	May be titrated at ≥ 6 week intervals	van der Graaf, et al[24]
Lovastatin	Age 10-17 Heterozygous familial hypercholesterolemia	10-40 mg/day	Initiated at 20 mg/day for ≥20% LDL reduction, may be titrated at ≥ 4 week intervals	Clauss, et al[25] Lambert, et al[26] Stein, et al[27]
Pravastatin	Age 8-18 Heterozygous familial hypercholesterolemia	20-40 mg/day	Age 8-13: 20 mg/day Age 14-18: 40 mg/day	Knipscheer, et al[28] Rodenburg, et al[29] Wiegman, et al[30]
Rosuvastatin	Age 10-17 Heterozygous familial hypercholesterolemia	5-20 mg/day	May be titrated at ≥ 4 week intervals	Avis, et al[31]
Simvastatin	Age 10-17 Heterozygous familial hypercholesterolemia	10-40 mg/day	May be titrated at ≥ 4 week intervals	de Jongh, et al[32] de Jongh, et al[33]

The above are approved as an adjunct to a diet that is low in cholesterol and saturated fat. The above agents are approved for both males and females (females must be at

least one year post-menarche) if, despite an adequate diet and other non-pharmacologic measures, the following are present:
LDL-C ≥ 190 mg/dL or
LDL-C ≥ 160 mg/dL and the patient has a family history of premature cardiovascular disease or two or more cardiovascular disease risk factors
Abbreviations: mg=milligrams, LDL=low density lipoprotein

As Table 4 outlines, statin therapies have demonstrated variable efficacy involving clinical trials of youth.(22-33) With the longest half-life, rosuvastatin is the most potent statin, followed by atorvastatin.(34) Simvastatin is a moderately potent statin at clinically tolerable maximum doses of 40 mg/day.(34-36) Lovastatin, pravastatin, and fluvastatin, respectively, are the least potent statins.(35,36) As many studies have demonstrated, reduced potency can be compensated for by an increase in the amount of statin given; however, dose escalation is often associated with an increased occurrence of adverse events.(23-36) As a result, selection of a specific statin therapy should be individualized and capable of reaching treatment goals. Equally important, consideration should be given to the prevalence and severity of reported side effects.
Although long term studies evaluating the safety and efficacy of lipid-lowering medications in youth are lacking, results of short term observational and randomized controlled trials are encouraging. For example, atorvastatin was found to be well tolerated with no statistically significant differences in adverse events reported for either the treatment or placebo groups.(23) Additionally, the percentage of patients with abnormal laboratory results was similar for both groups; the only noted difference was an increased percentage of patients with elevated triglycerides in the placebo group. Treatment with atorvastatin resulted in no significant difference in sexual development as assessed by Tanner staging.

Table 4: Statin Therapy Results

Study	Medication	Dose	Results			
			LDL-C	HDL-C	TC	TG
McCrindle, et al[23]	Atorvastatin	10-20 mg/day	-40%	+6%	-30%	-13%
van der Graaf, et al[24]	Fluvastatin	80 mg/day	-34%	+5%	-27%	-5%
Clauss, et al[25]	Lovastatin	40 mg/day	-27%	+3%	-22%	-23%
Lambert, et al[26]	Lovastatin	10 mg/day	-21%	+9%	-17%	-18%
Lambert, et al[26]	Lovastatin	20 mg/day	-24%	+2%	-19%	+9%
Lambert, et al[26]	Lovastatin	30 mg/day	-27%	+11%	-21%	+3%
Lambert, et al[26]	Lovastatin	40 mg/day	-36%	+3%	-29%	-9%
Stein, et al[27]	Lovastatin	10 mg/day	-17%	+4%	-13%	+4%
Stein, et al[27]	Lovastatin	20 mg/day	-24%	+4%	-19%	+8%
Stein, et al[27]	Lovastatin	40 mg/day	-27%	+5%	-21%	+6%
Knipscheer, et al[28]	Pravastatin	5 mg/day	-23%	+4%	-18%	+2%
Knipscheer, et	Pravastatin	10 mg/day	-24%	+6%	-17%	+7%

al[28]						
Knipscheer, et al[28]	Pravastatin	20 mg/day	-33%	+11%	-25%	+3%
Rodenburg, et al[29]	Pravastatin	20 mg/day or 40 mg/day	-29%	+3%	-23%	-2%
Wiegman, et al[30]	Pravastatin	20-40 mg/day	-24%	+6%	-19%	-17%
Avis, et al[31]	Rosuvastatin	5 mg/day	-38%	+4%	-30%	-13%
Avis, et al[31]	Rosuvastatin	10 mg/day	-45%	+10%	-34%	-15%
Avis, et al[31]	Rosuvastatin	20 mg/day	-50%	+9%	-39%	-16%
de Jongh, et al[32]	Simvastatin	10-40 mg/day	-41%	+3%	-31%	-9%
de Jongh, et al[33]	Simvastatin	40 mg/day	-40%	+5%	-30%	-17%

Adapted from National Heart Lung and Blood Institute (NHLBI): Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: Summary Report. Pediatrics 2011;128(S5):S213-S256: Table 9-11.
Abbreviations: mg=milligrams, LDL-C=low density lipoprotein cholesterol, HDL-C=high density lipoprotein cholesterol, TC=total cholesterol, TG=triglycerides

Van der Graaf and colleagues found that in youth treated with fluvastatin, 58 (68.2%) reported non-serious adverse events and only four were believed to be drug related.(24) Treatment with fluvastatin resulted in no abnormalities in hormone levels or sexual maturation.

In their study of lovastatin, Clauss and colleagues reported no clinically significant alterations in vital signs; growth; hormone levels including luteinizing hormone, follicle-stimulating hormone, dehydroepiandosterone sulfate, estradiol, and cortisol; menstrual cycle length; liver function tests; or muscle function tests.(25) Lambert and colleagues also found lovastatin generally well tolerated with no serious clinical adverse effects noted.(26) While increased, levels of aspartate aminotransferase did not exceed two times the upper limit of normal and alanine aminotransferase did not display significant changes in study participants. Creatine kinase was elevated, greater than three times the upper limit of normal, in three patients. All subjects remained asymptomatic and the elevated creatine kinase levels resolved spontaneously while no adjustment was need in their medication. Assessment of growth and sexual maturation, by Tanner staging and estimation of testicular volumes, in youth treated with lovastatin found no significant differences between the treatment groups and placebo at either 24 or 48 weeks.(27) While the authors reported no significant change in serum hormone levels or biochemical parameters of nutrition, they noted that the study was under powered to detect statistically significant changes in these safety parameters.

Use of pravastatin has been shown to have minimal adverse events dispersed evenly between the active drug recipients and those who received placebo.(28) Plasma thyroid-stimulating hormone, adrenocorticotropic hormone, cortisol, creatine phosphokinase, alanine aminotransferase, aspartate aminotransferase, total bilirubin, and alkaline phosphatase levels

failed to show significant changes from baseline in all treatment groups. Rodenburg and colleagues also evaluated the safety of pravastatin based on annual or biannual evaluation of plasma creatine phosphokinase levels, liver enzymes, sex steroids, gonadotropins, and hormones of the pituitary-adrenal axis.(29) Height, weight, age at menarche, Tanner staging, and testicular volume were also recorded at baseline and either annually or biannually. Two subjects demonstrated elevated creatine phosphokinase levels which returned to normal without adjustments in therapy, and were presumed to be due to extreme physical exercise. No occurrence of myalgia was associated with elevation in levels of creatinine phosphokinase. None of the subjects discontinued therapy due to adverse events or laboratory abnormalities. Similarly, Wiegman and colleagues examined the safety of pravastatin evaluated at baseline, one year, and two years via multiple variables including: sex steroids, endocrine function parameters, height, weight, body surface area, Tanner staging, menarche or testicular volume, alanine aminotransferase, aspartate aminotransferase, and creatine phosphokinase.(30) All safety parameters demonstrated no statistically significant differences between active drug recipients verses placebo in changes from baseline.

The safety of rosuvastatin was assessed by Avis and colleagues.(31) Two serious adverse events were reported including blurred vision in one patient in the placebo group and a vesicular rash progressing to cellulitis in one patient taking rosuvastatin 20 mg. Transaminase levels either remained normal or normalized without permanent discontinuation of treatment. While elevations in creatine kinase and reports of myalgia did occur, symptoms and creatine kinase levels normalized without permanent discontinuation of therapy. Normal progression of height, weight, and sexual development were observed.

The safety of simvastatin during short term therapy has also been reported. Levels of alanine aminotransferase, aspartate aminotransferase, creatine kinase, and physical examination all demonstrated no significant differences between simvastatin treated and placebo participants.(32) de Jongh and colleagues evaluated the safety of simvastatin in a second trial by monitoring adverse events as well as changes in alanine aminotransferase, aspartate aminotransferase, and creatine kinase levels.(33) Of note, none of the differences reported in events or laboratory values between simvastatin recipients and placebo reached statistical significance. Additionally, there were no statistically significant differences documented for height, body mass index, cortisol levels, testicular size and testosterone levels, menstrual cycle and estradiol levels, and Tanner staging. Dehydroepiandrosterone sulfate levels demonstrated a statistically significant decrease in the simvastatin group compared to placebo.

Long-term data regarding the impact of statin therapy on growth, development, and reduction of cardiac risk are limited, particularly for high intensity statin therapy. Recently, Kusters and colleagues evaluated the safety of statin therapy in children and adolescents with familial hypercholesterolemia after 10 years of treatment comparing laboratory safety markers as well as growth and maturation in untreated siblings.(37) Only three patients discontinued therapy due to adverse events. Safety parameters such as aspartate aminotransferase, alanine aminotransferase, creatine kinase, estimated glomerular filtration rate, c-reactive protein, and age of menarche did not differ between treated patients and siblings, demonstrating safety over

the 10 year treatment period. The authors do note; however, that the study was underpowered to detect the occurrence of rare events.

When initiating HMG-CoA reductase inhibitor therapy, as with any new medication therapy, it is imperative for clinicians to establish an accurate baseline, monitor for new symptoms, and counsel both patients and family members regarding potential adverse events. Females should be informed about the need to avoid pregnancy and breastfeeding while using statins.(38) Statins may be taken with or without meals, but are commonly given with the evening meal or at bedtime as this has the potential to improve LDL-C reduction.(34) As a major substrate of P450, such as CYP3A4, there are multiple drug interactions associated with statin therapy. Grapefruit juice has gained considerable notoriety as a potential food interaction; however it should be noted that more than a quart of grapefruit juice would have to be consumed to increase serum statin levels. Of more concern is the interaction between niacin and statins, which should be avoided due to increased toxicity of HMG-CoA reductase inhibitors. Macrolides, a class of drugs commonly prescribed, should be avoided as they increase serum statin levels leading to potentially enhanced myopathic effects. Additionally, patients should avoid herbal products and nutraceuticals, such as red yeast rice, which may further enhance adverse effects.

BILE ACID SEQUESTRANTS

Bile acid sequestrants, or bile acid binding resins, present an additional treatment option for youth with severe dyslipidemia. Bile acid sequestrants represent one of the oldest classes of medications available to treat dyslipidemia and were the only medication recommended in the 1992 NCEP Pediatric Panel Report, at a time when no data were available for statin use in youth.(7) While no longer a recommended first-line therapy, bile acid sequestrants do have potential as a treatment option either alone or in combination with a statin.(12,14) At present, colesevelam is the only bile acid sequestrant with FDA approval for youth age 10 years and older with heterozygous familial hypercholesterolemia.(39,40) Despite the lack of FDA approval, both colestipol and cholestyramine have been studied in pediatric patients.(41-49)

A number of clinical trials have evaluated the bile acid sequestrants in pediatric patients with heterozygous familial hypercholesterolemia and other forms of severe dyslipidemia. While palatability and tolerance remain potential barriers to effective therapy, in general, bile acid sequestrants have demonstrated significant reductions in both total cholesterol and LDL-cholesterol in study subjects.(40,43,44,48,49) Table 5 provides a summary of bile acid sequestrants, pediatric approval and indications, recommended dosing ranges, comments on therapy, and supporting clinical trials. As outlined in Table 6, studies demonstrated some variability in efficacy for the available bile acid sequestrants.(40,43,44,48,49)

Table 5: Bile Acid Sequestrants[40-49]

Medication	Pediatric Approvals & Indications	Dosing	Comments	Clinical Trials

Colesevelam	Age 10-17 Heterozygous familial hypercholesterolemia	1.875 g twice daily or 3.75 g daily	May be used as monotherapy or in combination with a statin	Stein, et al[40]
Colestipol	(Note: Not FDA Approved) Age 7-12 Primary hypercholesterolemia	5 g twice daily, 10 g daily, or 125-500 mg/kg/day	N/A	McCrindle, et al[43] Tonstad, et al[44]
	(Note: Not FDA Approved) Age ≥12 Primary hypercholesterolemia	10-15 g/day	N/A	
Cholestyramine	(Note: Not FDA Approved) Age 6-12 Hypercholesterolemia adjunct	240 mg/kg/day divided three times daily before meals	Initiate at 2-4 g twice daily	McCrindle, et al[48] Tonstad, et al[49]
	(Note: Not FDA Approved) Age ≥12	8 g/day divided twice daily before meals	N/A	

Colesevelam is approved as an adjunct to a diet that is low in cholesterol and saturated fat. Colesevelam is approved for both males and females (females must be at least one year post-menarche) if, despite an adequate diet and other non-pharmacologic measures, the following are present:
LDL-C ≥ 190 mg/dL or
LDL-C ≥ 160 mg/dL and the patient has a family history of premature cardiovascular disease or two or more cardiovascular disease risk factors
Abbreviations: g=grams, mg=milligrams, kg=kilograms, N/A=not applicable

Table 6: Bile Acid Sequestrant Results

Study	Medication	Dose	Results			
			LDL-C	HDL-C	TC	TG
Stein, et al[40]	Colesevelam	1.875 g/day	-6%	+5%	-3%	+6%
Stein, et al[40]	Colesevelam	3.75 g/day	-13%	+8%	-7%	+5%
McCrindle, et al[43]	Colestipol	10 g/day	-10%	+2%	-7%	+12%
McCrindle, et al[43]	Colestipol & Pravastatin	Colestipol: 5 g/day Pravastatin: 10 mg/day	-17%	+4%	-13%	+8%

Tonstad, et al[44]	Colestipol	2-12 g/day	-20%	-7%	-17%	-13%
McCrindle, et al[48]	Cholestyramine	8 g/day	-10% to -15%	+2% to +4%	-7% to -11%	+6% to +9%
Tonstad, et al[49]	Cholestyramine	8 g/day	-17%	+8%	-12%	N/A

Adapted from National Heart Lung and Blood Institute (NHLBI): Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: Summary Report. *Pediatrics*. 2011;128(S5):S213-S256: Table 9-11.
Abbreviations: g=grams, LDL-C=low density lipoprotein cholesterol, HDL-C=high density lipoprotein cholesterol, TC=total cholesterol, TG=triglycerides

Stein and colleagues assessed the safety of colesevelam at weeks 8-26 during an open-label study.(40) All subjects received colesevelam 3.75 grams per day in addition to a previously prescribed statin. Safety was measured via adverse events, vital signs and physical exam, laboratory monitoring, and Tanner staging. The most common adverse events related to the use of colesevelam were gastrointestinal, including diarrhea, nausea, vomiting, and abdominal pain. It is important to note that no choking or difficulty swallowing were reported with the use of colesevelam. Vital signs, physical exams, laboratory monitoring, and Tanner staging remained the same or progressed as expected throughout the study period.

McCrindle et al evaluated conventional high-dose colestipol versus a combination of low-dose colestipol plus pravastatin, but did not cite safety as an endpoint for their study.(43) The researchers did conduct safety monitoring in the form of laboratory tests, physical evaluation, and adverse event reporting. Significant deviations from baseline were noted for alkaline phosphatase, alanine aminotransferase, and aspartate aminotransferase at various time intervals with different medication regimens; however, the authors noted that when compared to reference values, none of the laboratory results were considered abnormal. Study participants in the two medication regimens did not significantly vary in weight gain, height changes, or body mass index. While the majority of patients experienced no adverse events, gastrointestinal symptoms such as constipation, gas or bloating, or stomach ache were more commonly reported by the patients taking the high-dose colestipol. The authors found similar suboptimal compliance with both regimens as determined by medication counts at the end of each study period. Tonstad and colleagues also assessed the tolerability of colestipol granules by monitoring side effects as well as by having subjects complete subjective evaluations.(44) Side effects associated with colestipol included constipation, dyspepsia, flatulence, nausea, reduction in appetite, and abdominal pain. The subjective evaluations indicated that only 21% of patients liked the taste of the colestipol; however, of those who had previously taken bile acid binding resin, 86% preferred the taste of the newer orange flavored granules. Thirty seven percent of subjects also reported that they frequently forgot to take the medication, while 44% intentionally eliminated the medication from their routine on special occasions or during trips.

The acceptability and compliance of cholestyramine was evaluated by McCringle et al.(48) Ultimately, 82% of children preferred the pill formulation of cholestyramine compared to 16%

who preferred the powder. Two percent of children in the study preferred neither form of the medication. Compliance was significantly impacted by medication formulation with patients taking the pill form reporting 61% compliance while those on the powder formulation were only 50% compliant. Furthermore, the authors noted that compliance was increased by at least 25% for 42% of patients when they switched to the pill formulation. Tonstad and colleagues assessed the safety of cholestyramine by measuring height velocity, erythrocyte folate, total plasma homocysteine, serum fat-soluble vitamins, and side effects.(49) Ultimately, weight and mean height velocity standard deviation scores were not statistically significant between treatment and placebo groups during the study. The cholestyramine active treatment group demonstrated decreased vitamin D levels and increased homocysteine levels. Differences in erythrocyte folate were not significant between the active treatment and placebo groups. Reported adverse events included intestinal obstruction, abdominal pain, nausea, and loose stools. Unpalatability was a common reason participants withdrew from the study.

As demonstrated by the previous studies, bile acid sequestrants do present an effective therapy option. Their side effect profile, tolerability issues, and drug interactions with statins make their use clinically challenging. It is generally recommended that all concurrent medications be given either one hour before or four hours after bile acid sequestrants to prevent decreased absorption of the additional therapies.(41,46) Use of bile acid sequestrants is generally limited to patients optimized on statin therapy who require additional therapy to achieve goal or those that cannot tolerate statins. Data on long-term safety, however, are generally lacking.

FIBRIC ACID DERIVATIVES

Experience with fibric acid derivatives in youth is limited. Currently there are no fibric acid derivatives with FDA approval for use in pediatric patients. Both fenofibrate and gemfibrozil, summarized in Table 7, are available in the United Sates, but lack pediatric data on safety, efficacy, and dosing.(50, 51) While there is very limited information on the use of bezafibrate in youth, the product is not available in the United States.(52) Fenofibrate activates peroxisome proliferator activated receptor α to increase lipolysis and elimination of triglyceride-rich particles via lipoprotein lipase and reduction of apoprotein C-III.(50,51) Clinically, fibric acid derivatives have limited applications. They are no longer recommended for use as adjunct therapy in combination with statins.(53) It should be noted that fibric acid derivatives have the potential to increase the incidence in adverse events, such as rhabdomyolysis, when used with statins.(45,50,51,53)

Table 7: Fibric Acid Derivatives[45,50,51]

Medication	Pediatric Approvals & Indications	Dosing	Comments	Clinical Trials
Fenofibrate	(Note: Not FDA Approved) Pediatric safety and efficacy not established	N/A	N/A	N/A

Gemfibrozil	(Note: Not FDA Approved) Pediatric safety and efficacy not established	N/A	N/A	N/A

Abbreviations: N/A=not applicable, mg=milligrams

NIACIN

While once a potential adjunct therapeutic option for youth with severe dyslipidemia who had not achieved their lipid goal, niacin is no longer recommended for combination therapy with statins.(53) Despite a lack of FDA approval, limited efficacy and safety data are published for the use of niacin in children 10 years of age and older as adjunct therapy.(53) Table 8 summarizes data on recommended dosing ranges, comments on dose adjustments, and references supporting clinical trials.

Table 8: Niacin[45, 55]

Medication	Pediatric Approvals & Indications	Dosing	Comments	Clinical Trials
Niacin	(Note: Not FDA Approved) Age ≥ 10	Initial: 100-250 mg/day (Max: 10 mg/kg/day) divided three times daily with meals	May titrate weekly by 100 mg/day or every 2-3 weeks by 250 mg/day	Colletti, et al[55]

Abbreviations: mg=milligrams, kg=kilograms

Colletti and colleagues conducted a retrospective review to evaluate the efficacy and adverse effect profile of niacin for children with severe hypercholesterolemia.(55) The effects on serum lipid profiles are detailed in Table 9. Adverse effects were common, affecting 76% of children, and similar to those reported for adults including: flushing, abdominal pain, vomiting, headache, and elevated liver enzymes. Due to the high prevalence of adverse effects, use of niacin should be limited to patients not achieving goal with other therapies or those who cannot tolerate alternative options.

Table 9: Niacin

Study	Medication	Dose	Results			
			LDL-C	HDL-C	TC	TG
Colletti, et al[55]	Niacin	500-2,250 mg/day	-17%	+4%	-13%	+13%

Adapted from National Heart Lung and Blood Institute (NHLBI): Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: Summary Report. *Pediatrics*. 2011;128(S5):S213-S256: Table 9-11.

Abbreviations: mg=milligrams, LDL-C=low density lipoprotein cholesterol, HDL-C=high density lipoprotein cholesterol, TC=total cholesterol, TG=triglycerides

EZETIMIBE

Ezetimibe presents a potential therapy option either as monotherapy or when synergistically paired with an HMG-CoA reductase inhibitor.(56-58) At present, ezetimibe is FDA approved for youth 10 years of age and older with heterozygous familial hypercholesterolemia.(59) Ezetimibe targets cholesterol levels via inhibition of cholesterol absorption in the small intestines resulting in decreased hepatic cholesterol stores and increased blood clearance. Table 10 summarizes data on recommended dosing ranges and references supporting clinical trials whereas Table 11 details efficacy of therapy.

Table 10: Ezetimibe[59]

Medication	Pediatric Approvals & Indications	Dosing	Comments	Clinical Trials
Ezetimibe	Age ≥10 Heterozygous familial hypercholesterolemia	10 mg/day	N/A	Yeste, et al[56] Clauss, et al[57] van der Graaf, et al[58]

Abbreviations: mg=milligrams, N/A=not applicable

Table 11: Ezetimibe

Study	Medication	Dose	Results				
Yeste, et al[56]	Ezetimibe	10 mg/day	LDL-C		HDL-C	TC	TG
			PH	-42%	N/A	-31%	N/A
			FH	-30%	-15%	-26%	N/A
Clauss, et al[57]	Ezetimibe	10 mg/day	LDL-C		HDL-C	TC	TG
			FH	-28%	N/A	-22%	N/A
			FCHL		N/A	-13%	N/A
van der Graaf, et al[58]	Ezetimibe & Simvastatin	Ezetimibe: 10 mg/day Simvastatin: 10-40 mg/day	LDL-C		HDL-C	TC	TG
			-49%		+7%	-38%	-17%

Adapted from National Heart Lung and Blood Institute (NHLBI): Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: Summary Report. *Pediatrics*. 2011;128(S5):S213-S256: Table 9-11.
Abbreviations: mg=milligrams, LDL-C=low density lipoprotein cholesterol, HDL-C=high density lipoprotein cholesterol, TC=total cholesterol, TG=triglycerides, PH=polygenic hypercholesterolemia, FH=familial hypercholesterolemia, FCHL=familial combined hyperlipidemia, N/A=not applicable

Tolerability of ezetimibe was prospectively evaluated by Yeste and colleagues via a combination of biochemical markers and adverse event reports.(56) No change was seen in hemogram,

transaminases, creatinine, calcium, phosphorus, and vitamins A and E for any of the 17 patients. Additionally, there were no reports of adverse events during the study period. Clauss and colleagues retrospectively evaluated ezetimibe; therefore, safety parameters were less defined, but included intermittent measurement of liver enzymes, occasional CK levels, and adverse event reports.(57) There were no reported abnormalities in liver enzymes for study participants. Ultimately, one patient was discontinued from ezetimibe therapy for asymptomatic elevated CK levels, later determined to be likely unrelated to therapy.

Van der Graaf and colleagues assessed the safety of combination therapy with ezetimibe and simvastatin based on reported adverse events as well as laboratory monitoring and clinical examination.(58) After 53 weeks, 71% of study participants reported some types of treatment-emergent adverse events. Of those events reported, only influenza, nasopharyngitis, and headache occurred in greater than 5% of participants. Consecutive transaminase elevations of at least three times the upper limit of normal were reported in six participants; however, all values resolved with interruption or discontinuation of therapy. Elevations in creatine phosphokinase occurred infrequently and were not associated with myalgia at levels greater than three times the upper limit of normal. Height, weight, and sexual maturation were not significantly impacted by therapy. Ezetimibe affords flexibility in administration time with the ability to administer it without regard to meals or time of day.(45) Although fenofibrate may increase the risk of adverse effects and therapy should be monitored, gemfibrozil should be avoided due to the enhanced risk of myopathy and cholelithiasis with concurrent use. HMG-CoA reductase inhibitors have the risk of increasing myopathies and hepatic transaminases, but are generally considered a safe combination.

OMEGA-3 FISH OILS

Omega-3 fish oils are a class of therapy for which there is significantly limited data in youth. To date there are no FDA approved formulations of omega-3 fatty acid that include a pediatric indication. High dose omega-3 fatty acid supplementation was evaluated by de Ferranti et al, but ultimately the authors found no statistically significant improvement when subjects were compared to placebo.(60) Chahal and colleagues similarly found no significant impact on hypertriglyceridemia when treating pediatric patients with fish oil.(61)

PCSK9 INHIBITORS

PCSK9 inhibitors are a relatively new class of therapy that utilize monoclonal antibodies to target human proprotein convertase subtilisin kexin 9 (PCSK9). By binding to the PCSK9 the degradation of low density lipoprotein receptors (LDLR) is inhibited. The increase in LDLR allows for more LDL to be cleared from the blood and results in lower LDL-C levels.(62,63) Alirocumab is indicated as adjunct treatment for heterozygous familial hypercholesterolemia, but lacks a pediatric indication as well as safety and efficacy data.(62) Evolocumab is FDA approved for adolescent patients 13 years of age or older with homozygous familial hypercholesterolemia (HoFH) as adjunctive therapy.(63) Raal and colleagues evaluated evolocumab versus placebo as adjunct therapy to other lipid lowering regimens in adolescents

and adults with homozygous familial hypercholesterolemia.(64) Patients treated with evolocumab experienced a significant 30.9% reduction in LDL-cholesterol with no serious clinical adverse events and no anti-evolocumab antibody development. Treatment-emergent adverse events occurred at a higher rate with placebo (63%) than with evolocumab (36%). Evolocumab for HoFH is administered as a monthly subcutaneous injection which has the potential to negatively impact compliance in adolescent patients. Long-term safety and efficacy data is still being collected and additional trials of PCSK9 inhibitors in pediatric patients are in process.

CONCLUSION

As demonstrated by the 2011 NHLBI's guidelines, available information regarding the treatment of youth with lipid disorders has greatly expanded. HMG-CoA reductase inhibitors, or statins, are now considered first-line pharmacologic treatment for children and adolescents with severe dyslipidemia who fail treatment with diet and exercise alone, although statins are only FDA approved for youth with familial hypercholesterolemia. Despite their ability to effectively reduced cholesterol levels, use of bile acid sequestrants continue to pose challenges for pediatric patients due to their unpalatability and are typically utilized as adjunctive therapy or for patients not able to tolerate statins. Fibric acid derivatives, as a class of medications, not only lack an FDA approved agent, but also continue to lack significant pediatric safety and efficacy data. Niacin lacks FDA approval for pediatric patients and is plagued by significant adverse effects, making it an unlikely therapeutic option for youth. Ezetimibe provides clinicians with an alternative adjunct therapy option when synergistically paired with an HMG-CoA reductase inhibitor or used as monotherapy for patients intolerant to statins and bile acid sequestrants. Despite several marketed formulations, omega-3 fish oils currently lack FDA approval in pediatric patients and have failed to demonstrate statistically significant lipid lowering in pediatric and adolescent patients. Finally, PCSK9 inhibitors present an emerging adjunctive treatment option with more studies in the pediatric and adolescent population expected. In recent years, there has been a dramatic increase in data available on the use of lipid lowering medications for pediatric patients; however, long-term study data are still generally lacking and continues to present an active focus of research.

REFERENCES

1. McMahan CA, Gidding SS, Malcom GT, Tracy RE, Strong JP, McGill Jr HC. Pathobiological determinants of atherosclerosis in youth risk scores are as with early and advanced atherosclerosis. (PDAY) Pediatrics 2006; 118(4): 1447-1455.
2. Newman III WP, Freedman DS, Voors AW, et al. Relation of serum lipoprotein levels and systolic blood pressure to early atherosclerosis. (The Bogalusa Heart Study). N Engl J Med 1986; 314(3):138-44.
3. Berenson GS, Srinivasan SR, Bao W, Newman III WP, Tracy RE, Wattigney WA. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. (The Bogalusa Heart Study). N Engl J Med 1998; 338(23):1650-1656.

4. Cohen JC, Boerwinkle E, Mosley TH, Hobbs HH. Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. N Engl J Med 2006; 354:1264-1272.
5. Kathiresan S, Melander O, Anevski D, et al. Polymorphisms associated with cholesterol and risk of cardiovascular events. N Engl J Med 2008; 358(12):1240-1249.
6. Ference BA, Yoo W, Alesh I, et al. Effect of long-term exposure to lower low-density lipoprotein cholesterol beginning early in life on the risk of coronary heart disease: a Mendelian randomization analysis. J Am Coll Cardiol 2012; 60(25):2631-2639.
7. National Cholesterol Education Program (NCEP): Highlights of the Report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents. Pediatrics 1992; 89:495-501.
8. American Academy of Pediatrics. Committee on Nutrition. Cholesterol in childhood. Pediatrics 1998; 101 (1 Pt 1): 141-7.
9. Daniels SR, Greer FR. Lipid Screening and cardiovascular health in childhood. Pediatrics 2008; 122:198-208.
10. National Center for Chronic Disease Prevention and Health Promotion, Division of Adolescent and School Health. Youth Risk Behavior Sheet(YRBS): National Trends, 1991-2009: Obesity, Dietary Behaviors, and Weight Control Practices. http://www.cdc.gov/healthyyouth/yrbs/pdf/us_obesity_trend_yrbs.pdf. Updated October 5, 2011. Accessed December 2011.
11. McCrindle BW, Urbina EM, Dennison BA, Jacobson MS, Steinberger J, Rocchini AP, Hayman LL, Daniels SR. American Heart Association scientific statement: drug therapy of high-risk lipid abnormalities in children and adolescents. Circulation 2007; 115:1948-67.
12. National Heart Lung and Blood Institute (NHLBI): Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: Summary Report. Pediatrics 2011; 128(S5):S213-S256.
13. CDC-US Medical Eligibility Criteria for Contraceptive Use. MMWR. 2010;59(RR04):1-85.
14. Kavey RW, Allada V, Daniels SR, Hayman LL, McCrindle BW, Newburger JW, Parekh RS, Steinberger J. American Heart Association scientific statement: cardiovascular risk reduction in high-risk pediatric patients. Circulation 2006; 114:2710-38.
15. Sibley C, Stone NJ. Familial hypercholesterolemia: a challenge of diagnosis and therapy. Cleve Clin J Med 2006; 73:57-64.
16. Atorvastatin product monograph. Pfizer. New York, NY. 2007.
17. Fluvastatin product monograph. Novartis. East Hanover, NJ. 2006.
18. Lovastatin product monograph. Merck & Co. Whitehouse Station, NJ. 2007.
19. Pravastatin product monograph. Bristol-Myers Squibb Company. Princeton, NJ. 2007.
20. Rosuvastatin product monograph. AstraZeneca. Wilmington, DE. 2011.
21. Simvastatin product monograph. Merck & Co. Whitehouse Station, NJ. 2006.
22. Haney EM, Huffman LH, Bougatsos C, Freeman M, Steiner RD, Nelson HD. Screening and treatment for lipid disorders in children and adolescents: systematic evidence review for the US preventive services task force. Pediatrics 2007; 120:e189-214.
23. McCrindle BW, Ose L, Marais AD. Efficacy and safety of atorvastatin in children and adolescents with familial hypercholesterolemia or severe hyperlipidemia: a multi-center, randomized, placebo-controlled trial. J Pediatr 2003; 142:74-80.

24. van der Graaf A, Nierman MC, Firth JC, Wolmarans KH, Marais AD, de Groot E. Efficacy and safety of fluvastatin in children and adolescents with heterozygous familial hypercholesterolemia. Acta Paediatr 2006; 95(11):1461-1466.
25. Clauss SB, Holmes KW, Hopkins P, Stein E, Cho M, Tate A, Johnson-Levonas AO, Kwiterovich PO. Efficacy and safety of lovastatin therapy in adolescent girls with heterozygous familial hypercholesterolemia. Pediatrics 2005; 116(3):682-8.
26. Lambert M, Lupien PJ, Gagné C, et al. Treatment of familial hypercholesterolemia in children and adolescents: effect of lovastatin. Pediatrics 1996; 97(5):619-628.
27. Stein EA, Illingworth DR, Kwiterovich Jr PO, et al. Efficacy and safety of lovastatin in adolescent males with heterozygous familial hypercholesterolemia. JAMA 1999; 281(2):137-144.
28. Knipscheer HC, Boelen CCA, Kastelein JJP, et al. Short-term efficacy and safety of pravastatin in 72 children with familial hypercholesterolemia. Pediatr Res 1996; 39(5):867-871.
29. Rodenburg J, Vissers MN, Wiegman A, et al. Statin treatment in children with familial hypercholesterolemia: The younger, the better. Circulation 2007; 116:664-668.
30. 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.
31. Avis HJ, Hutten BA, Gagné C, et al. Efficacy and safety of rosuvastatin therapy for children with familial hypercholesterolemia. J Am Coll Cardiol 2010; 55(11):1121-1126.
32. 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.
33. de Jongh S, Lilien MR, op't Roodt J, Stroes ES, Bakker HD, Kastelein JJ. Early statin therapy restores endothelial function in children with familial hypercholesterolemia. J Am Coll Cardiol 2002; 40(12):2117-2121.
34. Rosenson RS. Rosuvastatin: a new inhibitor of HMG-CoA reductase for the treatment of dyslipidemia. Expert Rev Cardiovasc Ther 2003; 1(4):495-505.
35. Jones PH, Davidson MH, Stein EA, et al. Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR* trial). Am J Cardiol 2003; 92(2):152-160.
36. Brown AS, Bakker-Arkema RG, Yellen L, et al. Treating patients with documented atherosclerosis to National Cholesterol Education Program- recommended low-density-lipoprotein cholesterol goals with atorvastatin, fluvastatin, lovastatin, and simvastatin. J Am Coll Cariol 1998; 32(3):665-672.
37. Kuster DM, Avis HJ, de Groot E, et al. Ten-year follow-up after initiation of statin therapy in children with familial hypercholesterolemia. JAMA 2014; 312(10):1055-1057.
38. Simvastatin: pediatric drug information. Lexicomp Online, Pediatric and Neonatal Lexi-Drugs Online, Hudson, Ohio: Lexi-Comp Inc.; 2015.
39. Colesevelam product monograph. Daiichi Sankyo, Inc. Parsippany, NJ. 2009.
40. Stein EA, Marais D, Szamosi T, et al. Colesevelam hydrochloride: efficacy and safety in pediatric subjects with heterozygous familial hypercholesterolemia. J Pediatr 2010; 156(2):231-236.e1-3.

41. Gold Standard, Inc. Colestipol. Clinical Pharmacology [database online]. Available at: http://www.clinicalpharmacology.com. Accessed 1/4/2008.
42. Colestipol. In: DRUGDEX® System [intranet database]. Version 5.1. Greenwood Village, Colo: Thomson Healthcare. 2007.
43. McCrindle BW, Helden E, Cullen-Dean G, Conner WT. A randomized crossover trial of combination pharmacologic therapy in children with familial hyperlipidemia. Pediatr Res 2002; 51(6):715-21.
44. Tonstad S, Sivertsen M, Aksnes L, Ose L. Low dose colestipol in adolescents with familial hypercholesterolaemia. Arch Dis Child 1996; 74(2):157-160.
45. Taketomo CK, Hodding JH, Kraus DM, eds. Lexi-Comp's Pediatric Dosing Handbook. 15th edition. Hudson, OH: Lexi-Comp; 2008.
46. Gold Standard, Inc. Cholestyramine. Clinical Pharmacology [database online]. Available at: http://www.clinicalpharmacology.com. Accessed 1/4/2008.
47. Cholesytramine. In: DRUGDEX® System [intranet database]. Version 5.1. Greenwood Village, Colo: Thomson Healthcare. 2007.
48. McCrindle BW, O'Neill MB, Cullen-Dean G, Helden E. Acceptability and compliance with two forms of cholestyramine in the treatment of hypercholesterolemia in children: A randomized, crossover trial. J Pediatr 1997; 130(2):266-273.
49. Tonstad S, Knudtzon J, Sivertsen M, Refsum H, Ose L. Efficacy and safety of cholestyramine therapy in peripubertal and prepubertal children with familial hypercholesterolemia. J Pediatr 1996; 129(1):42-49.
50. Fenofibrate. In: DRUGDEX® System [intranet database]. Version 5.1. Greenwood Village, Colo: Thomson Healthcare. 2007.
51. Gemfibrozil. In: DRUGDEX® System [intranet database]. Version 5.1. Greenwood Village, Colo: Thomson Healthcare. 2007.
52. Wheeler KA, West RJ, Lloyd JK, Barley J. Double blind trial of bezafibrate in familial hypercholesterolaemia. Arch Dis Child 1985; 60(1):34-37.
53. Food and Drug Administration. Withdrawal of approval of indications related to the coadministration with statins in applications for niacin extended-release tablets and fenofibric acid delayed-release capsules. Federal Register, April 18, 2016.
54. Niacin product monograph. AbbVie Inc. North Chicago, IL. 2015.
55. Colletti RB, Roff NK, Neufeld EJ, Baker AL, Newburger JW, McAuliffe TL. Niacin treatment of hypercholesterolemia in children. Pediatrics 1993; 92(1):78-82.
56. Yeste D, Chacon P, Clemente M, et al. Ezetimibe as monotherapy in the treatment of hypercholesterolemia in children and adolescents. J Pediatr Endocrinol Metab 2009; 22:487-492.
57. Clauss S, Wai KM, Kavey REW, et al. Ezetimibe treatment of pediatric patients with hypercholesterolemia. J Pediatr 2009; 154:869-872.
58. van der Graaf A, Cuffie-Jackson C, Vissers MN, et al. Efficacy and safety of co-administration of ezetimibe and simvastatin in adolescents with heterozygous familial hypercholesterolemia. J Am Coll Cardiol 2008; 52(17):1421-1429.
59. Ezetimibe product monograph. Merck & CO., Inc. Whitehouse Station, NJ. 2012.

60. de Ferranti SD, Milliren CE, Denhoff ER, et al. Using high-dose omega-3 fatty acid supplements to lower triglyceride levels in 10- to 19-year-olds. Clin Pediatr (Phila) 2014; 53(5):428-438.
61. Chahal N, Manlhoit C, Wong H, McCrindle BW. Effectiveness of omega-3 polysaturated fatty acids (fish oil) supplementation for treating hypertriglyceridemia in children and adolescents. Clin Pediatr (Phila) 2014; 53(7):645-657.
62. Praluent product monograph. Sanofi-Aventis. Bridgewater, NJ. 2015.
63. Repatha (evolocumab) product monograph. Amgen Inc. Thousand Oaks, CA. 2015.
64. Raal F, Honarpour N, Blom D, et al. Inhibition of PSCK9 with evolocumab in homozygous familial hypercholesterolemia (TESLA Part B): a randomized, double-blind, placebo-controlled trial. Lancet 2015; 385(9965):341-350).