

USE OF LIPID LOWERING MEDICATIONS IN YOUTH

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ABSTRACT

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. 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. Since the publication of the first guidelines, rates of pediatric obesity have significantly increased, resulting in a concomitant increase in dyslipidemia. 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. 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. 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.

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 role in premature cardiovascular disease, control of dyslipidemia provides clinicians with an opportunity for 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). 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 (7-11). Table 2 details the risk factors and risk conditions described in the NHLBI guidelines (9).

Table 1. Compariso	n of Recommendations fo	or Treatment	
Guidelines	NCEP, AAP – 1992 & 1998	AAP – 2008	NHLBI, AAP – 2011
Pharmacologic Treatment Initiation Parameters* *After an adequate trial of diet and lifestyle management.	 Age > 10 years with LDL-C ○ ≥ 190 mg/dL ○ > 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 	 Age ≥ 8 years with LDL-C ≥ 190 mg/dL ≥ 160 mg/dL in addition to a positive family history of premature CVD or presence of risk factors ≥ 130 mg/dL in addition to presence of diabetes mellitus Age < 8 years with LDL-C: o ≥ 500 mg/dL 	 Ages 10-21 years with LDL-C ≥ 190 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 ac sequestrants Cholesterol absorption inhibito Statins	id rs	•	Statins
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Table 2. NHLBI Risk Factors and Risk Conditions (9)				
NHLBI, AAP 2011 Guidelines	Risk Factors and Risk Conditions			
High Level Risk Factors	Hypertension requiring drug therapy			
	Tobacco use			
	BMI ≥ 97 th percentile			
	High risk conditions			
Moderate Level Risk Factors	Hypertension not requiring drug therapy			
	BMI \geq 95 th percentile, < 97 th 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 due to their developmental stage, the possibility of extended durations of treatment, and the potential use of concurrent medications that may be counterproductive by increasing lipid levels. 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 when patients are developing their independence counseling that addresses how to integrate their therapy into their own

social norms is important for achieving compliance to pharmacotherapy as well both as lifestyle modifications. Additionally, the cost of therapy significantly impacts compliance and should be factored into therapy decisions especially as youth transition into adulthood and may be faced with changes in insurance coverage. 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 risk and benefit 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 some 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 methods where the benefits generally outweigh any theoretical or proven risk for patients with hyperlipidemias (12).

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 (i.e., diet and lifestyle modification) (8-11). Statins first debuted in clinical practice in 1987 with the FDA's approval of lovastatin. At present, there are seven HMG-CoA reductase inhibitors with FDA approval, at varying dosages, for youth with heterozygous familial hypercholesterolemia. Lovastatin, simvastatin, atorvastatin and fluvastatin are approved for children 10 years of age and older. Pitavastatin and pravastatin are approved starting at 8 years of age and rosuvastatin is indicated in children as early as age 6 (13-21). Table 3 provides a summary of HMG-CoA reductase inhibitors, pediatric approval and indications, recommended dosing ranges. comments on dosing, and supporting clinical trials (13-21).

Table 3. HMG-	CoA Reductase Inhibit	ors		
Medication	Pediatric Approvals	Dosing	Comments	Supporting
	& Indications			Clinical Trials
Atorvastatin	Age 10-17	10-20	May be titrated at ≥	McCrindle, et
	Heterozygous	mg/day	4-week intervals	al (22)
	familial			
	hypercholesterolemia			
Fluvastatin	Age 10-16	20-80	May be titrated at ≥	van der Graaf,
	Heterozygous	mg/day	6-week intervals	et al (23)
	familial			
	hypercholesterolemia			
Lovastatin	Age 10-17	10-40	Initiated at 20	Clauss, et al
	Heterozygous	mg/day	mg/day for ≥20%	(24)
	familial		LDL reduction,	Lambert, et al
	hypercholesterolemia		may be titrated at ≥	(25)
			4-week intervals	Stein, et al
				(26)
Pravastatin	Age 8 and older	20-40	Age 8-13: 20	Knipscheer, et
	Heterozygous	mg/day	mg/day	al (27)
	familial		Age 14-18: 40	Wiegman, et al
	hypercholesterolemia		mg/day	(28)

				Rodenburg, et
				al (29)
Rosuvastatin	Age 6 and older	5-20	May be titrated at ≥	Avis, et al (30)
	Heterozygous	mg/day	4-week intervals	
	familial			
	hypercholesterolemia			
Simvastatin	Age 10-17	10-40	May be titrated at ≥	de Jongh, et al
	Heterozygous	mg/day	4-week intervals	(31)
	familial			de Jongh, et al
	hypercholesterolemia			(32)
Pitavastatin	Age 8 and older	1-4	May be titrated at ≥	Ferrari, et al
	Heterozygous	mg/day	4-week intervals	(20)
	familial			
	hypercholesterolemia			

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 \geq 190 mg/dL or LDL-C \geq 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 (21-32). With the longest half-life, rosuvastatin is the most potent statin, followed by atorvastatin (33). Given this knowledge, if pediatric patients who are initiated on statin therapy are having trouble meeting LDL-C goals, consideration should be given to switching to rosuvastatin or atorvastatin given potency prior to exploring second-line therapy options. Simvastatin is a moderately potent statin at clinically tolerable maximum doses of 40 mg/day (33-35). Lovastatin, pravastatin, and fluvastatin, respectively,

are the least potent statins (34, 35). As many studies have demonstrated, reduced potency can be compensated by an increase in the amount of statin given; however, dose escalation is often associated with an increased occurrence of adverse events (21-35). 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 (36).

Table 4. Statin Ther	Table 4. Statin Therapy Results					
Study	Medication	Dose	Results			
			LDL-C	HDL-C	TC	TG
McCrindle, et al	Atorvastatin	10-20	-40%	+6%	-30%	-13%
(22)		mg/day				
van der Graaf, et al (23)	Fluvastatin	80 mg/day	-34%	+5%	-27%	-5%
Clauss, et al (24)	Lovastatin	40 mg/day	-27%	+3%	-22%	-23%
Lambert, et al (25)	Lovastatin	10 mg/day	-21%	+9%	-17%	-18%
Lambert, et al (25)	Lovastatin	20 mg/day	-24%	+2%	-19%	+9%
Lambert, et al (25)	Lovastatin	30 mg/day	-27%	+11%	-21%	+3%
Lambert, et al (25)	Lovastatin	40 mg/day	-36%	+3%	-29%	-9%
Stein, et al (26)	Lovastatin	10 mg/day	-17%	+4%	-13%	+4%
Stein, et al (26)	Lovastatin	20 mg/day	-24%	+4%	-19%	+8%
Stein, et al (26)	Lovastatin	40 mg/day	-27%	+5%	-21%	+6%
Knipscheer, et al (27)	Pravastatin	5 mg/day	-23%	+4%	-18%	+2%
Knipscheer, et al (27)	Pravastatin	10 mg/day	-24%	+6%	-17%	+7%
Knipscheer, et al (27)	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 (28)	Pravastatin	20-40 mg/day	-24%	+6%	-19%	-17%
Avis, et al (30)	Rosuvastatin	5 mg/day	-38%	+4%	-30%	-13%
Avis, et al (30)	Rosuvastatin	10 mg/day	-45%	+10%	-34%	-15%
Avis, et al (30)	Rosuvastatin	20 mg/day	-50%	+9%	-39%	-16%
de Jongh, et al (31)	Simvastatin	10-40 mg/day	-41%	+3%	-31%	-9%
de Jongh, et al (32)	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.

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 (22). 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. Van der Graaf and colleagues found that in youth treated with fluvastatin, 58 (68.2%) reported non-serious adverse events. Only four were believed to be drug related. Treatment with fluvastatin resulted in no abnormalities in hormone levels or sexual maturation (23).

In their study of lovastatin, Clauss and colleagues reported no clinically significant alterations in vital signs; growth; hormone levels including luteinizing follicle-stimulating hormone, hormone, dehydroepiandosterone sulfate, estradiol. and cortisol; menstrual cycle length; liver function tests; or muscle function tests (24). Lambert and colleagues also found lovastatin generally well tolerated with no serious clinical adverse effects noted (25). 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 (26). 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 (27). 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 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 (28). 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. Laboratory monitoring including liver enzymes and creatine kinase levels, and markers of growth and development, such as Tanner staging (30). 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 (31). de Jongh and colleagues evaluated the safety of simvastatin in a second trial by monitoring adverse as well changes events as in alanine aminotransferase, aspartate aminotransferase, and creatine kinase levels (32). 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.

Braamskamp and colleagues investigated the efficacy and safety of pitavastatin in pediatric patients diagnosed with hyperlipidemia. 106 patients were enrolled in the study, ages 6-17, for a 12-week period (37). Patients were randomly assigned to 4 different groups categorized by dose 1 mg, 2 mg, 4 mg, or placebo (37). The results showed a reduction in all 3 dose groups in comparison to placebo, the 1 mg group showed a 23.5% reduction in LDL-C, the 2 mg group showed a 30.1% reduction, and the 4 mg group showed a 39.3% reduction (37). There was also a 52week extension period where patients assigned to the 1 mg group were up-titrated to a maximum dose of 4 mg to try and achieve an LDL-C level of >110 mg/dL (37). There were no safety issues of concern throughout the study. The results indicated that pitavastatin is safe and efficacious for use in pediatric patients, 6-17 years of age, and it was well-tolerated (37).

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 (36). 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 (36).

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. 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 (38). 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 possible interaction of gemfibrozil and statins, which should either be avoided as it can increase the toxicity of HMG-CoA reductase inhibitors. Macrolides and antifungal azoles are classes of drugs commonly prescribed to children, and they should be avoided as often as possible 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 (4). 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 (9, 10). 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 demonstrate 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			
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	8 g/day	N/A	
Approved)	divided twice		
Age ≥12	daily before		
	meals		

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 \geq 190 mg/dL or LDL-C \geq 160 mg/dL and the patient has a family history of premature cardiovascular disease or two or more cardiovascular disease risk factors.

Table 6. Bile Acid Sequestrant Results						
Study	Madiaation	Dece	Results			
Sludy	Wedication	Dose	LDL-C	HDL-C	тс	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

Abbreviations: g=grams, mg=milligrams, kg=kilograms, N/A=not applicable.

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 from. All subjects received colesevelam 3.75 grams per day in addition to a statin (40). Safety was measured via adverse events, vital signs and physical exam, laboratory monitoring, and Tanner staging. The most common adverse events related to 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 and colleagues 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 (40). 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 has been studied (48). Eighty two percent (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. Compliance 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). 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, while bile acid sequestrants do present an effective therapy option, their side effect profile, issues of tolerability 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 longterm safety, however, are generally lacking. It should also be noted that bile acid sequestrants can increase triglyceride levels and should not be used in patients with increased triglyceride levels.

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 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). 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). However, the use of fibrates should be considered and can be beneficial in pediatric patients who also have triglyceride abnormalities (TG levels > 500 mg/dL) (9, 53).

NIACIN

Niacin provides a potential adjunct therapeutic option for youth with severe dyslipidemia who have not achieved their lipid goal. Extended-release niacin is the only formulation that has FDA-approval for use in children \geq 16 years of age (54). Despite a lack of FDA approval for ages younger than 16, limited efficacy and safety data are published for the use of niacin in children 10 years of age as older as adjunct therapy (54). Table 7 summarizes data on recommended dosing ranges, comments on dose adjustments, and references supporting clinical trials.

Colletti and colleagues conducted a retrospective review to evaluate the efficacy and adverse effect profile of niacin for children with severe hypercholesterolemia (54). The effects on serum lipid profiles are detailed in Table 8. Adverse effects were common, affecting 76% of children, and similar to reported for adults including: flushing, those 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 adjunctive options. As with fibrates, niacin can also be considered for the purposes of treating pediatric patients who are concurrently diagnosed with hypertriglyceridemia (9).

Table 7. Niacin						
Medication	Pediatric Approvals & Indications	Dosing	Comments	Clinical Trials		
Niacin	Extended release: >16years of ageNote:Immediaterelease is notFDAApproved:Age \geq Adjunct therapy	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 (54)		

Abbreviations: mg=milligrams, kg=kilograms.

Table 8. Niacin							
Study	Medication	Dose	Results				
Colletti, et al	Niacin	500-2,250 mg/day	LDL-C	HDL- C	тс	TG	
(34)			-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 is FDA approved for adolescents 10 years of age and older with FH (53, 55), and it presents a potential therapy option either as monotherapy or when synergistically paired with an HMG-CoA reductase inhibitor (56-58). Due to its favorable tolerability, it has become the most frequently used second-line agent (59). Table 9 summarizes data on recommended dosing ranges and references supporting clinical trials while Table 10 details efficacy of therapy.

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.

Table 9. Ezetimibe							
Medication	Pediatric Approvals &	Dosing	Comments	Clinical Trials			
	Indications						
Ezetimibe	Age ≥10	10 mg/day	N/A	Yeste, et al (56)			
	Homozygous familial			Clauss, et al (57)			
	hypercholesterolemia			van der Graaf, et al			
				(58)			

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

Table 10. 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.

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, onlv 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 6 participants; however, all values resolved with interruption or discontinuation of Elevations in creatine phosphokinase therapy. 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). HMG-CoA reductase inhibitors have the risk of increasing myopathy and elevation in hepatic transaminases, but are generally considered a safe combination with ezetimibe.

OMEGA-3 FISH OILS

Omega-3 fish oils are a class of therapy for which there is significantly limited data in youth. To date the FDA approved formulations of omega-3 fatty acid lack a pediatric indication. High dose omega-3 fatty acid supplementation was evaluated by de Ferranti and colleagues, 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).

Khorshidi and associates performed a systematic review and meta-analysis of the effect of omega-3 supplementation on lipid profiles in children and adolescents. They found that omega-3 supplementation improved triglyceride levels in patients diagnosed with hypertriglyceridemia that were less than or equal to 13 years of age; however, there was no significant effect seen in HDL, LDL, or TC values (62). Omega-3 fish oils can be considered in those who have elevated triglyceride levels.

FAMILIAL HYPERCHOLESTEROLEMIA AND THERAPEUTIC ADVANCES

Familial hypercholesterolemia (FH) is a common, but often misdiagnosed inherited gene disorder (63). The most common gene mutation seen in FH is in the lowdensity lipoprotein receptor gene (LDLR) accounting for 85-90% of cases, followed by the apolipoprotein (ApoB) gene (5-15% of cases) and the proprotein convertase subtilisin kexin 9 (PCSK9) genes (1% of cases) (63, 64). Patients who are diagnosed with FH have abnormally elevated LDL levels from birth. FH is associated with a twenty-fold increased risk in premature cardiovascular disease and cardiovascular events (65). There are two different types of FH, heterozygous (HeFH) and homozygous (HoFH). Heterozygous patients have one mutated allele and are more commonly seen in practice, while homozygous patients have two mutated alleles and are very rare (66). Distinction between the two types is imperative because HoFH patients tend to be treatment resistant and carry a worse prognosis, if left untreated, these patients rarely make it past age 20 (66).

Lipid lowering in these patients can be quite challenging, especially HoFH patients. Most typical therapies for lipid lowering require functional LDL receptors, therefore given the gene mutations which often render the receptors inactive, modest reductions of 10-25% in HoFH patients are usually all that will be gained (67). HeFH patients tend to see higher rates of reduction (25-40%) (68). However, first line treatment for both forms of FH is still high-intensity statin therapy at moderate to high doses to be initiated as early as age 8 (69). All seven statins are FDA-approved for the treatment of FH and have been proven to slow down the progression of carotid intima-media thickness (63). Statins also reduce the incidence of cardiovascular events and cardiac death (63). Until recently, long term data on the use of statins in this patient population was not available, but in 2019, a 20-year follow-up study of statins in pediatric patients with FH was published (70). The results found that the incidence of cardiovascular events and death was much lower in patients treated with statins (70). If LDL-C goals are not being met with the use of statins alone, the next recommend agent is ezetimibe; however, this should not be used in patients younger than 10 years of age (59).

Ezetimibe is the second-line option to statins in these patients. It's use in combination with statins has demonstrated a reduction of LDL-C levels below 135 in more than 90% of children with FH (71). In one of the only studies that assessed the coadministration of simvastatin and ezetimibe in children with HeFH, it was found to be safe, well tolerated and provided a higher LDL reduction (15%) compared with simvastatin alone in HeFH patients (72). However, when it was investigated as a monotherapy option for children with HeFH, it only produced LDL-C lowering of 27% (71, 73). It is more appropriate to use as an adjunct therapy in this population of patients.

Alternative medications that can be considered other second-line options are bile acid sequestrants (71). Colesevelam is safe to use, but limited to children >10 years of age (71). These drugs however have minimal LDL-C lowering effects, usually only seeing a 10-20% reduction, and more importantly are very poorly tolerated due to gastrointestinal side effects (71).

PCSK9 Inhibitors

Given the difficulty and importance of treating these patients, especially those with HoFH, there is a need

for stronger lipid lowering options, which is where PCSK9 inhibitors come into play. These are a more recent class addition to the therapy options for managing FH, which help to reduce the degradation of LDL receptors and the removal of LDL-cholesterol (74). In a recent study assessing the efficacy/safety of agents in patients with familial lipid-lowering hypercholesterolemia, it was concluded that PCSK9 inhibitors were the most effective in lowering lipid levels (75). They have none of the same side effects as statins and produced similar CV benefits. Therefore, based on these conclusions, PCSK9 inhibitors are recommended as first-line agents in patients with hypercholesteremia that have intolerances or resistance to statins (75). There is currently one PCSK9 inhibitor approved for pediatric use. Repatha (evolocumab) was originally approved for use in patients 13 years of age and older (76), but the HAUSER-RCT study assessed the use of Repatha in patients ages 10-17 years of age for 24 weeks. It showed that the drug improved lipid levels (by approximately 38% in HeFH patients and 21-24% in HoFH patients) and was safe for use as the incidence of adverse events was similar in both the drug and placebo groups (71, 77). So now it is considered safe to use in pediatric patients 10 years of age and older. The HAUSER-RCT trial was then continued for another 80 weeks to further assess the safety and efficacy of Repatha (78). This new trial, HAUSER-OLE, further confirmed that the drug was safe and well-tolerated (78).

Praluent (Alirocumab) is another PCSK9 inhibitor that is available for treatment of FH, however it is not currently approved for use in pediatric patients (79). Nevertheless, there are studies currently assessing the safety and efficacy within this population. Bruckert and associates utilized Praluent and conducted an open-label phase 3 study specifically in pediatric patients (8-17 years of age) diagnosed with HoFH that were inadequately controlled (80). Patients received 75 or 150 mg of the drug based on weight (<50 or >50 kg, respectively) every 2 weeks for 12 weeks (80). The primary endpoint was percent change in LDL-C levels from week 0 to 12 (80). Interestingly, the results showed only a 4.1% decrease in LDL-C levels by week 12 (80). The secondary endpoints (assessing percent change LDL-C levels from baseline to weeks 24 and 48, changes in other lipid parameters from baseline to weeks 12, 24, 48, patients with a reduction of more than 15% in LDL-C levels at weeks 12, 24 and 48, and absolute change in LDL-C from baseline to weeks 12, 24, and 48) produced incredibly variable results (80). Overall, there were quite small changes in LDL-C levels observed in this study with mean reductions of LDL-C levels noted to range anywhere from ~33 to 52 mg/dL (80). More importantly, previous studies have shown that PCSK9 inhibitors are linked to a decrease in major coronary/vascular events and all-cause mortality, so although the results produced small values, the changes seen are still clinically significant based on these added benefits (80). It was also noted that this study produced similar results when compared to the ODYSSEY study which assessed the use of Praluent in adult patients with HoFH (80). The drug was deemed safe and there were no issues with tolerability (80). The study supports the use of Praluent as an adjunct therapy in HoFH patients already on first- and second-line therapies and not reaching their goal LDL-C levels (80).

Another study assessed the use of Praluent in pediatric patients diagnosed with HeFH. The ODYSSEY KIDS study was a phase 2 dose-finding study that enrolled pediatric patients anywhere from 8-17 years of age (81). Patients were split into 4 cohorts and dosed every 2 weeks. Dosing was determined by weight and the primary endpoint assessed percent change in LDL-C from baseline to week 8 (81). Praluent demonstrated the best reduction in LDL-C levels in the highest dosed cohorts and was welltolerated. This study also supported the use of the drug (with further analysis) in patients who require adjunct therapy, there is a phase 3 trial planned to assess the doses from this study that resulted in the greatest reduction in LDL-C levels. Overall, it is important to note that HoFH patients are more likely to fail PCKS9 inhibitors (82). This is attributable to their This class of medication mechanism of action. requires functional LDL receptors, and this is impaired

or completely absent in HOFH patients (82). Therefore, effectiveness of PCSK9 inhibitors tends to be much higher in HeFH patients (82).

Leqvio (inclisiran) is also another PCSK9 inhibitor currently not approved for pediatric use (83). The mechanism of action of this drug differs from Repatha and Praluent. Leqvio is a small interfering RNA (siRNA) that utilizes the RNA interference mechanism to cause the catalytic breakdown of mRNA for PCSK9, thus stopping the translation of the protein (84). It also only requires administration twice yearly as opposed to biweekly (84). There are currently ongoing studies investigating the possibility of using Leqvio in pediatric patients. ORION-13 and ORION-16 are studies assessing the efficacy, safety and tolerability of Leqvio in pediatric patients diagnosed with HoFH and HeFH, respectively (84). They are two-part (1-year double blind, the other year open-label) phase 3 trials consisting of patients aged 12 to <18 years with FH (84). The primary endpoint is the percentage change in LDL-C from baseline to day 330 (84). Based on the results, this could be another drug option as adjunct therapy to consider for use.

Angiopoietin-Like Protein 3 (ANGPTL3)

Angiopoietin-like protein 3 (ANGPTL3) also presents a novel target of adjunctive therapy for patients with homozygous familial hypercholesterolemia that are not meeting LDL-C goals with first-line agents (85, 86). Evkeeva (evinacumab-dgnb) is a monoclonal ANGPTL3 inhibitor that is FDA-approved specifically for the adjunctive treatment of homozygous familial hypercholesterolemia in patients 5 years of age and older (87).

Lomitapide

Lomitapide is another potential treatment option for patients with HoFH. This medication works differently from more conventional options. It binds to microsomal triglyceride transfer protein (MTP) and prevents the production of lipoproteins that contain apo-B (88). This causes a decrease in the production

of very-low-density lipoprotein (VLDL) and chylomicrons. Since VLDL is converted into LDL, this mechanism ultimately causing a decrease in LDL-C levels (89). It is administered once daily at doses ranging from 5 to 60 mg (88). The side effect profile of lomitapide can be difficult for patients as it can cause severe gastrointestinal side effects (due to the decrease in absorption of fats in the intestines), most often diarrhea (89). But it is also associated with raised hepatic fats and enzymes (82). It is currently approved for adult use only, but it has become an option for use in pediatric patients through an expanded access program or a named patient basis (82). There was a case series done exploring the effect of lomitapide in 11 pediatric patients diagnosed with HoFH. It demonstrated that the drug was effective in reducing LDL-C with all 11 HoFH patients and showed a similar side effect profile to that seen in adult patients (82). GI complaints were moderated and did not cause any discontinuation of use (82). It also showed greater reduction in LDL-C levels at lower doses (82). The greatest benefit of lomitapide was associated with its ability to reduce or stop the need for lipoprotein apheresis in the patients incorporated in this case study (82). An interesting mention about lomitapide from the case series is that adult patient data shows that early intervention utilizing the drug showed a potential for increased life expectancy and a delay in the time to first major adverse cardiovascular event (82). There is also currently an ongoing phase 3, open label trial investigating the efficacy and safety of lomitapide in pediatric patients with HoFH, estimated completion date is April of 2024 (82).

Bempedoic Acid

Bempedoic acid is a new medication that exerts its effects very similarly to that of statins. It works in the same pathway as statins and targets cholesterol biosynthesis (90-92). It is administered however as a prodrug and converted to active drug only in the liver and not in the muscles (90-92). The other difference between the two classes is that bempedoic acid inhibits ATP-citrate lyase (ACL), while statins inhibit HMG CoA reductase (90-92). Due to the lack of activation in skeletal muscles, this drug is a promising alternative to patients unable to take statins due to muscle related symptoms (90-92). The medication is FDA approved for use in patients with HeFH and those with established cardiovascular disease (93). It has shown promising results in adult trials, but there are currently no published pediatric trials to date assessing the safety or efficacy of use of the drug (93). There does however appear to be a trial in development: "An Open-Label Study to Evaluate the Pharmacokinetics, Pharmacodynamics, and Safety of Pediatric Bempedoic acid in Patients with Heterozygous Familial Hypercholesterolemia." The results are highly anticipated so that this can offer another promising drug class for use in patients intolerant or unable to meet their LDL-C goals.

FAMILIAL CHYLOMICRONEMIA SYNDROME

Familial chylomicronemia syndrome (FCS) is an incredibly rare autosomal recessive gene disorder (94). There is reduced or absent lipoprotein lipase activity causing disruption in chylomicron metabolism leading to severely elevated triglyceride levels resulting in acute recurrent pancreatitis (94). There is not however an increased risk of ASCVD with an FCS diagnosis (94). The best way to treat FCS is also often referred to as the most difficult as it requires patients to restrict dietary intake to <10-15% of daily calories (94). Other treatment options utilized are fibrates, omega-3 fatty acids and statins with variable responses, but the use of these medications is most commonly seen in patients who have multifactorial chylomicronemia syndrome (94). Given the difficulty of ensuring these patients maintain low levels of triglycerides, medications like volanesorsen are being examined (94, 95).

Volanesorsen

Volanesorsen	is	а	second-gener	ation	2'-O-
methoxyethyl	(2'-l	MOE)	antisense	thera	apeutic

oligonucleotide. It works by inhibiting apoC3 thus lowering triglyceride plasma levels (94). When it binds to apoC3, this interrupts mRNA translation which consequently promotes triglyceride clearance/lowering of triglyceride plasma levels (94). The efficacy and safety of volanesorsen was assessed in the APPROACH study (96). It included 67 patients that were randomized to either weekly volanesorsen or placebo for 3 months (97). The results showed a 77% reduction in triglyceride plasma levels at the end of the study period and there was only 1 event of pancreatitis in the study group (97). The largest trial performed assessing the use of volanesorsen was the COMPASS trial (97). It included 114 patients who were randomized to either weekly injections of volanesorsen or placebo for a total of 26 weeks (97). The results showed that patients in the treatment group saw a reduction in triglyceride levels, chylomicron triglycerides, VLDL levels and apoC3 levels by more than 70% (97). There were also no occurrences reported of pancreatitis in any of the patients randomized to the volanesorsen group (93). In both trials, volanesorsen proved itself as a promising agent for treatment of hypertriglyceridemia in FCS patients (95-98). This drug is not approved for use in the US but is approved in other countries.

CONCLUSION

As noted in 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

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pharmacologic treatment of children and adolescents with severe hypercholesterolemia who fail treatment with diet and exercise alone, although statins are only FDA approved for with familial vouth 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, a potential adjunct therapy, 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 intolerant to statins and bile acid patients sequestrants. Despite their inherit appeal and popularity amongst the lay public, omega-3 fish oils have failed to demonstrate statistically significant cholesterol lowering in pediatric and adolescent patients, but can be used to lower triglyceride levels. PCSK9 and ANGPTL3 inhibiting agents are promising novel treatment options in pediatric patients diagnosed with FH. While recent years have witnessed a dramatic increase in studies of lipid lowering medications in youth, the long-term safety and efficacy data continue to present an active focus of research.

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