Journal of Clinical Lipidology (2015) 9, S67–S76

Journal of Clinical Lipidology

Lipid-lowering medications for children and adolescents

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KEYWORDS:
Pediatric lipid-lowering medications;
HMG-CoA reductase inhibitors;
Statins;
Bile acid sequestrants;
Fibric acid derivatives;
Niacin;
Ezetimibe;
Omega-3 fatty acids

Abstract: As demonstrated by the 2011 publication of the National Heart, Lung, and Blood Institute Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents, the information available regarding the treatment of pediatric lipid disorders has greatly expanded. HMG-CoA reductase inhibitor, or statin, therapy is now considered a first-line pharmacologic intervention for pediatric patients with severe dyslipidemias failing treatment with diet and exercise alone. Despite their ability to effectively reduce cholesterol levels, bile acid sequestrants continue to pose challenges for pediatric patients because of their unpalatability and are typically used as adjunctive therapy or for patients not able to tolerate statins. Fibric acid derivatives, as a class of medications, not only lack a Food and Drug Administration (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 therapy option for pediatric patients. Ezetimibe provides clinicians with an alternative adjunct therapy option when synergistically paired with an HMG-CoA reductase inhibitor or it can be used as monotherapy for patients intolerant to statins and bile acid sequestrants. Finally, 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. Although recent years have witnessed a dramatic increase in data available for the use of lipid-lowering medications for pediatric patients, long-term study data are still generally lacking and continues to present an active focus of research.
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Introduction

The diagnosis, treatment, and monitoring of dyslipidemias in youth have undergone significant transformations in recent years. As detailed by the Pathobiological Determinants of Atherosclerosis in Youth and Bogalusa Heart studies, dyslipidemias play a vital role in both the initiation and 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 cardiac morbidity and mortality.

The first comprehensive pediatric guidelines for intervention on dyslipidemias were published as a report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents by the National Cholesterol Education Program in 1992 and were updated by the American Academy of Pediatrics in 1998.[4,5] In 2008, the American Academy of Pediatrics published an additional updated clinical report detailing screening and evaluation of cholesterol levels as well as prevention and treatment strategies for children

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Submitted March 3, 2015. Accepted for publication June 20, 2015.

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http://dx.doi.org/10.1016/j.jacl.2015.06.013

Table 1 Comparison of recommendations for treatment

Guidelines	NCEP, AAP—1992 and 1998[4,5]	AAP—2008[6]	NHLBI, AAP—2011[9]
Pharmacologic treatment initiation parameters: After an adequate trial of diet and lifestyle management.	• Age >10 y 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 or adolescent	• Age ≥8 y 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 y with LDL-C: ○ ≥500 mg/dL	• Ages 10–21 y with LDL-C ○ ≥190 mg/dL ○ 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 ○ 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 y 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

AAP, American Academy of Pediatrics; CVD, cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; NCEP, National Cholesterol Education Program; NHLBI, National Heart, Lung, and Blood Institute.

and adolescents.[6] 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.[7] Recently, pharmacotherapeutic options for pediatric patients have expanded with new study data on safety and efficacy for several lipid-lowering medications and FDA-approved indications.[8] In 2011, the National Heart, Lung, and Blood Institute (NHLBI) published an updated and integrated treatment guideline, Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents.[9] As with previous guidelines, lifestyle modifications with an emphasis on diet and exercise remain an integral part of treatment for pediatric lipid disorders; however, the recommendations for patients requiring further 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.[4–6,9] Table 2 details the risk factors and risk conditions described in the NHLBI guidelines.[9]

HMG-CoA reductase inhibitors

HMG-CoA reductase inhibitors (statins) are the medications recommended for first-line treatment of pediatric patients with severe dyslipidemias failing adequate response to diet and lifestyle modification.[8–11] The first statin debuted in 1987 with FDA approval of lovastatin. At present time, there are 7 HMG-CoA reductase inhibitors available and marketed in the United States. Except the most recently marketed statin, pitavastatin, all have FDA approval for pediatric patients with heterozygous familial hypercholesterolemia.[12–17] Table 3 provides a summary of HMG-CoA reductase inhibitors, pediatric approvals and indications, recommended dosing ranges, comments on dosing, and supporting clinical trials.

As Table 4 outlines, statin therapies demonstrated variable efficacy throughout the clinical trials involving pediatric and adolescent patients.[18–29] With the longest terminal half-life, rosuvastatin is the most potent of the statins followed by atorvastatin.[30] Simvastatin is a moderately potent statin at clinically tolerable maximum doses of

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