Correlates of Achieving Statin Therapy Goals in Children and Adolescents with Dyslipidemia

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Objective To determine the real-world effectiveness of statins and impact of baseline factors on low-density lipoprotein cholesterol (LDL-C) reduction among children and adolescents.

Study design We analyzed data prospectively collected from a quality improvement initiative in the Boston Children's Hospital Preventive Cardiology Program. We included patients ≤21 years of age initiated on statins between September 2010 and March 2014. The primary outcome was first achieving goal LDL-C, defined as <130 mg/dL, or <100 mg/dL with high-level risk factors (eg, diabetes, etc). Cox proportional hazards models were used to assess the impact of baseline clinical and lifestyle factors.

Results Among the 1521 pediatric patients evaluated in 3813 clinical encounters over 3.5 years, 97 patients (6.3%) were started on statin therapy and had follow-up data (median age 14 [IQR 7] years, 54% were female, and 24% obese, 62% with at least one lifestyle risk factor). The median baseline LDL-C was 215 (IQR 78) mg/dL, and median follow-up after starting statin was 1 (IQR 1.3) year. The cumulative probability of achieving LDL-C goal within 1 year was 60% (95% CI 47-69). A lower probability of achieving LDL-C goals was associated with male sex (HR 0.5 [95% CI 0.3-0.8]) and higher baseline LDL-C (HR 0.92 [95% CI 0.87-0.98] per 10 mg/dL), but not age, body mass index percentile, lifestyle factors, or family history.

Conclusions The majority of pediatric patients started on statins reached LDL-C treatment goals within 1 year. Male patients and those with greater baseline LDL-C were less likely to be successful and may require increased support. *(J Pediatr 2016;178:149-55).*

Current clinical practice guidelines in the US attempt to identify and treat children and adolescents with monogenic dyslipidemias (eg, familial hypercholesterolemia [FH], an autosomal-dominant disorder of low-density lipoprotein cholesterol [LDL-C] metabolism estimated to affect 1 in 200-500 people); polygenic dyslipidemias (eg, accumulation of multiple common genetic variants with small effect on LDL-C); and moderate elevations of LDL-C regardless of the cause in combination with a comorbidity that substantially increases cardiovascular disease (CVD) risk (eg, diabetes). The recommendations are that children and adolescents ≥10 years of age, or ≥8 years of age in severe cases, with markedly elevated LDL-C in isolation (≥190 mg/dL [4.91 mmol/L]) and those with moderately elevated LDL-C in combination with additional CVD risk factors (≥160 mg/dL [4.14 mmol/L] or ≥130 mg/dL [3.36 mmol/L] depending on the type of comorbidity and family history) should be considered for statin therapy if the LDL-C remains above treatment thresholds after at least 6 months of lifestyle interventions.[1] LDL-C goals of <130 mg/dL (3.36 mmol/L), or <100 mg/dL (2.59 mmol/L) for greater risk children, are advised.

Short- and medium-term randomized controlled trials of statins in children with FH have demonstrated decreases in LDL-C by 20%-40%.[2-4] Data are lacking about the efficacy of statin therapy in achieving LDL-C goals in children and

ALT	Alanine transferase
CK	Creatinine kinase
CVD	Cardiovascular disease
FH	Familial hypercholesterolemia
HR	Hazard ratio
LDL-C	Low-density lipoprotein cholesterol
NHLBI	US National Heart, Lung, and Blood Institute
SCAMP	Standardized Clinical Assessment and Management Program
QI	Quality improvement
ULN	Upper limit of normal

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M.M. is partially supported by the Tommy Kaplan Fund, Department of Cardiology, Boston Children's Hospital, and a research fellowship from Boston University. J.Z. is partially supported by the National Heart, Lung, and Blood Institute (HL111335 K23). S.d.F. receives royalties from UpToDate on topics related to pediatric cholesterol disorders. The other authors declare no conflicts of interest.

Portions of the study were presented at the American Heart Association Scientific Sessions, Chicago, IL, November 2014.

0022-3476/$ - see front matter. Published by Elsevier Inc.
http://dx.doi.org10.1016/j.jpeds.2016.08.003

adolescents outside of a clinical trial environment. Furthermore, the degree to which anthropometric factors and lifestyle behaviors influence therapy outcomes in a pediatric population is unknown. We sought to determine the real-world clinical efficacy of statin therapy to reduce LDL-C in pediatric patients managed at a referral lipid clinic, and secondarily, to describe the impact of modifiable and nonmodifiable baseline clinical and lifestyle factors that may impair children from achieving therapy goals.

Methods

A quality improvement (QI) initiative was implemented in the preventive cardiology program of Boston Children's Hospital for all children and adolescents seen for a lipid disorder after September 1, 2010. The QI initiative prospectively collected clinical data via the use of a Standardized Clinical Assessment and Management Plan (SCAMP). Providers (physicians, fellows, nurse practitioners, and nurses) completed the standardized forms for each patient encounter and interval blood draws. In addition to collecting pertinent health information, the SCAMP suggested management by way of treatment algorithms informed by the 2011 US National Heart, Lung, and Blood Institute (NHLBI) pediatric integrated CVD guidelines.[5] Health care providers could choose to follow this guidance or deviate and record the reason for deviation. The study was approved by the research ethics board at the Boston Children's Hospital with a waiver of individual participant consent.

Eligible patients included those newly initiated on statin therapy during the SCAMP QI observation period from September 1, 2010, to March 1, 2014, who had at least one follow-up assessment after starting statin therapy. We included patients ages 8-21 years at start of statin therapy and excluded any patients with homozygous FH (untreated LDL-C ≥450 mg/dL) and patients who had initiated statin therapy before the observation period.

Primary and Secondary Outcomes

The primary outcome was defined as achieving LDL-C therapy goal of < 130 mg/dL for patients without a high-risk condition or <100 mg/dL for those with a high-level risk condition. High-risk conditions were defined in accordance with the NHLBI pediatric guidelines as type 1 or 2 diabetes mellitus, end-stage renal disease, heart transplant, and Kawasaki disease with current aneurysms. The primary outcome was defined as the time to first achieving LDL-C target. Sensitivity analyses of the primary outcome explored two more permissive definitions of successfully lowering LDL-C in clinical practice as: (1) the NHLBI guideline goals plus 10 mg/dL; and (2) the greater of either the guideline threshold or a 50% decrease in LDL-C from baseline. Additional analyses were stratified for sex and standard (LDL-C <130 mg/dL) vs high-risk (LDL-C <100 mg/dL) goal. Secondary outcomes examined the relative and absolute reduction in LDL-C from baseline levels after initiation of statin therapy in the short term (0-60 days after starting statin therapy) and subsequent follow-up (>60 days after starting statin therapy).

Anthropometric and Clinical Assessments

Weight was recorded by a trained clinical provider via a standing scale to the nearest 0.1 kg with patients in their own clothing without jacket or shoes. Height was measured with a vertical stadiometer in patients without shoes to the nearest 0.1 cm. Lifestyle behaviors were recorded by providers as summary clinical impressions at the end of the clinic visit via a yes/no checkbox or a continuous reported measure for a series of lifestyle behaviors (**Figure 1**; available at www.jpeds.com). The behaviors that were assessed (ie, nutrition, physical activity, screen time) were chosen on the basis of evidence that these factors contribute to pediatric lipid disorders.[1] Family history of premature CVD was recorded for first- and second-degree relatives. Major hepatic or myopathic side effects due to statin therapy were defined as clinically detected cases of: (1) hepatic dysfunction (evidence of reduced hepatic synthetic function with elevated serum alanine transferase [ALT] > 3 × upper limit of normal [ULN]); or (2) clinical rhabdomyolysis (muscle symptoms, elevated serum creatinine kinase [CK > 3 × ULN], myoglobinuria, with or without renal dysfunction) that developed while on statin therapy.

Laboratory Assessments

Lipid measurements were obtained from fasting peripheral blood samples, generally after an 8-hour fast. Lipid measurements were obtained either during the morning of the clinic visit or at an outside laboratory around the time of the clinic visit. Fasting status was collected at each cholesterol measurement, and analyses were restricted to fasting samples. Interim cholesterol measurements between clinic visits also were recorded and included in the analyses. Total cholesterol, high-density lipoprotein cholesterol, and triglycerides were measured and LDL-C was calculated according to the Friedewald equation.[6] If triglycerides were ≥400 mg/dL (4.52 mmol/L), a direct LDL-C usually was obtained.

Quality Control of Database

The SCAMP QI dataset was interrogated for entry errors. All anthropometric and laboratory values that were outside of 3 SD of the cohort mean were confirmed manually in the hospital electronic health record. Data points on anthropometrics and cholesterol measurements missing from the SCAMP dataset and available in the medical record were extracted and added to the dataset. In addition, the following data points were confirmed manually in the electronic health record: starting date, statin type, and starting dose. The design of the dataset did not capture the change in medication or dose during follow-up or any measure of medication adherence.

Statistical Analyses

Descriptive statistics were generated as counts, frequencies, medians, and means as appropriate. The cumulative incidence of achieving LDL-C targets at specific time points after starting statin therapy were generated. Bivariate Cox proportional hazard models were conducted to test the impact of baseline anthropometric, clinical, and lifestyle factors on achieving LDL-C therapy goals. A P value < .05 was considered statistically