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

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Abstract

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 (e.g. diabetes, etc.). Cox proportional hazards models assessed 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

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[IQR 7] years), 54% were female, 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 1.0 (IQR 1.3) year. The cumulative probability of achieving LDL-C goal within 1 year was 60% (95% CI 47, 69). 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) were associated with not achieving LDL-C goals, but not age, BMI percentile, lifestyle factors or family history.

Conclusions—The majority of pediatric patients started on statins reached LDL-C treatment goals within 1 year. Males and those with higher baseline LDL-C were less likely to be successful and may require increased support.

Keywords

Dyslipidemia; Pediatrics; Statins; Low-density lipoprotein cholesterol

Current clinical practice guidelines in the United States attempt to identify and treat children and adolescents with monogenic dyslipidemias (e.g. Familial Hypercholesterolemia [FH], an autosomal dominant disorder of 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 CVD risk (e.g. 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 (7). LDL-C goals of <130 mg/dL [3.36 mmol/L] (or <100 mg/dL [2.59 mmol/L] for higher 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% (8–10). Data are lacking about the efficacy of statin therapy in achieving LDL-C goals in children and 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 non-modifiable 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 using 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 (6). 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 those ages 8 – 21 years at start of statin therapy and excluded any patients with homozygous FH (untreated LDL-C $\geq$ 450 mg/dL) and patients who had initiated statin therapy prior to the observation period.

Primary and secondary outcomes

The primary outcome was defined as achieving a LDL-C therapy goal of LDL-C $<$ 130 mg/dL for patients without a high-risk condition or a LDL-C $<$ 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 10mg/dL, and 2) the higher of either the guideline threshold or a 50% decrease in LDL-C from baseline. Additional analyses were stratified for: 1) sex and 2) standard (LDL $<$ 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 using a standing scale to the nearest 0.1 kg with patients in their own clothing without jacket or shoes. Height was measured using 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 3; available at www.jpeds.com). The behaviors that were assessed (i.e. nutrition, physical activity, screen time) were chosen based on evidence that these factors contribute to pediatric lipid disorders (7). 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 $\times$ upper limit of normal [ULN]), or 2) clinical rhabdomyolysis (muscle symptoms, elevated serum creatinine kinase [CK $>$ 3 $\times$ 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 were also recorded and included in the analyses. Total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG) were measured and LDL-C was calculated according to the Friedewald equation (11). If TG was ≥ 400 mg/dL [4.52 mmol/L], a direct LDL-C was usually obtained.

Quality control of database

The SCAMP QI dataset was interrogated for entry errors. All anthropometric and laboratory values that were outside of three standard deviations of the cohort mean were manually confirmed 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 manually confirmed 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 < 0.05 was considered statistically significant with no adjustment conducted for multiple testing. Multivariable adjusted models were constructed using age, sex, and significant covariates from the bivariate modelling ($p < 0.05$). Kaplan-Meier curves were generated for the primary outcome in overall and stratified analyses. Change in lifestyle factors over time was tested using mixed models with random intercepts for each subject. A linear mixed effects model was fit with LDL-C as the outcome, time as the covariate and a random intercept for each subject. There was a knot fit at day 60 to create a linear spline model with two separate slopes. Similar linear mixed effect models examined the absolute and relative change in LDL-C after starting statins in 60 day categorical increments in the first year of follow-up. Analyses were conducted in SAS version 9.3 (Cary, NC) and R version 3.1 (Vienna, Austria).

RESULTS

During the 3.5 year study period of September 1, 2010 to March 1, 2014, there were 1521 patients and 3813 clinical encounters, including 1001 patients seen for the first time. Among this group, 261 patients were treated with statins at some time point during the observation period. Of the 261 patients treated with statins, 116 (44%) were newly initiated on statin therapy during the study period, of whom baseline and follow-up LDL-C data were available for 97 children and adolescents (Figure 1) who form the study sample.

Baseline characteristics of these children and adolescents are presented in Table I. The mean (standard deviation [SD]) age of starting statins for males and females was 12 (4) and 14 (4) years, respectively. The median (interquartile range [IQR]) baseline LDL-C was 215 (IQR 78) mg/dL [5.56 (IQR 2.02) mmol/L]. The median (IQR) time between the first subspecialty clinic visit and starting statins was 18 (49) months. There were 16 patients started on statins with < 5 months of follow-up in subspecialty lipid clinic, which generally occurred when lifestyle interventions had begun prior to the first visit in a previous medical setting. Patients newly initiated on statin therapy had a mean (SD) of 2.6 (1.1) assessments per person after starting statins and were followed for a median (IQR) of 1.0 (1.3) year, totaling 114 patient-years of follow-up. The total number of LDL-C assessments and unique patients tested within 60 days intervals in the first year is shown in Figure 4 (available at www.jpeds.com).

The initial statin was simvastatin for 70 patients (72%; starting dose 5mg per day for 1 patient, 10mg per day for 26 patients, and 20mg per day for 43 patients), atorvastatin for 24 patients (25%; starting doses 10mg per day for 22 patients and 20mg per day for 2 patients) and pravastatin for 3 patients (3%; starting dose 10mg per day for 2 patients and 20mg per day for 1 patient). The mean (SD, range) starting dose indexed for weight for simvastatin, atorvastatin, and pravastatin was 0.34 (0.18, 0.10–0.99) mg/kg, 0.22 (0.10, 0.10–0.46) mg/kg, and 0.40 (0.33, 0.17–0.78) mg/kg, respectively. There was no significant difference in mean starting dose (indexed for weight) by sex, overall (β [SE] = 0.01 [0.04] mg/kg higher for males as compared with females; $p=0.8$) or stratified by statin type ($p<0.05$ for all). Starting statin type used did not vary by sex ($p<0.05$).

During the follow-up period, 1 patient was started on a second drug therapy (ezetimibe). Omega-3 fatty acid supplements were taken by 9 patients on statins (9%) during follow-up. There were no known pregnancies during the observation period. There were no recorded discontinuations of statin therapy as all patients who started statins during the observation period were recorded as prescribed statins at the most recent follow-up. We assessed for potential non-adherence (<5% decrease in LDL-C between pre-statin baseline and most recent follow-up) and potential loss to follow-up. We defined potentially lost to follow-up after no follow-up for 15 months, as the usual maximum interval between follow-ups for pediatric patients in this cohort on statins is 12 months plus a 3 months scheduling window. As the purpose of the study was to assess real-world outcomes of pediatric patients initiated on statin therapy, all subsequent analyses included those assessments of those potentially non-adherent and prior to potential loss to follow-up. There were 4 patients who had less than a 5% drop in LDL-C between baseline pre-statin and the last follow-up assessment. There were 12 patients who had more than 15 months between their last follow-up and the end of the observation period. There were no significant differences in baseline characteristics between those potentially lost to follow-up and the rest of the group (Table III; available at www.jpeds.com). Among the 19 patients excluded due to lack of follow-up data, the majority were prescribed statins close to the end of the follow-up period ($n=10$) or were >18 years of age and eligible for transition to adult care ($n=7$). Two excluded patients had >15 months between the most recent follow-up and end of the observation period, and were <18 years of age.

ACHIEVING LDL-C THERAPY GOAL

The probability of achieving LDL-C therapy goal (<130 mg/dL, or <100 mg/dL in patients with a high-level CVD risk factor) within one, two, and three years after starting a statin was 60% (95% CI 47, 69), 73% (95% CI 60, 82), and 87% (95% CI 67, 95), respectively (Figure 2, A; available at www.jpeds.com). Fifty percent of patients achieved LDL-C therapy goal within 306 (95% CI 180, 369) days. The likelihood of achieving therapy targets did not substantially differ: a) between risk thresholds (high vs. regular risk threshold), b) when a slightly more lenient cutoff was used (allowing an additional 10 mg/dL buffer) or c) if a 50% reduction from baseline LDL-C was included as a successful outcome if higher than the primary therapy goal (Figures 5,6,7; available at www.jpeds.com).

BASELINE CLINICAL AND LIFESTYLE PREDICTORS OF ACHIEVING LDL-C GOAL

At baseline among patients starting statins with complete report for all four modifiable lifestyle risk factors (inadequate exercise, nutritional risk factors, elevated screen time, and cigarette smoke exposure), 62% (51/82), 35% (29/82), and 23% (19/82) reported at least one, two, or three of four non-optimal modifiable lifestyle factors, respectively. In bivariate analyses, males were less likely to achieve LDL-C goals than females (HR=0.48 [95% CI 0.28, 0.80]; p=0.004; Figure 2, B) as were patients with higher baseline LDL-C (HR=0.92 [95% CI 0.87, 0.98]; p=0.006 per 10 mg/dL increase in LDL-C). Other baseline lifestyle factors were not associated with achieving goals in bivariate Cox models (Tables II and IV; Table IV available at www.jpeds.com). In the multivariable-adjusted model adjusting for age, sex and baseline LDL-C, male sex (as compared with females) and higher baseline LDL-C (per 10 mg/dL [0.26 mmol/L]) remained associated with not achieving LDL-C goals (HR=0.50 [95% CI 0.29, 0.86]; p=0.01, and HR=0.92 [95% CI 0.86, 0.99]; p=0.02, respectively).

CHANGE IN LIFESTYLE FACTORS AFTER INITIATING STATIN THERAPY

Change in lifestyle factors over time were tested using mixed models with random intercepts for each subject. None of these tests reached significance (p-values > 0.05) (Table V; available at www.jpeds.com), implying that we were not able to detect any improvement or worsening of measured lifestyle factors over time after initiating statin therapy.

RELATIVE AND ABSOLUTE DECREASE IN LDL-C AFTER INITIATING STATIN THERAPY

The relative and absolute change in LDL-C from baseline after starting statins is displayed in Figure 8 and 9 (available at www.jpeds.com), respectively. Accounting for repeated measures and adjusted for age and sex, LDL-C decreased on average within the first 60 days by 37% (SE 23) or 83 (SE 6) mg/dL [2.15 (0.16) mmol/L] from baseline levels. Generating a linear spline for the mixed effects model with a knot at 60 days (Figure 10; available at www.jpeds.com) demonstrated that LDL-C remained largely stable after 60 days post statin initiation (average decrease of 0.2 mg/dL [0.005 mmol/L] per year; p=0.5).

HEPATIC OR MYOPATHIC SIDE-EFFECTS OF STATIN USE IN PEDIATRIC PATIENTS

No patients presented with clinically-relevant hepatic or myopathic side-effects resulting in hepatic injury or rhabdomyolysis during the follow-up period. In the first year after starting

statins, a total of 2 out of 97 patients had at least one episode of isolated transaminitis (ALT $3\times$ ULN) from among 207 ALT measurements. One of these patients, prescribed atorvastatin, was noted to have a mildly elevated ALT on one occasion without a clear cause and had a normal ALT at the most recent follow-up, suggesting the one abnormal reading may have been related to an intercurrent illness. The second patient, prescribed simvastatin, had a complicated medical history including a stem-cell transplant for leukemia; ALT was mildly elevated on multiple occasions and had an ALT between $1-3\times$ ULN at the most recent follow-up.

In the first year after starting statins, a total of 2 out of 97 patients had CK in the myositis range (CK $>5\times$ ULN) without accompanying muscle symptoms from among a total of 202 CK measurements. One patient was prescribed atorvastatin and the other was prescribed simvastatin. Both episodes of asymptomatic elevated serum CK were attributed to increased physical activity or intercurrent viral illness. Both patients had normal CK levels at the most recent follow-up.

DISCUSSION

Statins are recommended in childhood if lifestyle modification is not sufficient to lower LDL-C; it is estimated that over 700,000 US children and adolescents may be eligible for statin therapy according to the 2011 NHLBI Guidelines (12, 13). Despite these recommendations and the large number potentially eligible, data are lacking about success in reaching therapeutic goals among youth who take statins, as well as determinants of success.

Reported outcomes in our study are as good as or better than those reported in adults in the general population, and adults with FH. In the 2003–4 National Health and Nutrition Examination Survey (NHANES), 61% of US adults in the general population that reported to be on statin therapy had achieved risk-factor specific LDL-C goals (14); estimates across the globe vary, with 20–70% reported to achieve LDL-C goals depending on risk status, LDL-C goal, age, sex and race (15–23). Data on adults with FH achieving LDL-C goals in clinical practice demonstrate modest achievement of therapy goals. The Spanish SAFEHEART (Spanish Familial Hypercholesterolemia Cohort Study) and US CASCADE-FH (CAscade SCreening for Awareness and DEtection of FH) registries have recently published their experiences of 2,170 and 1,295 adults with FH, respectively. In both studies, fewer than 30% of patients with FH achieved a treated LDL-C $<100\text{mg/dL}$, the adult target goal (11.2% in SAFEHEART and 25% in CASCADE-FH). In the SAFEHEART study, 40.2% of adult FH patients without CVD achieved an LDL-C $<130\text{mg/dL}$ at a mean of 5-years of follow-up. Pijmans *et al* found among 1,249 adults with FH in the Netherlands that 21% of patients achieved an LDL-C $<100\text{mg/dL}$ and 55% of patients achieved a LDL-C $<130\text{mg/dL}$ (24). The high rate of achieving goals observed in the current study could be due to the higher LDL-C goal in the pediatric age range, the influence of parental supervision on adherence, and/or better physiologic response. In addition, the studied population was cared for in a multidisciplinary specialty clinic focused on pediatric lipid disorders, which could augment success. It should be noted that our data represents longitudinal follow-up, e.g. we describe success in achieving goal during follow-up; our rates are likely to be higher than prevalence estimates because levels may increase out of

range after the LDL goal is achieved. The patient population that consents to initiate statins during childhood may be more adherent and/or less concerned about adverse events compared with a patient population that initiates statin therapy in middle to late adulthood.

We found that males and patients with higher baseline LDL-C had lower success in achieving therapy goals. Adherence issues, which we were unable to accurately capture in the current study, may contribute to these findings among males. In addition, prescribing patterns or patient and family therapy preferences may differ for males compared with females. Lower success in children and adolescents with higher LDL-C at baseline may be related to a reluctance on the part of pediatric practitioners to start at higher statin doses or increase doses rapidly related to fears about adverse effects. These findings suggest that alternative treatment strategies may be needed for males or those with higher baseline LDL-C, such as more frequent follow-up and monitoring.

Unlike in adult studies (25), we did not observe a worsening of lifestyle factors over time after starting statin therapy. Notably, despite receiving at least six months of lifestyle intervention in a multidisciplinary subspecialty clinic, patients in this study of high-risk children and adolescents had high prevalence of obesity and non-optimal lifestyle factors.

We found that LDL-C decreased by ~40% (~80 mg/dL) from baseline levels among children and adolescents started on statin therapy and this decrease was largely sustained throughout the observation period. The magnitude of this reduction is similar to the reductions achieved in rigorous short and medium term controlled trials, demonstrating that clinical trial success in reducing LDL-C in children and adolescents is possible in real world clinical environments. A Cochrane review of clinical trials on the use of statins in children with FH identified 5 trials involving 566 children; the meta-analysis results showed a mean decrease at the end of follow-up (median 24 weeks) of 32% [95% 29–35] (10). Reporting from a clinical setting, Carreau et al completed an audit of 185 children and teenagers with dyslipidemia followed from three months to seven years between 2002 and 2009 (26). They reported a relative decrease in LDL-C of 20% from pre-statin (Pravastatin) baseline levels (mean 231 [SD 53] mg/dL) to the most recent follow-up. The larger decreases seen in our study are likely due to the use of higher potency statins (atorvastatin and simvastatin vs. pravastatin) and secular trends in improvement in achievement of LDL-C target levels (27).

We did not detect any major clinically-relevant hepatic or myopathic adverse effects resulting due to statin therapy in this pediatric population during the 114 patient-years of follow-up. As these events are rare in the general adult population (<0.1%), we would be underpowered to detect rare side effects.

Our observational study has additional limitations. First, unlike a randomized clinical trial, we did not have uniform follow-up at each time point for all patients. This may bias our results as only patients who were tested could reach goal or contribute to our estimate of LDL-C reduction. It is possible that non-uniform follow-up would bias both analyses to the null as we assumed untested patients did not reach goal, and could not contribute data to reaching goal earlier if untested. Patients with poor response or inadequate dosing would be tested more often and therefore bias results to show a smaller reduction in LDL-C.

Alternatively, non-adherent patients may be lost to follow-up and would not be accounted for in the follow-up data. Research on the transition from pediatric to adult care for patients with dyslipidemia and the proportion lost to follow-up is lacking.

Second, we included all pediatric patients with elevated LDL-C who started statin therapy regardless of the underlying cause of dyslipidemia. We are unable to accurately determine the proportion with monogenic FH as genotyping is not yet common practice in the US. In addition, our analyses focused on baseline factors. Third, we were not able to adequately account for medication or dose changes, or noncompliance that occurred during follow-up. The greater success in achieving therapeutic goals at 3.5 years of follow-up compared with 1 year of follow-up is likely due to increases in statin doses and the use of additional agents. Fourth, lifestyle factors were determined by clinician assessment based on medical history and not quantitative direct measures. Fifth, the sample sizes were small in some of the subgroups of the stratified sensitivity analyses (eg, comparing patients with low vs. high risk targets), limiting our ability to detect any differences in outcomes. Finally, given that the longest follow-up was approximately 3 years, whether youth initiated on statins are able to sustain low LDL-C over decades is not addressed in the current study. Meeting LDL-C treatment goals through statin therapy for youth with very elevated LDL-C levels is achievable in a real world subspecialty clinical environment.

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ABBREVIATIONS

LDL-C	Low-density lipoprotein cholesterol
HDL-C	High-density lipoprotein cholesterol
CVD	Cardiovascular disease
FH	Familial Hypercholesterolemia
NHLBI	National Heart, Lung and Blood Institute
SCAMP	Standardized Clinical Assessment and Management Program
QI	Quality improvement

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Figure 1.
Flow chart of the study sample participants drawn from the subspecialty lipid clinic population over the 3.5 year QI observation period.

Figure 2. Cumulative probability of pediatric patients achieving LDL-C target (<130 mg/dL; or <100 mg/dL with a high-level CVD risk factor) after initiating statin therapy overall (panel a) and stratified by sex (panel b).

SCAMPs® Program**Lipid SDF 1: Initial Evaluation****Assessment:**

CVD Risk Factor	Yes	No	Unk	Family History (1° & 2° Relatives)	Yes	No	Unk
↑LDL	☐	☐	☐	Elevated Cholesterol	☐	☐	☐
↓HDL	☐	☐	☐	Elevated Triglycerides	☐	☐	☐
↑TGs	☐	☐	☐	Hypertension	☐	☐	☐
↑Lipoprotein(a)	☐	☐	☐	Type II Diabetes	☐	☐	☐
Hypertension/Elevated BP	☐	☐	☐	Obesity	☐	☐	☐
Overweight/Obese	☐	☐	☐	Thrombotic Events: PVD, Recurrent DVT, Recurrent PE	☐	☐	☐
Suspected Insulin Resistance	☐	☐	☐	Early Atherosclerotic Disease ¹	☐	☐	☐
Excess Screen Time	☐	☐	☐				
Inadequate Exercise	☐	☐	☐				
Nutritional Factors	☐	☐	☐				
Cigarette Smoke	☐	☐	☐				
High Risk Condition				Moderate Risk Condition	Yes	No	
Kawasaki Disease with Current Aneurysms	☐	☐		KD with Regressed Coronary Aneurysms	☐	☐	
Post Orthotopic Heart Transplant	☐	☐		HIV	☐	☐	
Chronic Renal Disease	☐	☐		Congenital Heart Disease	☐	☐	
Diabetes Mellitus Type 1	☐	☐		Chronic Inflammatory Disease (SLE, JRA)	☐	☐	
Diabetes Mellitus Type 2	☐	☐		Childhood Cancer	☐	☐	
Other CVD Risk Factor(s):							

¹Female < 65y or Male < 55y with any of the following: Positive Angiography, Angina, Angioplasty, CABG, MI, PAD, Revascularization, Stents or Stroke

Figure 3.

Data form for the clinician assessment of cardiovascular disease (CVD) risk factors and co-morbidities at the end of the clinical encounter

Figure 4.

Histogram of total number of LDL-C values (top) and unique pediatric patients with at least one LDL-C measurement (bottom) included in analyses in 60 day intervals in the first year of follow-up after starting statin therapy.

Figure 5.

Cumulative probability of achieving LDL-C target stratified by regular and high risk target.

Figure 6. Cumulative probability of achieving LDL-C target for the more permissive outcome allowing an additional 10 mg/dL (right panel) compared to the primary outcome (left panel).

Figure 7.

Cumulative probability of achieving LDL-C target allowing a 50% reduction of LDL-C to be considered achieving therapy goal if higher than fixed thresholds.

Figure 8.

Average percent reduction in LDL-C (SE) at during follow-up among pediatric patients after starting statin therapy over 60-day time bins in the first year after initiating statins adjusted for repeated measures in linear mixed effect (LME) models (A) and individual percent change in patient LDL-C measures from baseline over three years after initiating statins (B).

Figure 9.

Average LDL-C (SE) at baseline and during follow-up among pediatric patients after starting statin therapy over 60-day time bins in the first year after initiating statins adjusted for repeated measures in linear mixed effect (LME) models (A) and individual patient LDL-C measures over three years after initiating statins (B).

Figure 10.

LDL-C at baseline and during follow-up among pediatric patients after starting statin therapy. A mixed model was fit with LDL as the outcome, time as the covariate and a random intercept for each subject. There was a knot fit at day 60 to create a linear spline model with two separate slopes (depicted in orange line). From day 0 to day 60 there was a significant decrease in slope (-76.2 mg/dL [1.97 mmol/L] in the first 60 days, $p < 0.001$), and from day 60 and beyond there was a decreasing slope of 0.2 mg/dL [0.005 mmol/L] per year ($p = 0.5$) that did not reach significance.

Table 1

Baseline clinical and laboratory characteristics (first clinic visit during the study period) of pediatric patients initiated on statin therapy during the 3.5 year study period

	Pediatric patients started on statins during observation period	
	Overall (n=97)	
	n with variable	Median (IQR) or n (%)
Age (yrs)	97	14 (7)
Sex (female)	97	52 (54%)
BMI (percentile) -age 18 yrs	88	78 (52)
Overweight (BMI 85–94 th %ile)	88	20 (23%)
Obese (BMI >=95 th %ile)	88	21 (24%)
Systolic BP (mmHg)	87	113 (20)
Diastolic BP (mmHg)	87	66 (10)
Comorbidities:		
Diabetes, type 1 or 2	97	7 (7%)
Post-heart transplant	97	1 (1%)
Kawasaki disease	97	1 (1%)
Family history:		
Family history of dyslipidemia	95	93 (98%)
Family history of early CVD	95	85 (89%)
Lipid levels:		
Total cholesterol (mg/dL)	95	280 (67)
LDL-C (mg/dL)	97	215 (78)
HDL-C (mg/dL)	95	49 (15)
Triglycerides (mg/dL)	95	94 (52)

IQR=interquartile range, BMI=body mass index, %ile=percentile, BP=blood pressure, CVD=cardiovascular disease, TC=total cholesterol, LDL-C=low-density lipoprotein cholesterol, HDL-C=high-density lipoprotein cholesterol

Table 2

Results from bivariate Cox proportional hazard models assessing the association of baseline factors with the time-to-event of achieving LDL-C therapy target level. An elevated Hazard Ratio (HR) would be interpreted as being associated with a more rapid and likely achievement of LDL-C therapy goals after initiating statin therapy. Sample size changes slightly between models as all baseline variables were not available for all patients.

Baseline Factor	n	HR (95% CI)	p-value
Age (per year)	97	1.03 (0.96, 1.11)	0.38
Sex (male vs female [ref])	97	0.48 (0.28, 0.80)	<0.01 *
BMI (per kg/m ²)	88	0.98 (0.95, 1.02)	0.30
BMI percentile (per percentile)	88	1.00 (0.99, 1.00)	0.40
Baseline cholesterol measurements			
Baseline LDL-C (per mg/dL)	97	0.92 (0.87, 0.98)	<0.01 *
Baseline HDL-C (per mg/dL)	95	1.13 (0.93, 1.37)	0.2
Baseline TG (log-transformed)	95	1.60 (0.98, 2.62)	0.07
Statin initiated			
Statin starting dose (mg)	97	1.02 (0.97, 1.07)	0.45
Statin type (Atorvastatin vs Simvastatin [ref])	97	0.90 (0.49, 1.68)	0.94

BMI=body mass index, HR = hazard ratio, CI = confidence interval,

*
= p <0.05.

Comparison of baseline clinical and laboratory characteristics of study sample that may have been lost to follow-up, defined as having greater than 15 months between the last follow-up LDL-C and end of observation period, compared to other participants.

Table 3

	Patients with complete follow-up data		Patients with > 15 months between last follow-up LDL-C and end of observation period		p-value (Fisher Exact or Wilcoxon-Rank Sum Test)
	n with variable	Median (IQR) or n (%)	n with variable	Median (IQR) or n (%)	
Overall (n=85)			Overall (n=12)		
Age (yrs)	85	13.4 (6.9)	12	14.5 (4.5)	0.5
Sex (female)	85	44 (52%)	12	8 (67%)	0.3
BMI (percentile)-age 18 yrs	77	78 (48)	11	82 (52)	0.9
Normal weight (BMI<85 th %ile)	77	41 (53%)	11	6 (55%)	0.9
Overweight (BMI 85-94 th %ile)		17 (22%)		3 (27%)	
Obese (BMI ≥95 th %ile)		19 (25%)		2 (18%)	
Systolic BP (mmHg)	77	113 (21)	10	111 (8)	0.6
Diastolic BP (mmHg)	77	65 (11)	10	67 (10)	0.5
Comorbidities:					
Diabetes, type 1 or 2	85	7 (8%)	12	0 (0%)	0.6
Post-heart transplant	85	1 (1%)	12	0 (0%)	1.0
Kawasaki disease	85	1 (1%)	12	0 (0%)	1.0
Family history:					
Family history of dyslipidemia	84	83 (99%)	11	10 (91%)	0.2
Family history of early CVD	84	76 (90%)	11	9 (82%)	0.3
Lipid levels:					
Total cholesterol (mg/dL)	83	281 (69)	12	264 (63)	0.5
LDL-C (mg/dL)	85	220 (79)	12	207 (69)	0.8
HDL-C (mg/dL)	83	48 (16)	12	52 (18)	0.8
Triglycerides (mg/dL)	83	94 (50)	12	102 (71)	0.8

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IQR=interquartile range, BMI=body mass index, %ile=percentile, BP=blood pressure, CVD=cardiovascular disease, TC=total cholesterol, LDL-C=low-density lipoprotein cholesterol, HDL-C=high-density lipoprotein cholesterol

Table 4

Results from bivariate Cox proportional hazard models assessing the association of baseline lifestyle factors with the time-to-event of achieving LDL-C therapy target level. An elevated Hazard Ratio (HR) would be interpreted as being associated with a more rapid and likely achievement of LDL-C therapy goals after initiating statin therapy. Sample size changes slightly between models as all baseline variables were not available for all patients.

Categorical measures of lifestyle factors	n	HR (95% CI)	p-value
Inadequate exercise (yes vs. no [ref])	87	1.03 (0.59, 1.79)	0.91
Nutritional concern (yes vs. no [ref])	87	0.65 (0.38, 1.12)	0.12
Excess screen time (yes vs. no [ref])	82	0.91 (0.51, 1.64)	0.75
Cigarette smoke exposure (yes vs. no [ref])	87	0.99 (0.31, 3.19)	0.99
Family history of dyslipidemia (yes vs. no [ref])	95	0.36 (0.09, 1.50)	0.22
Family history of early CVD (yes vs. no [ref])	95	1.00 (0.43, 2.34)	0.99
Continuous measures of lifestyle factors			
Average MVPA (min./week)	74	1.00 (1.00, 1.00)	0.20
Average mild PA (min./week)	37	1.00 (1.00, 1.00)	0.40
Average weekday screen time (hr./week)	78	1.00 (0.94, 1.07)	0.89
Average weekend screen time (hr./week)	63	1.12 (0.99, 1.26)	0.11

MVPA = moderate-vigorous physical activity, PA = physical activity, min = minutes, hr= hours

Table 5

Changes in lifestyle factors over time assessed using mixed effect regression models with random intercept for each subjects. The effects for continuous variables can be interpreted as the additive change in variable per year since statins were started. The effects for binomial variables can be interpreted as the multiplicative change in the variable per year since statins were started.

		Change over time after initiating statin therapy (coefficient [95% CI])	p-value
Continuous variables – additive effects	Average at statin start	Linear regression coefficient for change over	
Average MVPA (min./week)	246	–21 (–90, +49)	0.5
Average mild PA (min./week)	292	–16 (–64, +31)	0.5
Average weekday screen time (hr./week)	3.3	–0.4 (–1.0, +0.3)	0.2
Average weekend screen time (hr./week)	2.8	0.1 (–0.3, +0.6)	0.5
Binary variables – Odds Ratios (multiplicative effects)	Probability at statin start	OR for change over time	
Cigarette smoke exposure (yes vs. no [ref])	5%	2.2 (0.6, 8.4)	0.3
Excess screen time (yes vs. no [ref])	29%	1.2 (0.7, 2.1)	0.4
Inadequate exercise (yes vs. no [ref])	43%	1.2 (0.8, 1.7)	0.5
Nutritional concern (yes vs. no [ref])	46%	1.5 (1.0, 2.3)	0.07

BMI=body mass index, MVPA = moderate-vigorous physical activity, PA = physical activity, min = minutes, hr= hours.