Original Article

Effectiveness and Safety of Statin Therapy in Children: A Real-World Clinical Practice Experience

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ABSTRACT

Background: Statin use for hypercholesterolemia in children is predominantly reported from short-term clinical trials. In this study, we assess the efficacy and safety of statin treatment in clinical pediatric practice.

Methods: Records of all patients who began statin treatment at age <18 years and remained on statins for >6 months from 5 pediatric lipid clinics were reviewed. Information at baseline and from all clinic evaluations after statin initiation was recorded, including lipid measurements, statin drug/dose, safety measures (anthropometry, hepatic enzymes, creatine kinase levels), and symptoms. Lipid changes on statin therapy were assessed from baseline to 6 ± 3 months and from 6 ± 3 months to last follow-up with a mixed-effects model, using

RÉSUMÉ

Contexte : Les statines sont fréquemment employées pour traiter l'hypercholestérolémie chez les enfants dans le cadre d'essais cliniques de courte durée. Dans l'étude présentée ici, nous évaluons l'efficacité et l'innocuité de l'emploi de statines dans la pratique clinique en pédiatrie.

Méthodologie : Nous avons passé en revue les dossiers de tous les patients de cinq cliniques pédiatriques des lipides qui ont commencé à prendre une statine avant l'âge de 18 ans et qui ont poursuivi le traitement pendant plus de six mois. Les valeurs mesurées au départ et à chacune des évaluations cliniques après l'instauration d'un traitement par une statine ont été consignées, notamment la lipidémie, le type et la dose de la statine prescrite, les paramètres d'évaluation de l'innocuité (anthropométrie, enzymes hépatiques, taux

Treatment with statins (hydroxy-methylglutaryl-coenzyme A reductase inhibitors) is recommended for children and adolescents with hyperlipidemia when low-density lipoprotein cholesterol (LDL-C) levels remain severely elevated despite lifestyle intervention, beginning as early as age 8 years.[1-3] Per the most recent guidelines from the National Heart, Lung, and Blood Institute (NHLBI), the American Academy of Pediatrics, and the National Lipid Association, the goal of statin treatment is reduced risk for future atherosclerotic cardiovascular disease (ASCVD), based on combined evidence

from autopsy series, vascular studies, longitudinal cohort reports, Mendelian randomization studies, and major cohort reports.[1,4-13] In randomized controlled trials (RCTs), treatment with statins has been shown to significantly lower LDL-C levels, with no differences between statin-treated and placebo-treated subjects for safety measures or adverse events, as documented by the evidence review for the 2011 NHLBI guidelines,[1] reported meta-analyses,[14] serially updated Cochrane systematic reviews,[15] and single reports of RCTs.[6,16,17] However, the application of strict inclusion and exclusion criteria in research trials like these often leads to a highly select group of subjects who do not reflect the larger population of children and adolescents with hyperlipidemia. In addition, the duration of treatment in a research trial is often short: for example, in the 2019 Cochrane review of statin therapy for children with high cholesterol, the median study duration was only 24 weeks.[15] RCTs assume a direct relationship between participants in a study and the larger

piecewise linear splines to describe temporal changes, controlling for repeated measures, sex, and age.

Results: There were 289 patients with median low-density lipoprotein cholesterol (LDL-C) of 5.3 mmol/L (interquartile range [IQR]:4.5–6.5) and mean age of 12.4 ± 2.9 years at statin initiation. Median duration of therapy was 2.7 years (IQR: 1.6–4.5) with 95% on statins at last evaluation. There were significant decreases in total cholesterol, LDL-C, and non–high-density lipoprotein cholesterol (non–HDL-C) from baseline to 6 ± 3 months ($P < 0.001$) and from 6 ±3 months to last follow-up ($P < 0.001$). Triglycerides and HDL-C were unchanged but the triglyceride to HDL-C ratio decreased significantly by late follow-up. At final evaluation, median LDL-C had decreased to 3.4 mmol/L (IQR:2.8–4.2). No patient had statins discontinued for safety measures or symptoms.

Conclusions: In real-world clinical practice, intermediate-term statin treatment is effective and safe in children and adolescents with severe LDL-C elevation.

de créatine kinase) et les symptômes. La variation de la lipidémie chez les patients recevant une statine a été évaluée sur deux périodes, soit entre le début du traitement et l'évaluation effectuée à 6 ± 3 mois ainsi qu'entre l'évaluation effectuée à 6 ± 3 mois et la dernière évaluation de suivi, à l'aide d'un modèle à effets mixtes et de splines linéaires par morceaux pour décrire les changements temporels, en contrôlant pour les mesures répétées, le sexe et l'âge.

Résultats : L'étude portait sur 289 patients ayant un taux de cholestérol des lipoprotéines de basse densité (C-LDL) médian de 5,3 mmol/l (intervalle interquartile [IIQ] : 4,5 à 6,5) et âgés de 12,4 ± 2,9 ans en moyenne au moment de l'instauration du traitement par une statine. La durée médiane du traitement était de 2,7 ans (IIQ : 1,6 à 4,5), 95 % des sujets étant toujours sous statine à la dernière évaluation. Les taux de cholestérol total, de C-LDL et de cholestérol des lipoprotéines non de haute densité (C-non-HDL) avaient diminué de manière significative entre le début du traitement et l'évaluation à 6 ± 3 mois ($p < 0,001$) et entre l'évaluation à 6 ± 3 mois et la dernière évaluation de suivi ($p < 0,001$). Les taux des triglycérides et du C-HDL n'avaient pas bougé, mais le rapport triglycérides/C-HDL avait diminué considérablement vers la fin du suivi. À l'évaluation finale, le taux de C-LDL avait diminué à 3,4 mmol/l (IIQ : 2,8 à 4,2). Aucun patient n'avait abandonné le traitement par une statine en raison de problèmes d'innocuité ou des symptômes.

Conclusions : En situation réelle dans la pratique clinique, le traitement à moyen terme par une statine est efficace et sûr chez les enfants et les adolescents présentant une élévation grave du taux de C-LDL.

population of interest, and between the experimental conditions and the real world. In truth, both the patient population and the use of drugs in clinical practice frequently deviate from the carefully scripted situation in controlled trials.[18] Understanding an interaction like this requires integration of diverse sources of data. In terms of statin therapy for children with hyperlipidemia, this kind of diversity is largely absent, with only rare reports of statin treatment in children and adolescents in the real world, referred to pediatric lipid clinics by their pediatricians, for management of hyperlipidemia.[19-22] This study aims to assess the effectiveness and safety of statin treatment in children and adolescents in real-world clinical pediatric practice.

Methods

We performed a multi-institutional retrospective review of all patients who began receiving statin treatment at < 18 years of age and who remained on statins for > 6 months between 1997 and 2014 at 5 Pediatric Lipid Clinics (Preventive Cardiology— Lipid Clinic, Golisano Children's Hospital, University of Rochester Medical Center, Rochester, NY, USA; The Labatt Family Heart Centre, The Hospital for Sick Children, Department of Pediatrics, University of Toronto, Toronto, Ontario, Canada; Preventive Cardiology—Lipid Clinic, Nemours/Alfred I. DuPont Hospital for Children, Wilmington, Delaware, USA; Preventive Cardiology Program—Lipid Clinic, Children's National Hospital, George Washington University School of Medicine and Health, Washington, DC, USA; Pediatric Lipid Clinic, The Heart Institute, Cincinnati Children's Hospital Medical Center,

Cincinnati, Ohio, USA). Data from each centre were abstracted and entered into the Research Electronic Data Capture (REDCap) database, a web-based application for electronic capture of clinical study data, based at The Hospital for Sick Children, Toronto.[23] From current guidelines, the minimal LDL-C therapeutic goal was defined as < 3.4 mmol/L, and the optimal goal as < 2.9 mmol/L.[1-3,24-26] The protocol was approved by the institutional review board at each centre. Requirement for individual patient consent was waived given that it was a retrospective study.

Safety concerns were assessed independently by each centre, addressing known potential statin side effects, including drug-related myositis, hepatic dysfunction, incident diabetes mellitus, and impaired growth.[1-3,24,26] All clinical assessments and complaints, anthropometric measurements, hepatic (alanine amino-transferase [ALT], aspartate aminotransferase [AST]) and muscle enzyme (creatine phosphokinase [CK]) levels, and fasting glucose and glycosylated hemoglobin (HbA1c) measurements were recorded from patient records.

At each centre, information from patient records was entered into the REDCap database in response to defined questions, outlined below. Specifically, information from the first clinic evaluation, the visit at which statin medication was initiated, and each subsequent visit on statin therapy was entered into the database as follows:

- First clinic evaluation: Demographics, medications, family history of dyslipidemia and ASCVD, anthropometrics, lipid panel results, and lipid pattern diagnosis as defined in the pediatric literature. For each patient, the preventive cardiology provider made

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the diagnosis of the lipid phenotype independently, based on the presenting lipid pattern, and this diagnosis was recorded in the database. Familial heterozygous hypercholesterolemia (FH) was characterized by isolated elevation of total cholesterol and LDL-C levels; combined dyslipidemia (CD) was characterized by the combination of elevated triglycerides (TGs), reduced high-density lipoprotein cholesterol (HDL-C), and variable elevation of LDL-C, a pattern often seen in obese youth and/or in those with familial combined dyslipidemia.[1]

- Lipid measurements were obtained from fasting specimens at each institution with total cholesterol, HDL-C, and TGs measured directly and LDL-C calculated from the Friedewald equation.
- Statin initiation visit: Demographics, medications, anthropometrics, lipid panel results, safety measures, selected statin drug and dose.
- Subsequent visits: Statin drug/dose, symptoms, anthropometrics, lipid panel results, safety measures, medications.
- Changes in statin drug or dose and any additional lipid-lowering medication were recorded.
- Noncompliance was defined as the patient and/or parental estimate of the usual number of days per week that the statin dose was missed, recorded at each visit.
- Recorded safety measures were hepatic enzyme (ALT, AST) and CK levels, and fasting glucose/HbA1c results; abnormal levels were as defined by the NHLBI Expert Panel guidelines[2] (Table 1).
- Growth was assessed from recorded height and weight results with calculated body mass index (BMI), converted to percentile-for-age values.
- All provider reports of patient symptoms or adverse events were entered in the database.

Analysis

Data were exported from the REDCap database and analyses conducted using SAS software (version 9.4 of the SAS system for Windows; SAS Institute, Cary, NC). Descriptive statistics were generated as counts, frequencies, medians, means, and range as appropriate, with frequencies and proportions generated for dichotomous and polytomous variables. Lipid changes per duration of statin therapy were assessed separately from baseline to 6 ± 3 months (early), and from 6 ± 3 months to last follow-up (long term) using a mixed-effects model, with piecewise linear splines to separately describe early and long-term changes, controlling for repeated measures, sex, and age at statin initiation. Differences in lipid response to statins in subjects diagnosed with FH vs those diagnosed with CD were assessed by an n-1 χ^2 test for small sample sizes.

Results

Findings at referral

There were 289 patients, 57% male, with a mean age of 10.7 ± 3.7 years at original referral. No patient had any personal history of clinical ASCVD. A family history of

Table 1. Safety lab norms

Fasting glucose HbA1c	Normal range: < 100 mg/dL (5.6 mmol/L) Impaired glucose metabolism: 100 to 125 mg/dL (5.6 to 7.0 mmol/L) Type 1 diabetes mellitus: ≥ 126 mg/dL (7.0 mmol/L) A1c thresholds: Normal A1c: < 5.7%; at risk for diabetes: 5.7%–6.4%; diabetes: ≥ 6.5%
Serum aspartate amino-transferase/glutamic oxaloacetic transaminase	Normal range: ~5 to 40 units/L Abnormal: > 3 times the ULN
Serum alanine amino- transferase/glutamic pyruvic transaminase CK	Normal range: ~7 to 56 units/L Abnormal: > 3 times the ULN ULN: 150 U/L for females; 175 U/L for males Abnormal: > 3 times or > 10 times the ULN per hospital/lab norms Note: Serum CK levels vary among healthy subjects, even when correcting for muscle mass. Recent physical activity can temporarily increase CK. CK reference ranges vary with different assays and reference temperatures, and therefore among labs.

Timepoints: at referral; pre-statin initiation; after 6 ± 3 months on statin therapy; and at last statin follow-up (x = 2.7 years; interquartile range: 1.6, 4.5). To convert from mmol/L to mg/dL: for total cholesterol, non−high-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol, multiply by 38.67. For triglycerides, multiply by 88.57.

CK, creatinine kinase; HbA1c, glycosylated hemoglobin; ULN, upper limit of normal.

hyperlipidemia was recorded for 90% of patients. For 68%, a positive family history of early ASCVD was recorded. From baseline lipid results, 83% of patients were diagnosed by their physician as having FH with isolated elevation of total cholesterol and LDL-C levels; 17% were diagnosed with CD, with elevated TGs, reduced HDL-C, and variable elevation of LDL-C, a pattern often seen in obese youth and/or in those with familial CD.[1,25]

Statin therapy

Mean age at statin initiation was 12.44 ± 2.9 years, with 38 children (13%) aged less than 10 years. For 69% of patients, the initial statin used was atorvastatin, with 16% on rosuvastatin, 8% on simvastatin, 5% on pravastatin, and 2% on lovastatin. The starting dose was at or below the minimum dose recommended by the US Food and Drug Administration, in all patients; in 2 patients, the initial atorvastatin dose was half the minimum recommended dose. During the first year of treatment, the statin dose was increased for 48 patients (17%), and by last follow-up, an alternate statin had been prescribed for 72 patients (25%). The maximum dose recommended by the US Food and Drug Administration was prescribed for only 5 patients in the series. At last evaluation, 95% of patients remained on statin therapy: 48% on atorvastatin, 27% on rosuvastatin, 18% on simvastatin, 5% on pravastatin, 1% on lovastatin, and 1% on fluvastatin. The median duration of therapy was 2.7 years (interquartile range:

1.6—4.5); 46% of patients were on statins for more than 3 years. Compliance was estimated by the child and/or family at 91% (mean: 6.4 days/week).

Lipid and anthropometric results for the whole group are shown in Table 2, with a timepoint of 6 ± 3 months chosen to reflect the early response to statin treatment, and results at last evaluation representing late follow-up. Controlling for repeated measures, and sex and age at initiation, statin treatment was associated with a significant decrease in total cholesterol, LDL-C, and non—HDL-C from baseline to 6 ± 3 months post—statin initiation, and a further significant decrease from 6 ± 3 months to last follow-up at a median of 2.7 years (P < 0.001 for all measures at both timepoints). There was no significant change over time in either fasting TGs or HDL-C, but mean TG value went down, and the TG:HDL-C ratio decreased significantly between 6 ± 3 months post-initiation and last follow-up.(P = 0.04) At final evaluation, recommended minimal (3.4 mmol/L) and optimal (2.9 mmol/L) LDL-C treatment goals were achieved in 49% and 14% of patients; 9% of the group had LDL-C levels above 4.9 mmol/L at last evaluation. Analysis of serial anthropometric measures showed no significant impact on growth assessed by height-, weight-, and BMI-for-age percentiles during statin treatment.

When patients with FH and CD were compared, TGs and TG/HDL-C ratios were significantly higher, and total cholesterol, LDL-C, and HDL-C were significantly lower, in CD patients on baseline lipid profiles (Table 3). As shown, statins improved lipid measures in patients with both patterns, but LDL-C lowering was greater for FH patients, a decrease of 38% for FH patients vs 28% in the CD group (P > 0.05). By contrast, TGs decreased significantly more for CD patients (20% vs 7%; P < 0.005), as did the TG:HDL-C ratio (23% vs 10%; P = 0.02). At last follow-up, there was no significant difference in total cholesterol, LDL-C, or non—HDL-C levels between the 2 groups, but HDL-C remained significantly lower, and TGs and TG:HDL-C remained significantly higher, for CD patients.

Safety evaluation

Laboratory measures. Baseline levels of ALT, AST, and CK were normal in all patients. There was no significant change in mean ALT or CK levels during follow-up. Mean AST levels decreased slightly but significantly between the 6-month evaluation and last follow-up. Results from logistic regression analysis indicated that a longer time since initiation of statin therapy was not associated with increased odds of laboratory abnormalities (Fig. 1). There were 15 patients (5%) with isolated CK levels at ≥ 10 times the upper limit of normal at some point during follow-up, none with associated symptoms or exam findings; in each case, these normalized on repeat evaluation with no change in statin regimen. Ten patients (4%) had ALT and/or AST elevations detected on routine testing, without symptoms or exam findings; these levels normalized when patients went off statin, with medication restarted at the same dose without elevation recurrence in any patient. No patient with transient elevation of CK, AST, or ALT level was diagnosed with clinical myositis or hepatic disease. For one patient, bilirubin was noted to be consistently mildly elevated; this patient was eventually diagnosed as having Gilbert's disease. Fasting glucose and HbA1c levels were measured too inconsistently and infrequently to allow for analysis. No patient was diagnosed with incident diabetes mellitus during follow-up.

Growth. By univariable repeated-measures regression analysis adjusted for sex and age at statin initiation, there was no significant change in median age-specific percentiles for recorded measures of height, weight, or BMI from baseline to early follow-up, nor from early to late follow-up (Table 2).

Symptoms. Potentially statin-related symptoms were recorded for 20 patients (7%): muscle pain in 13 (twice for one patient), fatigue for 3, rash for 3, abdominal pain for one, and "yellow eyes" for one. No complaints were associated with abnormal physical exam findings or with any abnormality in safety laboratory measures; no patient was diagnosed with clinical

Table 2. Lipid and anthropometric variables at selected timepoints*

Measure[†] Median (IQR) (mmol/L)	At referral	Pre-statin	On statin: 6 ± 3 mo	P[‡] Pre-statin vs 6 ± 3 mo	On statin: last F/U (x: 3.1 y [1.6, 4.5])	P[‡] 6 ± 3 mo vs last F/U
Total cholesterol	7.6 (6.5—8.6)	7.1 (6.3—8.3)	5.5 (4.7—6.5)	< 0.001	5.2 (4.5—6.0)	< 0.001
LDL-C	5.7 (4.6—6.7)	5.3 (4.5—6.5)	3.7 (2.9—4.6)	< 0.001	3.4 (2.8—4.2)	< 0.001
HDL-C	1.2 (1.0—1.4)	1.2 (1.0—1.4)	1.2 (1.0—1.4)	0.20	1.2 (1.0—1.4)	0.06
TGs	1.2 (0.8—1.8)	1.1 (0.8—1.6)	1.0 (0.7—1.4)	0.65	1.0 (0.7—1.4)	0.33
Non—HDL-C	5.9 (5.2—7.0)	5.8 (5.1—7.0)	4.3 (3.4—5.1)	< 0.001	3.9 (3.2—4.8)	< 0.001
TGs/HDL-C	1.0 (0.6—1.5)	1.0 (0.6—1.5)	0.8 (0.6—1.3)	0.16	0.9 (0.6—1.4)	0.04
Weight-for-age, percentile	85 (58—97)	84 (51—96)	81 (47—97)	0.84	86 (53—97)	1.00
Height-for-age, percentile	52 (28—79)	50 (25—82)	47 (25—82)	0.15	46 (22—74)	0.67
BMI-for-age, percentile	88 (60—97)	89 (62—98)	87 (59—97)	0.52	87 (54—97)	0.47

BMI, body mass index; F/U, follow-up; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride.

* Time points: at referral; pre-statin initiation; after 6 ± 3 months on statin therapy; and at last statin F/U (x = 2.7 years [1.6, 4.5]).

[†] To convert from mmol/L to mg/dL: for total cholesterol, non—HDL-C, HDL-C, and LDL-C, multiply by 38.67. For TGs, multiply by 88.57.

[‡] The P-value columns come from the results of the mixed-effects model, with piecewise linear splines to separately describe early (6 ± 3 months) and long-term lipid changes (last F/U; median = 2.7 years), controlling for repeated measures, sex, and age at statin initiation. A significant P-value indicates that the change between the 2 timepoints is significant.

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Table 3. Comparison of lipid findings in patients with FH and CD over time

Lipid variable mmol/L* (median [IQR])	Total (n = 279)[†]	FH (n = 233; 84%)	CD (n = 46; 16%)	P[‡] FH vs CD
At referral:				
Total cholesterol	7.7 (6.6–8.6)	7.9 (6.8–8.7)	6.4 (5.8–7.5)	< 0.001
LDL-C	5.8 (4.7–6.7)	6.0 (5.0–6.9)	4.4 (3.9–5.1)	< 0.001
HDL-C	1.2 (1.0–1.4)	1.2 (1.1–1.4)	1.0 (0.9–1.2)	< 0.001
TGs	1.2 (0.8–1.8)	1.1 (0.8–1.6)	2.1 (1.6–3.4)	< 0.001
Non–HDL-C	5.9 (5.2–7.0)	6.6 (5.8–7.3)	5.4 (4.9–6.3)	< 0.001
TG/HDL-C	1.0 (0.6–1.5)	0.9 (0.7–1.1)	2.1 (1.8–2.8)	< 0.001
Pre-statin:				
Total cholesterol	7.2 (6.4–8.4)	7.3 (6.6–8.4)	6.3 (5.9–7.8)	0.001
LDL-C	5.4 (4.6–6.5)	5.5 (4.8–6.6)	4.5 (4.0–4.9)	< 0.001
HDL-C	1.3 (1.0–1.4)	1.3 (1.1–1.5)	1.0 (0.8–1.1)	< 0.001
TGs	1.1 (0.8–1.6)	1.1 (0.7–1.4)	1.9 (1.3–2.6)	< 0.001
Non–HDL-C	5.9 (5.2–7.0)	6.0 (5.3–7.1)	5.3 (4.8–6.8)	0.02
TG/HDL-C	1.0 (0.6–1.5)	0.9 (0.5–1.3)	1.9 (1.2–2.6)	< 0.001
On statin:				
6 ± 3 mo				
Total cholesterol	5.5 (4.8–6.5)	5.6 (4.8–6.5)	5.0 (4.4–6.1)	0.05
LDL-C	3.7 (2.9–4.6)	3.9 (3.0–4.7)	3.2 (2.4–4.4)	0.005
HDL-C	1.2 (1.0–1.4)	1.2 (1.0–1.5)	1.0 (0.9–1.2)	<0.001
TGs	1.0 (0.8–1.4)	0.9 (0.7–1.2)	1.1 (0.7–2.2)	< 0.001
Non–HDL-C	4.3 (3.4–5.1)	4.3 (3.5–5.2)	3.8 (3.2–5.1)	0.26
TG/HDL-C	0.8 (0.6–1.3)	0.7 (0.5–1.1)	1.8 (1.1–2.5)	< 0.001
On statin: last F/U (Median = 2.7 y)				
Total cholesterol	5.2 (4.5–5.9)	5.2 (4.5–6.1)	5.0 (4.1–5.8)	0.28
LDL-C	3.4 (2.7–4.2)	3.4 (2.8–4.2)	3.2 (2.3–3.9)	0.11
HDL-C	1.2 (1.0–1.4)	1.2 (1.0–1.4)	1.0 (0.9–1.1)	< 0.001
TGs	1.0 (0.7–1.4)	1.0 (0.7–1.3)	1.5 (1.1–1.9)	< 0.001
Non–HDL-C	3.9 (3.2–4.8)	3.9 (3.2–4.9)	3.9 (3.1–4.7)	0.94
TG/HDL-C	0.9 (0.6–1.4)	0.8 (0.5–1.2)	1.5 (1.0–2.1)	< 0.001

P value is the result of comparison between FH and CD results.

CD, combined dyslipidemia; FH, familial hypercholesterolemia; F/U, follow-up; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride.

* To convert from mmol/L to mg/dL: for total cholesterol, non-HDL-C, HDL-C and LDL-C, multiply by 38.67. For TGs, multiply by 88.57.

[†] Of the total series of 289 patients, 10 were not designated as FH or CD.

[‡] Comparison between lipid results for FH and CD patients at specified timepoints.

myositis or hepatic disease. No patient had statin medication discontinued or the dose changed because of symptoms.

Discussion

Statin medications significantly and consistently lowered total cholesterol, non–HDL-C, and LDL-C levels in these children and adolescents from real-world clinical practice. This series has the largest number of subjects and the longest duration among reported clinical series to date. For comparison, results of all recent reports of statin therapy in youth are provided in Table 4, including all observational studies published after 2008 (when the evidence review for the NHLBI guidelines was completed[1]) and all randomized trials and their follow-up studies not selected for inclusion in a meta-analysis[14] or the Cochrane review.[15] Table 4 includes a very important, recently published 20-year follow-up study of statin treatment with young adults who had participated in a 2-year RCT of statin treatment for FH as children.[9,27] There is no doubt that this study documents very important evidence supporting the safety, efficacy, and vascular response to long-term statin therapy initiated in FH patients in childhood, with important clinical implications based on review of parental histories. However, the patient group is not typical of the population of children with hypercholesterolemia, as it consists of only individuals with FH, with a genetically proven diagnosis in 98% of the subjects. In addition, clinical care and follow-up of these study subjects are not typical of usual care. After the initial 2-year trial period, the subjects and their siblings were followed at the research centre clinic for the next several years. Subsequently, they returned repeatedly to this centre for reevaluation and reassessment, with findings reported in a series of published reports.[4,5,7–9,28–30]

Although the results of these studies consistently provide important information, neither the subjects nor their care reflect the experience of real-world pediatrics. By contrast, the current series includes every hypercholesterolemic patient aged less than 18 years who was treated with statins for more than 6 months in the 5 participating pediatric lipid clinics. The patient population reflects the typical combination of FH and CD patients referred to pediatric lipid clinics. In these children and adolescents, the mean LDL-C decrease of 36% is similar to decreases previously reported, whether in meta-analyses, clinical trials, or case series (Table 4).[8,9,14–17,19–22,29–33] Self-reported compliance was high, at 91%, although the true compliance rate could not be quantified due to the retrospective nature of the study. These compliance results are comparable to those in other reports from pediatric lipid clinics where patients are referred; initiation of statin therapy in this setting likely reflects enhanced parental/family concern about dyslipidemia and risk for ASCVD.[19–22,31]
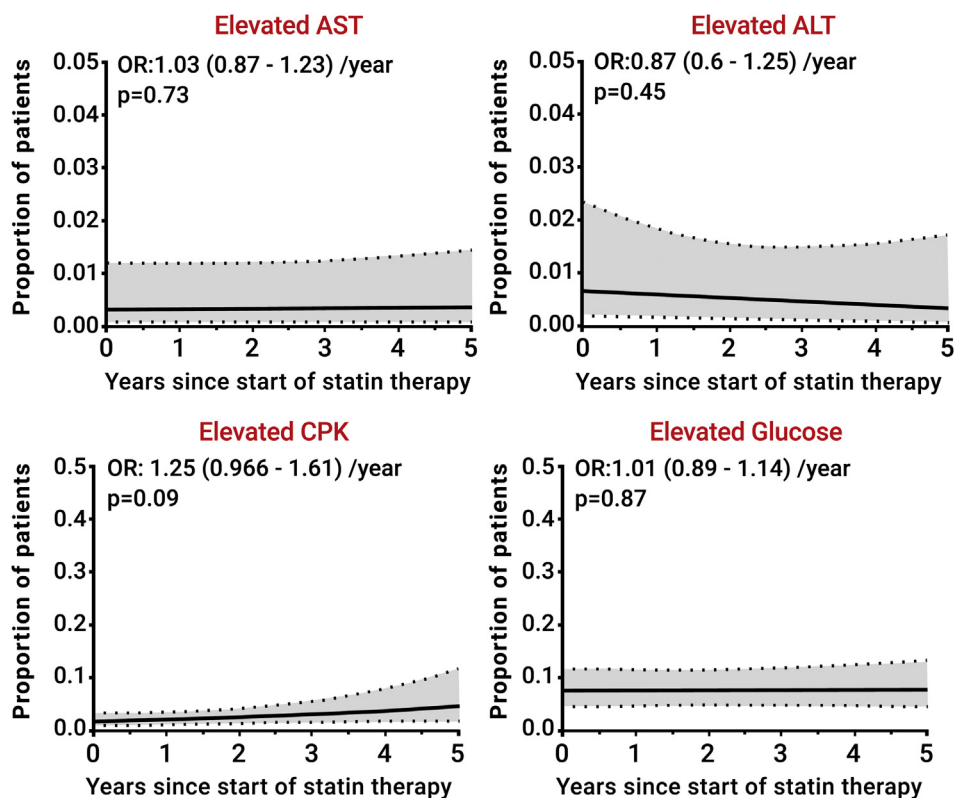
Figure 1. Logistic regression analysis indicated that a longer time since initiation of statin therapy was not associated with increased odds of laboratory abnormalities. ALT, alanine amino-transferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; OR, odds ratio.

By contrast, analysis of a large pediatric database of private health insurance claims assessed between 2003 and 2013 indicated a high level of noncompliance, with 86% of subjects having at least one period of nonadherence, defined as a gap of $\geq$ 90 days between medication dispensing points. When patients with diagnosed dyslipidemia from this database were analyzed separately, adherence was significantly higher, with 76% filling a second prescription during the first year after initial dispensing.[34] Sustained medication adherence is important in statin treatment of dyslipidemic children by whom long-term compliance is required; our study suggests that a high rate of compliance can be achieved when patients are treated in a pediatric lipid clinic setting.

Despite continuous follow-up and self-reported high compliance rates, minimal (3.4 mmol/L) and optimal (2.9 mmol/L) LDL-C treatment goals as defined by pediatric guidelines were reported in only 49% and 14% of patients, respectively.[1–3,26] These results are similar to those reported in most RCTs and clinical case series,[15–17,19,20,22–33] with the exception of a single pediatric preventive cardiology program that targeted these thresholds for more-intensive patient management.[21] Of note, the average LDL-C decrease of 36% in this series was similar to the 32% reported in the RCT cohort follow-up of Luirink et al.[9] in which only 20% of patients were reported to have LDL-C levels below the optimal LDL-C goal. Our results indicate only rare dose escalation to maximum levels, suggesting that in these 5 clinics, providers did not pursue aggressive LDL-C reduction. Surveys of practicing pediatricians and prescription drug plan

data show very low levels of statin treatment in children, despite documented severe LDL-C elevation; this finding may reflect concern that evidence for treatment efficacy and safety in clinical trials will not translate into practice.[35,36] In healthy, asymptomatic pediatric patients, there is ongoing tension between initiation of a powerful medication to achieve recommended treatment goals and the potential for statin side effects in young people who will require long-term—potentially lifelong— therapy for optimal results. Results from this case series provide reassurance that intermediate-term treatment with statins at prescribed doses is effective and safe in children and adolescents in real-world clinical practice settings.

Two patterns of LDL-C elevation are prevalent in youth, as reflected by the patient population referred to these lipid clinics: those with FH, found in ~1:250 individuals who typically have severely elevated LDL-C and non−HDL-C levels from birth due to loss-of-function mutations; and those with CD, noted in up to 40% of obese youth and in patients with familial CD who have moderate-to-severe elevation in TGs, low HDL-C, and variable elevation in LDL-C.[1,25] With lipid subpopulation analysis, both patterns are associated with high levels of total and small, dense LDL particles, a highly atherogenic combination because of enhanced entrapment and retention in the arteriolar subendothelial matrix, the initiating process in atherosclerosis.[37−42] Statin therapy has been shown to significantly improve the lipid subpopulation pattern by decreasing LDL particle number and increasing particle size in both settings.[7,43,44] For our study, lipid

Table 4. Pediatric statin reports

First author/pub yr	Study type	Subject #	Start statin age (y) (x/range; $x \pm$ SD; median/IQR)	B/L LDL-C (mmol/L) ($x \pm$ SD; median /IQR); or x/range	Statin duration ($x \pm$ SD; x/range; median/IQR)	% LDL-C decrease	Side effects →D/C	% on statin last F/U	% LDL-C ≤ 3.4 mmol/L
Carreau[19] 2011	Case series	185	11 y (range: 4.8−17.8)	7.1 (range: 4.8−12.1)	2.2 y (range: 0.25−7)	20.8%	2.2%	n/r	n/r
Gandelman[16] 2011	PK−PD	39	11.7 ± 1.9	5.8 ± 1.0	8 wk	39.7%	0	n/r	50%
Elis[20] 2014	Case series	89	15 ± 4 y	6.5 ± 1.3	13 ± 8 y	43%	0	100%	39%
Kusters[29]; Braamskamp[30] 2014/2015	RCT cohort (10 y s/p RCT)	194	12.9 y (CI: 12.5,13.4)	6.1 (5.9−6.3)	10 y*	27%	3/194	84%	n/r
Gelissen[31] 2014	Audit*	157	Range: 1−18 y	n/r	n/r	n/r	n/r	n/r	n/r
Braamskamp JAM[17,†] 2015	RCT	106 RCT; 112 open label ext.	10.6 ± 2.9	6.0 ± 1.2	12 wk RCT; 52 wk ext	31% RCT; 37.8% ext	2/106 RCT; 1/112 ext	98% RCT; 88.4% ext	23% RCT; /42% ext
Mendelson[21] 2016	Case series	97	147 (IQR: 7)	5.6 (IQR: 2.0)	1 y (IQR: 1.3)	∼37%	0	83.5%	60% at 1 y, 73% at 2 y, 87% at 3 y
Saltijeral[32] 2017	Registry	217	15 (IQR: 14−16)	4.1 (IQR: 3.4−5.0)	4.69 y (IQR: 2.48−6.38)	12.5%	n/r	n/r	41.5%
Humphries[33] 2018	Registry	158	10.7 ± 3.2	5.9 ± 1.5	2.7 ± 2.4 y	31%	n/r	n/r	44.4%
Bogsrud[22] 2018	Case series	176	12.5 ± 2.0	5.8 ± 1.2	2.4 y ± 1.9	38%	0	97%	58%
Luirink[9] 2019	RCT cohort 18 y s/p RCT	184	14.0 ± 3.1	6.1 ± 1.3	18 y Range:15−21	32%	2.2%	79%	20% < 100 mg/dL

Table shows observational series published after 2008 (when the evidence review for the NHLBI guidelines[1] was completed) and randomized trials and their follow-up studies not included in the 2019 Cochrane review.[15]

B/L, baseline; CI, confidence interval; D/C, discontinuation; ext, extension; F/U, follow-up; IQR, Interquartile range; LDL-C, low-density lipoprotein cholesterol; n/r, not reported; pub yr, publication year; RCT, randomized controlled trial; s/p, status post; x, mean.

* Hospital-based audit of inpatients and outpatients; only 22% of patients had hypercholesterolemia.

† Two-stage study: 12-week RCT; 52-week open extension.

subpopulation analysis was not available, but the response to statin treatment was clearly different in the 2 groups. Statins improved mean lipid measures in patients with both patterns, but the LDL-C−lowering effect was greater in children with FH. By contrast, TG levels decreased significantly more in the CD patients than did the TG:HDL-C ratio. A lower TG:HDL-C ratio is a desirable result, shown to be associated with larger LDL particles in children.[40] Statins have been used effectively in adults with CD[43,44]; the results of this study support consideration of statin treatment in youth with the CD pattern.

Measures of patient safety were assessed independently by each centre and reflect reported, potential statin adverse effects related to growth, muscle, and liver toxicity.[1−3,26] Serial measurement of anthropometrics showed no significant impact on growth assessed by height-, weight-, and BMI-for-age percentiles during statin treatment. In adults, initiation of statin treatment is associated with transient elevation in hepatic enzymes in up to 3% of patients, but true hepatic toxicity is extremely rare, and current guidelines no longer recommend routine measurement of liver enzyme levels.[45] In meta-analyses of statin trials in children, incidence of hepatic enzyme elevation did not differ between statin-treated and placebo groups, and there was no diagnosis of liver disease.[14,15] In our series, serial evaluation of hepatic enzymes showed no evidence of sustained elevation. Reported findings of muscle toxicity in adults range from asymptomatic increases in creatinine kinase levels, to myalgia without CK elevation, to myositis with CK elevation; extremely rarely, statin treatment has been associated with rhabdomyolysis.[46] Transient elevations of CK levels are common in normal children, related to activity, but muscle toxicity of any kind associated with statin treatment is rare, and rhabdomyolysis has not yet been reported.[1,14,15] However, even when all reports are combined, the total number of reported pediatric statin subjects is too small to evaluate this rare risk. In our study, potential muscle toxicity was assessed by clinical reports of muscle pain and by serial measurement of CK levels. No sustained elevation of CK levels occurred, and no clinical cases of myositis were diagnosed. In statin-treated youth, a recent analysis of serial CK levels as a measure of muscle-related adverse effects suggested that these are of little or no value.[47] In adults, statin therapy has been shown to increase the risk of new-onset diabetes, with risk directly correlated with greater intensity of therapy and extent of LDL-C lowering.[48,49] Adults with acquired diabetes also have been primarily older individuals at high baseline risk for type 2 diabetes.[50] In pediatric patients enrolled in statin trials, there have been no reported effects on fasting glucose and/or HbA1c, and no reported cases of incident diabetes.[1,14−17,27−32] Recent studies in adults and children suggest that there is no increased risk of diabetes mellitus in patients with FH treated with statins, raising the possibility that the gene mutations that cause FH may also provide protection against diabetes.[51−53] Existing pediatric guidelines[1−3,26] do not recommend routine evaluation of fasting glucose and HbA1c levels during statin treatment, and these measures were not assessed consistently enough for analysis in this series. In the past, adverse cognitive effects have been reported anecdotally in adults on statin treatment, but subsequently, multiple longitudinal studies and RCTs have not identified any adverse association between statins and cognitive function.[54] In this clinical series, there were no recorded complaints of memory loss or confusion. The impact of statins on cognitive development is an important question that cannot be addressed by this study. Taken together, there were no significant safety concerns associated with statin therapy in our study population. No patient required discontinuation of statin treatment because of clinical complaints; there were no clinically significant potential adverse effects; and no sustained changes in safety laboratory measures were reported.

Our retrospective observational study has limitations. Most importantly, we do not have uniform follow-up for all patients at each timepoint, which may bias results, as only patients who were tested could be included in the assessment of LDL-C reduction and of treatment safety. We included all pediatric patients with elevated LDL-C who started statin therapy from the 5 prevention clinics, regardless of the underlying cause of dyslipidemia. The assessment of the dyslipidemia diagnosis was clinical, per the pediatric cardiologist with no routine genotype determination. Although medication and dose were recorded at each visit, it was sometimes not possible to account for changes in dose or medication. Adherence was self-reported by the child or family, and there was no way to correlate lipid results with drug compliance. There is no objective measure of statin effect. Although the duration of statin therapy is among the longest reported from clinical series to date, long-term sustainability and safety of statin treatment in youth have not been addressed. Finally, adherence to heart-healthy lifestyle guidelines was not assessed, so potential synergy between lifestyle change and statin treatment could not be evaluated.

Conclusion

Despite these limitations, results from our study in real-world clinical practice indicate that intermediate-term treatment with statins is effective, safe, and well-tolerated, with consistently high compliance in children and adolescents with severe elevation of LDL-C.

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Disclosures

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