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Safety of Prescribing Statins in Childhood Dyslipidemia

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Abstract

Hyperlipidemia is on the rise in pediatrics, leading to early coronary artery disease complications. Familial hypercholesterolemia is an important risk factor, with the homozygous subtype being more dangerous, yet less prevalent than the heterozygous subtype. Statins are shown to be an effective treatment in this population. This systematic review will emphasize the safety of such drug class in pediatrics, while taking into consideration the latest cholesterol guideline. Cochrane Library, Clinicaltrials.gov, and PubMed were reviewed systematically in June 2019 and rechecked in November 2019 for the past 5 years with keywords like child, safety, hyperlipidemia, and statins, which resulted in nine randomized clinical trials. In short, statins are shown to be intermediately effective—median decrease of low-density lipoprotein cholesterol was 32% achieving the target of < 160 mg/dL in 67% of patients—in lowering lipid levels yet preventing early complications. They are also considered safely tolerated in most cases, even when taken for extended periods, but still not evidently permissible for children below 8 years old, which was the average age of all participants in the trials. Statins should not be given generally for pediatrics of less than 8 years old, in contrast to what was mentioned in the American Heart Association guideline (0–19 age range), since there is no evidence supporting their safety within this age group.

Keywords

- statins
- children
- safety
- familial hypercholesterolemia and hyperlipidemia

Introduction

Dyslipidemia is a disorder of genetic (familial dyslipidemia is an autosomal dominant disorder) or multifactorial backgrounds, and in most cases, it is of mixed etiologies.[1,2] This would make it difficult somehow for distinctive diagnosis. Fortunately, familial hypercholesterolemia (FH) (homozygous subtype is more aggressive and dangerous but less prevalent than the heterozygous subtype with 1/300,000 to 1/1,000,000 and 1/250 respective ratios[3,4]) is easily detected both clinically and by blood tests, where average untreated low-density lipoprotein cholesterol (LDL-C) in heterozygous and homozygous subtypes is $\geq$140 mg/dL and $>$ 500 mg/dL, respectively, excluding secondary causes of dyslipidemia for the patients' diagnosis.[5]

Cardiovascular disease (CVD) is a devastating disease of rapidly increasing prevalence nowadays, whereby it affects 41.5% of the U.S. population, among which 7% are suffering from coronary heart disease where dyslipidemia is one of its main causes.[6] Effects of this disorder manifest toward the second decade of life for the homozygous subtype, with coronary stenosis being detected in men with FH at 17 years, and in women with FH at 25 years of age, versus the typical detection at 40 years and above for heterozygous FH subtype.[7] Moreover, early atherosclerosis, determined by increased carotid intima-media thickness, is detected in untreated FH children.[7]

As a result, early awareness and prophylactic measures are a trending recommendation. This led research to adopt an approach that not only targeted youth, but also infants, who have

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been included in recent guidelines and can be mistakenly considered as a primary prevention benefit group for statins.[8]

Diet is the most effective interventional target till date and should be monitored for all patients (first line). Qualitative dietary approaches to monitor food composition by decreasing sugars and fats, along with counseling strategies for children and their parents, have a significant long-term impact on the outcomes (behavioral improvement in addition to laboratory results) as compared with a quantitative approach.[9,10] Since, as mentioned earlier, CVD risk is multifactorial and dyslipidemia can be precipitated by secondary causes that are classified into or influenced by modifiable and nonmodifiable factors (age, gender, blood pressure, diabetes, physical inactivity, family history, obesity and metabolic syndrome, tobacco exposure, diet and nutrition, lipid levels, inflammatory markers, predisposing conditions, and perinatal factors), adjusting those factors as summarized in this expert panel report[11] is a pivotal step to be implemented. However, not all patients or all cases are adequately responsive, and still some fail to be controlled, so pharmacological interventions are next to consider.

Many articles and reviews showed the efficacy and the impact of this drug class on LDL levels and other lipid profile parameters, which can promise a decrease in the coronary artery disease risk in such a population, even on the long run.[12,13] The most important aspect to look into would be the side effects profile followed by the benefit–risk ratio, pharmacogenomics, and pharmacoeconomics, especially in such a population.[14] In addition, such molecules in those cases are to be prescribed permanently, so it is crucial to consider their long-term side effects.[13]

On the other hand, the recently established guideline was very general because it included the patients with ages varying from zero to 19 years old as candidates for statins, which seems questionable.[8] Since the latest review articles had not tackled such a perspective, nor did they include recent related articles and trials, this purposely provoked the development of our systematic review. With that, many gaps and issues in the research are to be highlighted and discussed later on in this article like the lack of important details, considerations, and responsibilities[15] (i.e., compliance in such population[16]).

Method

The three main databases, Clinicaltrials.gov, PubMed, and Cochrane Library, are searched in June and later on in November 2019 for randomized clinical trials (RCTs) done in the last 5 years, using keywords referring to the age, drug, disease, and review interest (safety): child, children, pediatric, childhood, Statin, HMG-CoA reductase inhibitors, hyperlipidemia, hypercholesterolemia, dyslipidemia, safety, adverse effects, side effects, safety profile, long term safety, and adverse events. Results are scanned to exclude duplicates, pilot studies, and studies based on concurrent drugs (statin plus other antihyperlipidemic drugs). Nine RCTs are left to base our systematic review article on (►**Fig. 1**).

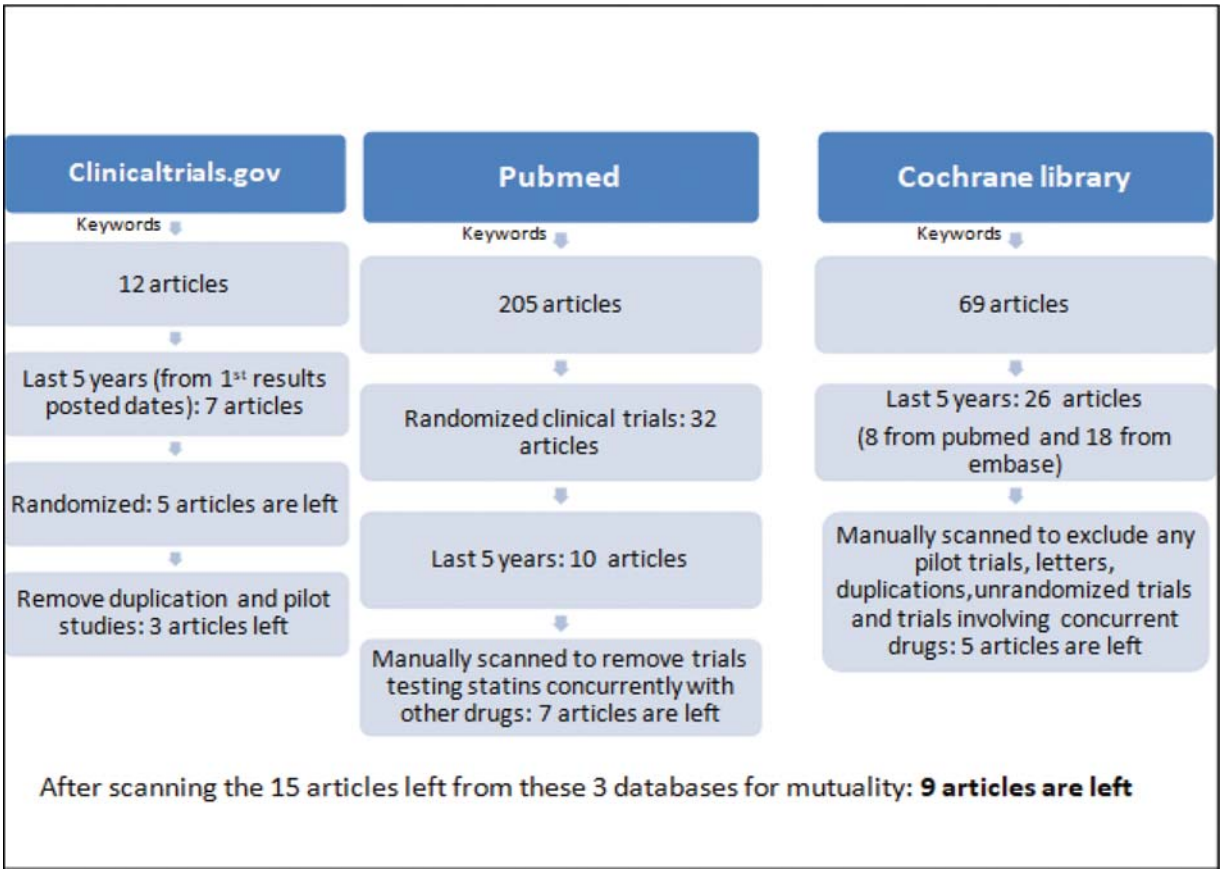

Fig. 1 Method adopted that resulted in 9 randomized clinical trials (RCTs) that are used in this review.

Results and Discussion

Many articles are not randomized trials by themselves, but follow-ups to a randomized trial that were inclusive to the criteria used.[17–19] As a result, these articles were not removed, yet they were considered in the analysis to reach the conclusions of this review, noting that trials tackling such a topic are scarce. Our method yielded nine articles, of which three articles are tackling pitavastatin; two tackling atorvastatin; another two tackling pravastatin; one tackling rosuvastatin; and the last one tackling simvastatin. The details of the results of this systematic method of filtration are summarized in ►**Table 1**.

This review article included the most recent relevant trials—selected with narrow inclusion criteria—which were not involved in the latest systematic reviews.[20] Its outcomes confirmed previous results of efficacy and safety, and reaffirmed our primary outcome, that statins could be prescribed safely for children aged 8 to 10 years or older, to prevent early consequences of FH.

In all trials studying efficacy and/or safety, children enrolled were generally 8 years old and above, except for some studies that lowered the age range to reach 4 year olds for simvastatin,[21] 5 years old for atorvastatin,[22] and 6 year olds for rosuvastatin,[3] atorvastatin,[4] and pitavastatin.[23] All of these studies had not reported any safety issues or discontinuations, and if present, they were not related to any adverse side effect encountered. Moreover, the side effects reported were only mild to moderate, and insignificant.

The issue of not prescribing statins in children below 8 years old follows the recommendation of the National Lipid Association Expert Panel who mentioned that lipid-lowering therapies should be initiated only at the age of 8 to 10 years old, alongside lifestyle modifications,[7] whereas the guideline algorithm included the 0 to 19 age range as a primary prevention benefit group. Even more strict were the 2011 U.S. integrated guidelines for Cardiovascular Health and Risk Reduction in Children, which note that children younger than 10 years old should not be treated with lipid-lowering medications unless they have LDL-C levels$\geq$ 400-mg/dL (mainly the case of homozygous FH [HoFH]).[7] However, in Australia, statins are approved for patients from the age of 6 years onwards,[7] based on the rosuvastatin trial mentioned above,[3] although it is Food and Drug Administration (FDA) approved for HoFH from 7 years old. Knowing that, the drug class—bile acid sequestrants (cholestyramine and cosevelam)—is the only permitted drug class (from several years ago) for children below 8 years old.[24]

A recent criticism (Medscape) to the American Heart Association (AHA) guideline claimed that the threshold for atherosclerotic CVD risk calculation is too low (7.5–10%) and should be increased to be at least 14%. In that scope, it would be suggestive that pediatrics too must have more strict thresholds for statin considerations.

No side effects were witnessed in the rosuvastatin trial,[3] except for low bicarbonate levels at a single visit. In a study using atorvastatin,[22] the most reported side effects in both groups were respiratory infections, acute gastroenteritis, and pyoderma, whereas knee pain, abdominal pain, and headaches were all seen in the atorvastatin group, besides a normalized creatine kinase (CK) level after a slight increase. Also, dosages as high as 20 mg atorvastatin/day for children older than 10 years were clearly safe. In another atorvastatin study,[4] no side effects were reported regarding growth or maturation, yet there were six discontinuations that were not related to side effects, but to unwillingness to take the pill or to inappropriateness to take it due to low LDL levels. Also, 24 children (8.9%) discontinued temporarily or tapered down their medicine during the trial. However, one serious side effect (Ewing's sarcoma) was reported and proclaimed by investigators to be therapy-related. It occurred with a 9-year-old child administering 80 mg atorvastatin. CK elevations were seen more in Tanner stage/scale TS2 children (12.9%) than TS1 children (4.4%).

As pediatrics grow, they go through changes (cognitive, hormonal, and sexual) in which, directly or indirectly, cholesterol plays a crucial role. Meanwhile, in an early study with pitavastatin, the endocrine function was not affected nor was anything detected in it.[25] This was also confirmed with a pravastatin-initiated study,[18] which resulted in no visible effect because enough LDL (blood laboratory values showed LDL in normal range) is still found for hormonal synthesis, noting that the upregulation of LDL receptors also facilitates more entry of LDL to be used for hormone production. In this study, a decrease of only 0.1 nmol/L in testosterone did not affect luteinizing hormone levels, and subsequently did not affect the sexual reproduction system negatively. Contrary to that are the findings in a previous study that detected a decrease of 0.66 nmol/L when moderate intensity statin was given for 1 year. Also, this study framed the effect on dehydroepiandrosterone as controversial, where some studies noticed a decrease, others detected an increase, and some had seen normalization. For simvastatin,[21] only 18 patients completed the study and 27 cases with side effects were reported, in addition to 7 cases from the open label part of the study, of which 5 were serious cases, none were therapy-related, and only 1 case of muscle pain was witnessed with increased CK levels that are still within the normal range. It is important to note that there was a low count of myopathy and rhabdomyolysis side effects in these studies.

In fact, if we looked further, the relation between childhood hyperlipidemia and the development of dyslipidemia in adulthood has not been settled yet.[3,26] A suboptimal reduction in LDL (less than 50% than the recommended guidelines) was noticed with high dosages of pitavastatin. This can be translated into less than expected efficacy, and thus lower CVD risk reduction that imposes a need for treatment change.[22,25] On the other hand, in a study with rosuvastatin, efficiency was equal for children above or below 10 years old with atorvastatin,[4] and it was similar regardless of age/ezetimibe use/apheresis.[3] In a simvastatin study,[21] simvastatin was given for children with mild typical Smith-Lemli-Opitz syndrome (SLOS; autosomal recessive multiple cognitive impairment syndrome characterized by accumulation of a cholesterol precursor due to gene mutation(s) of a related enzyme) concurrently with dietary cholesterol supplementation, and was found to be effective even in decreasing cerebrospinal fluid, levels of cholesterol (simvastatin is

Table 1 Summarizes the results stating the main issues extracted

Molecule tested	Related article (s)	Sample size	Criteria	Outcomes	Limitations	Author/year
Atorvastatin	Effect of Atorvastatin on Dyslipidemia and Carotid Intima-Media Thickness in Children with Refractory Nephrotic Syndrome: A Randomized Clinical Trial	30 out of 60 1:1 ratio	-Age: 5–18 y -10 mg dose -Time: 1 y - R, PC, Pa, DB	From 23: -AEs same in 2 groups -No significant efficacy	Post hoc power = 68%	Pankaj, 2018
	A 3-year Study of Atorvastatin in Children and Adolescents with Heterozygous FH	272 out of 400	-Age: 6–15 y -Time: 3 y -All doses -MC, open-label	From 206: 21 (7.7%) mild to moderate SEs	Small sample for 80 mg dose	Gisle, 2016
Pitavastatin	Efficacy and Safety of Pitavastatin in Children and Adolescents at High Future Cardiovascular Risk	106	-Age: 6–17 y -Time: 12 + 52 wk -Max dose: 4mg -R, DB, PC	-No safety issues -75% mild SEs	-Short study -Small sample size	Marjet, 2015
	Efficacy and Safety of Pitavastatin in Japanese Male Children with Familial Hypercholesterolemia	14 males	-Age: 10–15 y -Time: 52 wk - MC, R, DB, Pa	-Not severe SEs nor treatment related -71% with 2mg -100% with 1 mg	-No females -Small sample size	Mariko, 2016
	Efficacy and Safety of Pitavastatin in Children and Adolescents with Familial Hypercholesterolemia in Japan and Europe		Open- label extension study	-Minimum effect of ethnicity - No important differences	-Short study -Difference in demographic traits between studies	Mariko, 2018
Rosuvastatin	Efficacy of Rosuvastatin in Children with Homozygous Familial Hypercholesterolemia and Association with Underlying Genetic Mutations	13 out of 20	-Age: 6–18 y -Max dose: 20 mg -Time: 24 wk -R, DB, crossover then open-label	-Few not serious SEs -Moderate LDL ↓ of 85 mg/dL	-Short duration -No study impact on CVD	Evan, 2017
Simvastatin		23				

Table 1 (*Continued*)

Molecule tested	Related article (s)	Sample size	Criteria	Outcomes	Limitations	Author/year
	A Placebo-Controlled Trial of Simvastatin Therapy in Smith-Lemli-Opitz Syndrome		-Max dose: 40 mg -Age: 4–18 y -Time: 2 y -R, DB, PC, crossover	-Good efficacy -No safety issues -Reported SEs not treatment related	Limited results due to: -Small sample size -Short study	Christopher, 2016
Pravastatin - continued with mixed molecules	Long-Term Statin Treatment in Children with FH: More insight into Tolerability and Adherence	214	-10 y follow-up after 2 y trial -Questionnaire -Age: 8–18 y	-SEs = 19.5% but not serious -Success with 205 persons	Cannot generalize: -Small sample compared with FDA -Firm inclusion/exclusion criteria	Marjet, 2015
	Gonadal Steroids, Gonadotropins and DHEAs in Young Adults with FH who had Initiated Statin Therapy in Childhood	309 = 214 + 95 (unaffected siblings)	-10 y follow-up after 2 y trial -R, PC -Age: 8–18 y	-150 remained -No effect on growth	-Control group used -No stratification	Marjet, 2015

Abbreviations: AE, adverse event; CVD, cardiovascular disease; DHEA, dehydroepiandrosterone; FDA, Food and Drug Administration; FH, familial hypercholesterolemia; LDL, low-density lipoprotein; SE, side effect.

Note: Type of trials: DB, double blind; MC, multicentered; Pa, parallel trial; PC, placebo controlled; R, randomized. The red fringe/arrow = the trial is a follow-up study of the two marked trials.

lipophilic and can enter blood–brain barrier), and children irritability (symptom of SLOS).

Despite the current absence of suitable statin dosage forms for pediatrics, adherence was shown to be of better quality in young people which was attributed to habitual adaptation, rather than prevention character.[17]

Since dyslipidemia is a disorder characterized as chronic, patients need long-term treatment and care, with one of the important approaches relying on referring to long-term studies for clinicians to be able to take the appropriate decision(s). Although a 10-year follow-up was done in some studies,[17,18] this cannot be generalized for all molecules of the same class (mean study duration = 1 year) and may be considered a limitation accused of short duration compared with the lifetime intake necessity in children with FH.

Despite the fact that this current review does not follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, its main limitation is the little number of articles found after filtration, owing to the search of only three databases for a not-so prevalent topic, while also excluding unregistered trials. However, a common limitation was found in most of the above studies: the sample size was not large enough for many tested molecules, even with some studies including over 100 children. For example, the mean number of enrolled children was 20 in studies testing for rosuvastatin,[3] pitavastatin,[25] simvastatin,[21] and atorvastatin.[22] In a study initiated with pravastatin,[17] a limitation in the form of a small sample size was stated even though the study included 214 children. This is mainly because compared with the FDA report of fatal rhabdomyolysis of (0.15/1 million) risk ratio, encountering the latter condition in a sample of 214 children is nearly negligible.

Other small limitations were restricted to individual studies. In a pravastatin study,[18] they mentioned it would be better to choose untreated FH children as a control group rather than unaffected siblings, but due to ethical issues, this was not adopted. And due to the small sample size, it was inapplicable to stratify patients on different molecules with different potencies and dosages in an attempt to test if this can alter gonads functions. In an atorvastatin study,[22] the susceptibility of type two errors was high owing to its low power (68%). In addition, they claimed that treatment effects may be altered because of diet and angiotensin-converting enzyme inhibitor variables.

This article can motivate future investigations to be assertive toward findings that can answer several questionable issues mentioned above, mainly regarding safety in younger children in longer and larger clinical trials. Other issues that could be resolved are proving or disproving the efficacy of any other alternative or clearly specifying the benefit group criteria for this population, possibly through detailed algorithms.

Conclusion

In conclusion, even if statins were found to be effective and safely tolerated in pediatrics, we cannot extrapolate or generalize prescribing them for children below 8 years old, as the recent AHA cholesterol guideline had stated.

Despite the good intention of helping such a population, the one benefit/efficacy is only modest. Based on that, the guideline has passed over the possibility of exposing such a population to harm: one that is due to the various and rapid pharmacokinetic and dynamic profiles as well as changes in pediatrics, and another due to extra burdens (i.e., financial). When such a treatment is to be lifelong, the trials administered are not based on long enough of a duration or on large sample sizes.

Note

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Conflict of Interest

None declared.

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