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STATIN TREATMENT AND POTENCY ROLE IN CHILDREN WITH FAMILIAL HYPERCHOLESTEROLEMIA: A REVIEW OF EFFICACY AND SAFETY

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Abstract:
Familial hypercholesterolemia (FH)is a genetic disorder that causes elevated levels of low-density lipoprotein cholesterol (LDL-C), increasing the risk of premature cardiovascular disease (CVD) at an early age. FH is classified into two forms: heterozygous FH (HeFH) and homozygous FH (HoFH). The identification of FH in children is crucial, as untreated patients have a higher risk of developing CVD than the general population. Statins are the first-line agents for FH treatment in children and aim to lower LDL-C levels and reduce the risk of CVD, especially in young adults. This review aims to provide a rationale for statin therapy in the management of pediatric FH and discusses the potential benefits and risks associated with statin efficacy. The article also discusses the overview of statins, statin potency, and the potential risks associated with statin therapy.

Keywords: Hyperlipoproteinemia Type II, Hydroxymethylglutaryl-CoA Reductase Inhibitors, Children

Introduction

Familial hypercholesterolemia (FH) is a genetic disorder characterized by elevated levels of low-density lipoprotein cholesterol (LDL-C). This disease is caused by mutations in the genes responsible for regulating the metabolism of LDL-C, leading to a reduced ability of the body to remove cholesterol from the bloodstream. The prevalence of FH is estimated to be 1 in 250 to 1 in 500 people and increases the risk of cardiovascular disease (CVD) at an early age [1].

FH is classified into two forms: heterozygous FH (HeFH) and homozygous FH (HoFH). HeFH is the most common form and is caused by a single-copy gene mutation, while HoFH is a rarer form that occurs when two copies of the mutated gene are present [2]. HeFH is associated with high levels of LDL-C from childhood, and individuals affected with this form of FH are at a high risk of developing

premature CVD. HoFH is a much more severe form of the disease, and individuals with this form of FH have extremely high levels of LDL-C, leading to severe CVD in early adulthood [3].

Identification of FH in children is crucial, as treatment can be started at a younger age, before the manifestations of CVD [4] Untreated HF patients have a 10–20 times greater risk of developing CVD than the general population [5]. People with FH who receive early treatment have significantly lower rates of CVD and mortality [6]. In contrast, delayed diagnosis and treatment of FH can lead to premature CVD and other complications that can severely affect quality of life [7].

Statins are the first-line agents for FH treatment in children and the general population. The primary goal of FH treatment is to lower LDL-C levels and reduce the risk of CVD, especially as young adults since usually the first sign of the disease is myocardial infarction and many times, death [8]. Statins significantly reduce LDL-C levels in pediatric FH patients and are generally well tolerated [9].
The purpose of this review is to provide a rationale for statin therapy in the management of pediatric FH and discuss the potential benefits and risks associated with statin efficacy.

Methodology:
This narrative review aims to investigate the role of statin potency in the treatment of familial hypercholesterolemia in children. The search was conducted using articles found on PubMed and Google Scholar that were written in English. The keywords used were statins, statin-potency, familial hypercholesterolemia, familial hypercholesterolemia therapy and children. These terms then were crossed in the following combinations: “statin” or “statin potency” AND “familial hypercholesterolemia” or “familial hypercholesterolemia therapy” AND “children” or “pediatrics”.

Overview of statins
Statins are competitive inhibitors of HMG-CoA reductase, the enzyme that catalyzes the rate-limiting step of cholesterol synthesis in the liver [10]. By reducing the activity of this enzyme, statins decrease the production of cholesterol, particularly LDL-C, which is known to be a significant contributor to the development of atherosclerosis and CVD [11].

Statins upregulate the expression of LDL receptors on the surface of hepatocytes, which enhances the clearance of circulating LDL-C from the bloodstream, leading to a further reduction in its level [12]. In addition to their cholesterol-lowering effects, statins exhibit pleiotropic effects that are likely to contribute to their overall cardiovascular benefits [13]. These include the reduction of inflammation, improvement of endothelial function, and stabilization of atherosclerotic plaques. It has been suggested that these effects could account for the residual risk reduction observed in patients treated with statins, even in the presence of optimal LDL-C levels [14].

Statin potency
Potency is a pharmacological term used to describe the strength of a drug in reducing LDL-C levels. The measurement of potency is typically determined by the percentage reduction of LDL-C achieved by the drug [15]. Patients with elevated levels of LDL-C may necessitate the administration of more potent statins to attain their treatment objectives. Moreover, individuals with additional cardiovascular disease (CVD) risk factors, such as a history of heart disease or diabetes, may derive benefits from more potent statins 16. Nevertheless, it is crucial to strike a balance between the advantages of statin therapy and the potential risks of side effects such as hepatic damage and muscular pain. The selection of a specific statin therapy should be tailored to the individual and capable of achieving the desired treatment goals, considering the incidence and severity of reported adverse effects [17].

Statins are categorized based on their efficacy in reducing LDL-C levels into three distinct groups. The first group comprises low-intensity statins, which can reduce LDL-C levels by no more than 30%. The second category consists of moderate-intensity statins that can lower LDL-C levels between 30%

and 49%. Finally, high-intensity statins constitute the third group and can reduce LDL-C levels by 50% or more. This classification system is useful in guiding the selection of the appropriate statin therapy for individual patients with varying degrees of LDL-C elevation [18].***Fig 1***

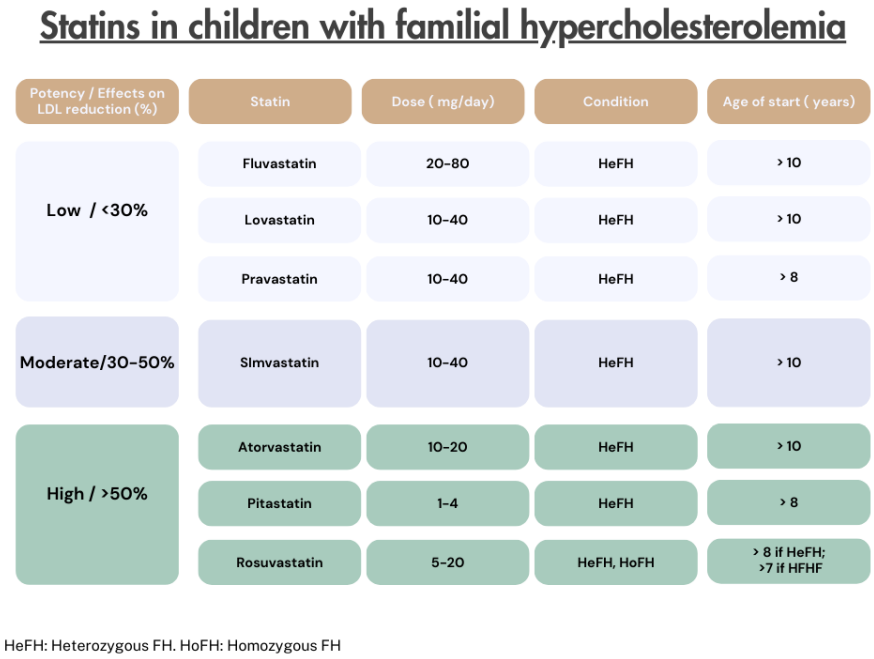

Figure 1. Statins in children with familial hypercholesterolemia

The administration of statin therapy is generally safe and well-tolerated. Although there exists a risk of adverse events associated with the administration of statin therapy, most side effects can be managed by adjusting the dose or switching to a different statin. Furthermore, the established advantages of statin therapy in mitigating the risk of cardiovascular disease are grounded in extensive clinical research and evidentiary support [19].In the United States, pravastatin and pitavastatin have been approved by the FDA for children aged ≥ 8 years with HeFH ***(Fig.2)*.**

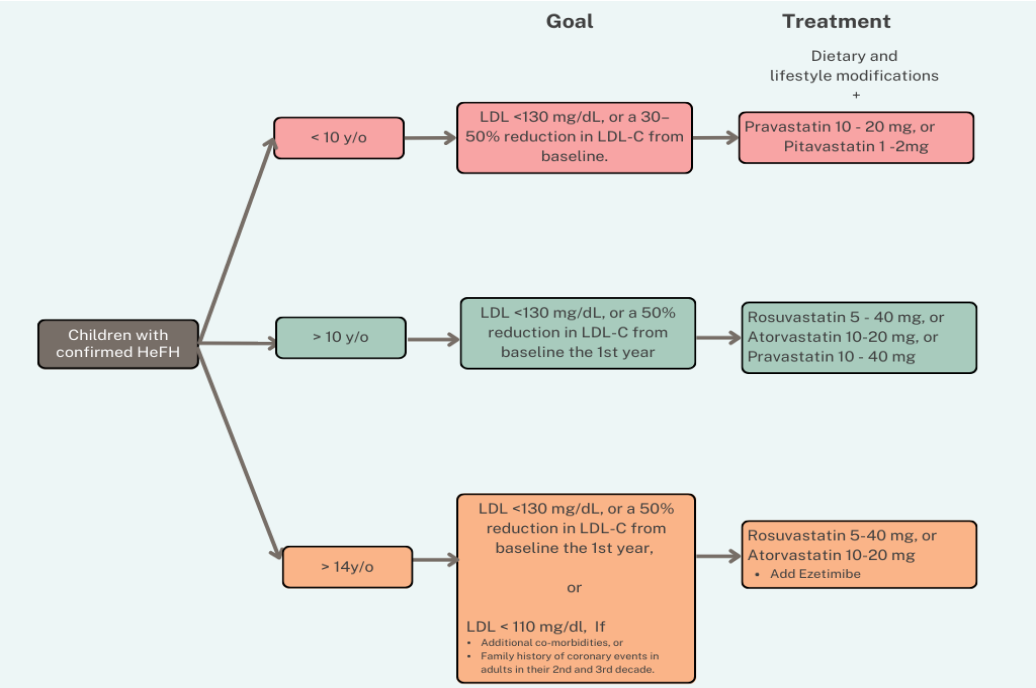

Figure 2. Proposed algorithm of heterozygous FH in children and adolescents

Lovastatin, simvastatin, fluvastatin, atorvastatin, and rosuvastatin have been approved for use in children aged ≥10 years with FH. At the higher prescribed doses, atorvastatin and rosuvastatin are more potent than the other approved medications [20]. Rosuvastatin was recently approved for use in children from 7 years old with HoHF [21] (***Fig.3)***

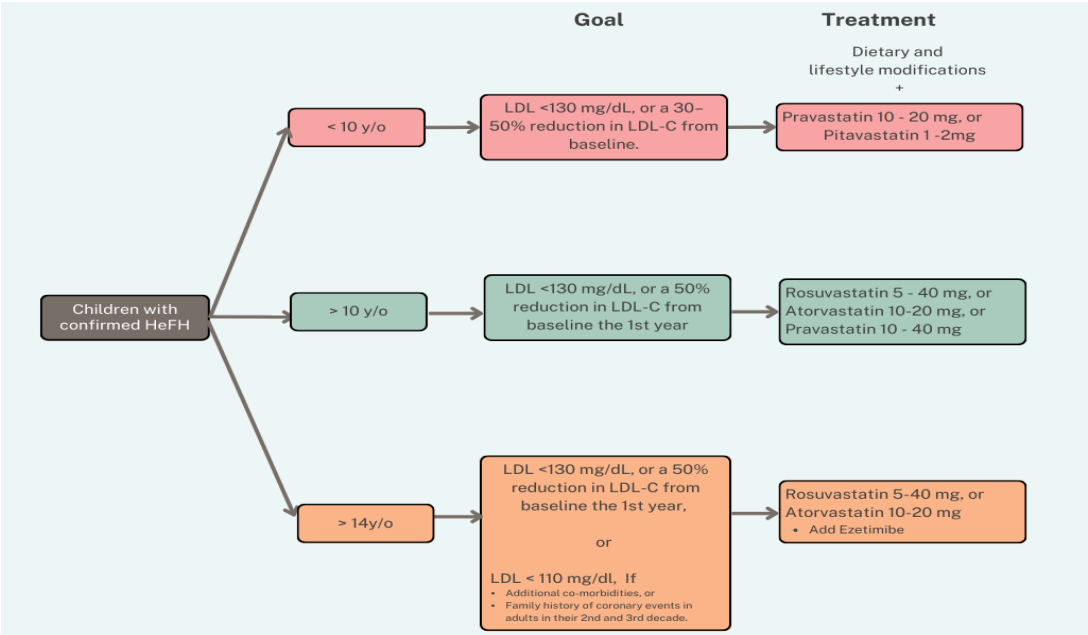

FIgure 2. Proposed algorithm of heterozygous FH in children and adolescents

Low potency statins

Fluvastatin. In patients with HeFH, fluvastatin (20 mg as a starting dose, and a maximum of 80 mg/day) significantly reduced LDL-C levels by 30.6% in the treatment group compared to the placebo group ($p<0.001$). The mean decrease in LDL-C levels was 47.8 mg/dL in the fluvastatin group, compared to an increase of 3.3 mg/dL in the placebo group. The study also found that fluvastatin was well tolerated, with no significant differences in adverse events between the treatment and placebo groups. The most common adverse events reported were upper respiratory tract infections and headaches [22].

Lovastatin. Lovastatin has been found to reduce the LDL-C levels between 25-29% given at a starting dose of 10 mg/day, and a maximum of 40 mg/day in children aged 8-18 years [23].

Pravastatin. Several studies have investigated the efficacy of pravastatin in reducing LDL-C levels in children with familial hypercholesterolemia. Studies have reported an LDL-C reduction of 24-30%, besides, carotid Intima-Media thickness regression compared with placebo. No differences were observed in growth, muscle or liver enzyme levels, or pubertal development between groups [24,25,].

Moderate potency statins

Simvastatin. The study by de Jongh [26] showed reductions of 30% in total cholesterol levels and a 39.8% reduction in LDL-C levels. Also, simvastatin showed an improvement in endothelial dysfunction toward normal levels after the short term. Simvastatin therapy showed a better response in children with the C646Y mutation LDL receptor genotype [27].

High potency statins

Atorvastatin. The magnitude of LDL-C reduction in children with FH varies between studies but ranges from 39% to 50.1% compared to baseline levels [28]. Treatment with atorvastatin over 3 years in children and adolescents with HeFH had no impact on growth/maturation, was well tolerated, and only 2.2% of the subjects discontinued treatment because of adverse events [29].

Pitavastatin. In terms of its effect on LDL-C levels in adults, pitavastatin is approximately six times stronger than atorvastatin and 1.7 times more potent than rosuvastatin [30]. Pitavastatin in children shows a reduction based on the given dose. With 1 mg/day, the reduction was 23-28.5%, and with the 2 mg dose, the reduction observed was between 30.1-36.3% [31].

Rosuvastatin. Rosuvastatin is a drug indicated for the treatment of the heterozygous and homozygous forms of FH. In patients with the heterozygous form, the reduction in LDL-C levels ranged from 47.3% to 50.8% [32,33]. For patients with the homozygous form, rosuvastatin achieved a 41% reduction in LDL-C levels by 41% compared to baseline. The largest mean reduction in LDL-C-C with rosuvastatin was observed in the subgroup with two defective LDLR mutations. [34]

What are the risks associated with statin use in FH children?

As with any other medication, there are potential risks and side effects associated with the use of statins in children with FH.Overall, statins are generally well-tolerated.

Despite concerns about the potential risk for liver dysfunction due to statin therapy in children, available evidence does not support an increased risk of liver failure in this population.[35].

In adults, the likelihood of rhabdomyolysis of patients taking statins is estimated to be less than 0.1%. However, the risk of rhabdomyolysis can vary and may depend on factors such as the dosage and potency of statin used, as well as comorbidities or concurrent usage of medications that may heighten the risk. The risk of rhabdomyolysis in children diagnosed with FH who receive statin therapy is relatively lower compared than that in adult patients, although the overall risk remains relatively low [36].

There is no evidence indicating a difference in sexual development, as assessed by the Tanner staging method, between the group receiving statins and the group receiving a placebo [37].

Data have been accumulating on the potential adverse effects of these drugs on glycemic control in patients with type 2 diabetes [38]. However, the risk of type 2 diabetes in children with FH on statin therapy is unclear [39]. A recent study assessing the association between treatment with statins and changes in insulin resistance markers in children and adolescents in Slovenia found no significant changes [40].

Children with FH who are receiving statin therapy should undergo routine monitoring of their cholesterol levels, liver function tests, and creatine kinase levels. If a child experiences muscle symptoms, it is recommended to reduce the statin dose, switch statins, or consider the use of alternative treatments for children who cannot tolerate statin therapy [41]. It is important to manage potential drug interactions, particularly with medications that increase the risk of myopathy [42].

Conclusion

The early detection of FH in children is of fundamental importance, given that untreated FH may lead to an elevated risk of CVD at a young age. Statins represent the primary therapeutic option for managing FH in children, and all individuals diagnosed with FH, regardless of age, should commence statin therapy promptly. High-potency statins offer a feasible way to achieve treatment objectives and mitigate the risk of CVD in this cohort. However, clinicians should adopt a personalized approach to therapy and remain aware of the potential benefits and risks associated with each type of statin.

REFERENCES

1. Bouhairie, V. E., & Goldberg, A. C. (2015). Familial hypercholesterolemia. Cardiology clinics, 33(2), 169–179. https://doi.org/10.1016/j.ccl.2015.01.001.
2. Ruel, I., Brisson, D., Aljenedil, S., Awan, Z., Baass, A., Bélanger, A., Bergeron, J., Bewick, D., Brophy, J. M., Brunham, L. R., Couture, P., Dufour, R., Francis, G. A., Frohlich, J., Gagné, C., Gaudet, D., Grégoire, J. C., Gupta, M., Hegele, R. A., Mancini, G. B. J., … Genest, J. (2018). Simplified Canadian Definition for Familial Hypercholesterolemia. The Canadian journal of cardiology, 34(9), 1210–1214. https://doi.org/10.1016/j.cjca.2018.05.015

3. Gidding, S. S., Champagne, M. A., de Ferranti, S. D., Defesche, J., Ito, M. K., Knowles, J. W., McCrindle, B., Raal, F., Rader, D., Santos, R. D., Lopes-Virella, M., Watts, G. F., Wierzbicki, A. S., & American Heart Association Atherosclerosis, Hypertension, and Obesity in Young Committee of Council on Cardiovascular Disease in Young, Council on Cardiovascular and Stroke Nursing, Council on Functional Genomics and Translational Biology, and Council on Lifestyle and Cardiometabolic Health (2015). The Agenda for Familial Hypercholesterolemia: A Scientific Statement from the American Heart Association. Circulation, 132(22), 2167–2192. https://doi.org/10.1161/CIR.0000000000000297
4. 19. Capra ME, Pederiva C, Banderali G, Biasucci G. Prevention starts from the crib: the paediatric point of view on detection of families at high cardiovascular risk. Ital J Pediatr. 2021;47:51. doi: 10.1186/s13052-021-00985-x. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
5. Vallejo-Vaz, A. J., Kondapally Seshasai, S. R., Cole, D., Hovingh, G. K., Kastelein, J. J., Mata, P., Raal, F. J., Santos, R. D., Soran, H., Watts, G. F., Abifadel, M., Aguilar-Salinas, C. A., Akram, A., Alnouri, F., Alonso, R., Al-Rasadi, K., Banach, M., Bogsrud, M. P., Bourbon, M., Bruckert, E., … Ray, K. K. (2015). Familial hypercholesterolaemia: A global call to arms. Atherosclerosis, 243(1), 257–259. https://doi.org/10.1016/j.atherosclerosis.2015.09.021
6. Ann Marie Navar, Lawrence J. Fine, Walter T. Ambrosius, Arleen Brown, Pamela S. Douglas, Karen Johnson, Amit V. Khera, Donald Lloyd-Jones, Erin D. Michos, Mahasin Mujahid, Daniel Muñoz, Khurram Nasir, Nicole Redmond, Paul M Ridker, Jennifer Robinson, David Schopfer, Deborah F. Tate, Cora E. Lewis, Earlier treatment in adults with high lifetime risk of cardiovascular diseases: What prevention trials are feasible and could change clinical practice? Report of a National Heart, Lung, and Blood Institute (NHLBI) Workshop, American Journal of Preventive Cardiology, Volume 12, 2022,7.- Versmissen, J., Oosterveer, D. M., Yazdanpanah, M., Defesche, J. C., Basart, D. C., Liem, A. H., Heeringa, J., Witteman, J. C., Lansberg, P. J., Kastelein, J. J., & Sijbrands, E. J. (2008). Efficacy of statins in familial hypercholesterolaemia: a long term cohort study. BMJ (Clinical research ed.), 337, a2423. https://doi.org/10.1136/bmj.a2423
7. 8.- Civeira, F., Arca, M., Cenarro, A., & Hegele, R. A. (2022). A mechanism-based operational definition and classification of hypercholesterolemia. Journal of clinical lipidology, 16(6), 813–821. https://doi.org/10.1016/j.jacl.2022.09.006
8. Endo A, Tsujita Y, Kuroda M, Tanzawa K. Inhibition of cholesterol synthesis in vitro and in vivo by ML-236A and ML-236B, competitive inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A reductase. Eur J Biochem.1977; 77:31–36.
9. Goldberg, A. C., Hopkins, P. N., Toth, P. P., Ballantyne, C. M., Rader, D. J., Robinson, J. G., Daniels, S. R., Gidding, S. S., de Ferranti, S. D., Ito, M. K., McGowan, M. P., Moriarty, P. M., Cromwell, W. C., Ross, J. L., Ziajka, P. E., & National Lipid Association Expert Panel on Familial Hypercholesterolemia (2011). Familial hypercholesterolemia: screening, diagnosis and management of pediatric and adult patients: clinical guidance from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. Journal of clinical lipidology, 5(3 Suppl), S1–S8. https://doi.org/10.1016/j.jacl.2011.04.003
10. McKenney J. M. (2003). Pharmacologic characteristics of statins. Clinical cardiology, 26(4 Suppl 3), III32–III38. https://doi.org/10.1002/clc.4960261507
11. Liu, A., Wu, Q., Guo, J., Ares, I., Rodríguez, J. L., Martínez-Larrañaga, M. R., Yuan, Z., Anadón, A., Wang, X., & Martínez, M. A. (2019). Statins: Adverse reactions, oxidative stress and metabolic interactions. Pharmacology & therapeutics, 195, 54–84.
12. Oesterle, A., Laufs, U., & Liao, J. K. (2017). Pleiotropic Effects of Statins on the Cardiovascular System. Circulation research, 120(1), 229–243. https://doi.org/10.1161/CIRCRESAHA.116.308537
13. Chou R, Cantor A, Dana T, et al. Statin Use for the Primary Prevention of Cardiovascular Disease in Adults: A Systematic Review for the U.S. Preventive Services Task Force [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2022 Aug. (Evidence Synthesis, No.

219.) Table 1, Statin Dosing and ACC/AHA Classification of Intensity. Available from: https://www.ncbi.nlm.nih.gov/books/NBK583664/table/ch1.tab1/
14. Iyen B, Akyea RK, Weng S, Kai J, Qureshi N. Statin treatment and LDL-cholesterol treatment goal attainment among individuals with familial hypercholesterolaemia in primary care. Open Heart. 2021 Oct;8(2):e001817. doi: 10.1136/openhrt-2021-001817. PMID: 34702779; PMCID: PMC8549660.
15. Zhang, Q., Dong, J., Yu, Z. (2020). Pleiotropic use of Statins as non-lipid-lowering drugs. International Journal of Biological Sciences, 16(14), 2704-2711. https://doi.org/10.7150/ijbs.42965.
16. Almeida, S. O., & Budoff, M. (2019). Effect of statins on atherosclerotic plaque. Trends in cardiovascular medicine, 29(8), 451–455. https://doi.org/10.1016/j.tcm.2019.01.001
17. Grundy S, Stone N, Bailey A, et al. 2018AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol. J Am Coll Cardiol. 2019 Jun, 73 (24) e285–e350.https://doi.org/10.1016/j.jacc.2018.11.003
18. Hussain, A., & Ballantyne, C. M. (2021). New Approaches for the Prevention and Treatment of Cardiovascular Disease: Focus on Lipoproteins and Inflammation. Annual review of medicine, 72, 431–446. https://doi.org/10.1146/annurev-med-100119-013612
19. Sunil, B., & Ashraf, A. P. (2020). Statin Therapy in Children. En A. Abukabda, M. Suciu, & M. Andor (Eds.), Cardiovascular Risk Factors in Pathology. IntechOpen. https://doi.org/10.5772/intechopen.91367
20. Martin PD, Warwick MJ, Dane AL, Hill SJ, Giles PB, Phillips PJ, et al. Metabolism, excretion, and pharmacokinetics of rosuvastatin in healthy adult male volunteers. Clinical Therapeutics. 2003;25(11):2822-2835
21. Van der Graaf, A., Nierman, M. C., Firth, J. C., Wolmarans, K. H., Marais, A. D., & de Groot, E. (2006). Efficacy and safety of fluvastatin in children and adolescents with heterozygous familial hypercholesterolaemia. Acta paediatrica (Oslo, Norway : 1992), 95(11), 1461–1466. https://doi.org/10.1080/08035250600702602
22. Stein EA, Illingworth DR, Kwiterovich PO, et al. Efficacy and safety of lovastatin in adolescent males with heterozygous familial hypercholesterolemia: a randomized controlled trial. JAMA. 1999;281:137–143. [PubMed] [Google Scholar]
23. Knipscheer, H. C., Boelen, C. C., Kastelein, J. J., van Diermen, D. E., Groenemeijer, B. E., van den Ende, A., Büller, H. R., & Bakker, H. D. (1996). Short-term efficacy and safety of pravastatin in 72 children with familial hypercholesterolemia. Pediatric research, 39(5), 867–871. https://doi.org/10.1203/00006450-199605000-00021
24. Wiegman, A., Hutten, B. A., de Groot, E., Rodenburg, J., Bakker, H. D., Büller, H. R., Sijbrands, E. J., & Kastelein, J. J. (2004). Efficacy and safety of statin therapy in children with familial hypercholesterolemia: a randomized controlled trial. JAMA, 292(3), 331–337. https://doi.org/10.1001/jama.292.3.331
25. de Jongh, S., Lilien, M. R., op't Roodt, J., Stroes, E. S., Bakker, H. D., & Kastelein, J. J. (2002). Early statin therapy restores endothelial function in children with familial hypercholesterolemia. Journal of the American College of Cardiology, 40(12), 2117–2121. https://doi.org/10.1016/s0735-1097(02)02593-7
26. Couture, P., Brun, L. D., Szots, F., Lelièvre, M., Gaudet, D., Després, J. P., Simard, J., Lupien, P. J., & Gagné, C. (1998). Association of specific LDL receptor gene mutations with differential plasma lipoprotein response to simvastatin in young French Canadians with heterozygous familial hypercholesterolemia. Arteriosclerosis, thrombosis, and vascular biology, 18(6), 1007–1012. https://doi.org/10.1161/01.atv.18.6.1007
27. McCrindle, B. W., Ose, L., & Marais, A. D. (2003). Efficacy and safety of atorvastatin in children and adolescents with familial hypercholesterolemia or severe hyperlipidemia: a multicenter, randomized, placebo-controlled trial. The Journal of pediatrics, 143(1), 74–80. https://doi.org/10.1016/S0022-3476(03)00186-0

28. Langslet, G., Breazna, A., & Drogari, E. (2016). A 3-year study of atorvastatin in children and adolescents with heterozygous familial hypercholesterolemia. Journal of clinical lipidology, 10(5), 1153–1162.e3. https://doi.org/10.1016/j.jacl.2016.05.010
29. Adams SP, Alaeiilkhchi N, Wright JM. Pitavastatin for lowering lipids. Cochrane Database of Systematic Reviews 2020, Issue 6. Art. No.: CD012735. DOI: 10.1002/14651858.CD012735.pub2. Accessed 23 February 2023.
30. Harada-Shiba, M., Kastelein, J. J. P., Hovingh, G. K., Ray, K. K., Ohtake, A., Arisaka, O., Ohta, T., Okada, T., Suganami, H., & Wiegman, A. (2018). Efficacy and Safety of Pitavastatin in Children and Adolescents with Familial Hypercholesterolemia in Japan and Europe. Journal of atherosclerosis and thrombosis, 25(5), 422–429. https://doi.org/10.5551/jat.42242
31. Avis HJ, Hutten BA, Gagné C, Langslet G, McCrindle BW, Wiegman A, et al. Efficacy and safety of rosuvastatin therapy for children with familial hypercholesterolemia. Journal of the American College of Cardiology. 2010;55(11):1121-1126. https://doi.org/10.1016/j.jacc.2009.10.042
32. Braamskamp MJ, Langslet G, McCrindle BW, Cassiman D, Francis GA, Gagné C, et al. Efficacy and safety of rosuvastatin therapy in children and adolescents with familial hypercholesterolemia: Results from the CHARON study. Journal of Clinical Lipidology. 2015;9(6):741-750. https://doi.org/10.1016/j.jacl.2015.07.011
33. Stein EA, Dann EJ, Wiegman A, et al. Efficacy of Rosuvastatin in Children With Homozygous Familial Hypercholesterolemia and Association With Underlying Genetic Mutations. J Am Coll Cardiol. 2017;70(9):1162-1170. https://Doi.org/10.1016/j.jacc.2017.06.058
34. Anagnostis, P., Vaitsi, K., Kleitsioti, P. et al. Efficacy and safety of statin use in children and adolescents with familial hypercholesterolaemia: a systematic review and meta-analysis of randomized-controlled trials. Endocrine 69, 249–261 (2020). https://doi.org/10.1007/s12020-020-02302-8
35. Vuorio, A., Kuoppala, J., Kovanen, P. T., Humphries, S. E., Tonstad, S., Wiegman, A., Drogari, E., & Ramaswami, U. (2017). Statins for children with familial hypercholesterolemia. The Cochrane database of systematic reviews, 7(7), CD006401. https://doi.org/10.1002/14651858.CD006401.pub4
36. Vuorio, A., Kuoppala, J., Kovanen, P. T., Humphries, S. E., Tonstad, S., Wiegman, A., Drogari, E., & Ramaswami, U. (2019). Statins for children with familial hypercholesterolemia. The Cochrane database of systematic reviews, 2019(11), CD006401. https://doi.org/10.1002/14651858.CD006401.pub5
37. O'Keefe, J.H., Dinicolantonio, J.J., Lavie, C.J., and Bell, D.S.H. (2014). The Influence of statins on glucose tolerance and incipient diabetes. US Endocrinology 10 (1) 68-74. https://doi.org/10.17925/use.2014.10.01.68
38. Joyce, N. R., Zachariah, J. P., Eaton, C. B., Trivedi, A. N., & Wellenius, G. A. (2017). Statin Use and the Risk of Type 2 Diabetes Mellitus in Children and Adolescents. Academic pediatrics, 17(5), 515–522. https://doi.org/10.1016/j.acap.2017.02.006
39. Groselj U, Sikonja J, Mlinaric M, Kotnik P, Battelino T, Knowles JW. Analysis of Insulin Resistance Among Children and Adolescents in Slovenia With Hypercholesterolemia After Treatment With Statins. JAMA Netw Open. 2022;5(9):e2231097. Published 2022 Sep 1. doi:10.1001/jamanetworkopen.2022.31097
40. Wiggins BS, Backes JM, Hilleman D. Statin-associated muscle symptoms-A review: Individualizing the approach to optimize care [published correction appears in Pharmacotherapy. 2022 Jul;42(7):590]. Pharmacotherapy. 2022;42(5):428-438. doi:10.1002/phar.2681
41. Kavey RW, Manlhiot C, Runeckles K, et al. Effectiveness and Safety of Statin Therapy in Children: A Real-World Clinical Practice Experience. CJC Open. 2020;2(6):473-482. Published 2020 Jun 6. doi:10.1016/j.cjco.2020.06.002