ETHICAL AND CLINICAL DILEMMAS OF USING LIPID-LOWERING THERAPY IN CHILDREN WITH HEREDITARY DYSLIPIDEMIA

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The article reviews the bioethical concern in providing lipid-lowering therapy to children with hereditary dyslipidemia. The concern is associated with the gap between clinical recommendations and official prescribing information. The purpose of the research was to perform a comparative analysis of regulatory documents, clinical recommendations and prescribing information of 11 medicinal preparations including statins, cholesterol absorption inhibitors, fibrates, omega-3 polyunsaturated fatty acids and PCSK9 inhibitors. The analysis has shown the lack of pediatric-specific data regarding effectiveness and safety of 45% prescribed medications. It imposes direct age restrictions and prevents their use in patients under 18. At the same time, clinical guidelines advocate for early initiation of therapy to reduce the lifetime risk of cardiovascular complications in children with familial hypercholesterolemia. The discovered regulatory inconsistency creates a legal barrier and makes physicians encounter ethical difficulties. The results emphasize the need to update regulatory documents and conduct additional clinical studies to ensure a safe use of lipid-lowering drugs in pediatric practice.

Keywords: familial hypercholesterolemia, pediatrics, cardiology, lipid-lowering therapy

Author contribution: the authors contributed equally to the work.

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Received: 22.09.2025 **Accepted:** 28.10.2025 **Published online:** 20.11.2025

DOI: 10.24075/medet.2025.021

ЭТИЧЕСКИЕ И КЛИНИЧЕСКИЕ ДИЛЕММЫ ГИПОЛИПИДЕМИЧЕСКОЙ ТЕРАПИИ ПРИ НАСЛЕДСТВЕННЫХ ДИСЛИПИДЕМИЯХ У ДЕТЕЙ

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В статье рассмотрена биоэтическая проблема назначений гиполипидемической терапии детям с наследственными дислипидемиями, связанная с разрывом между клиническими рекомендациями и официальными инструкциями лекарственных средств. Целью исследования был сравнительный анализ нормативно-правовых документов, клинических рекомендаций и инструкций по применению 11 препаратов, включая статины, ингибиторы абсорбции холестерина, фибраты, омега-3-полиненасыщенные жирные кислоты и ингибиторы PCSK9. Анализ показал, что у 45% препаратов официально отсутствуют данные о безопасности и эффективности в педиатрии, что накладывает прямые возрастные ограничения и препятствует их применению у пациентов до 18 лет. В то же время клинические рекомендации настаивают на раннем начале терапии для снижения пожизненного риска кардиоваскулярных осложнений у детей с семейной гиперхолестеринемией. Обнаруженное нормативное несоответствие создает правовой барьер и ставит врачей в этически сложное положение. Результаты подчеркивают необходимость обновления регуляторных документов и проведения дополнительных клинических исследований для обоснования безопасного применения гиполипидемических средств в детской практике.

Ключевые слова: семейная гиперхолестеринемия, педиатрия, кардиология, гиполипидемическая терапия

Вклад авторов: авторы внесли равный вклад в написание статьи.

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Статья поступила: 22.09.2025. **Статья принята к печати:** 28.10.2025 **Опубликована онлайн:** 20.11.2025

DOI: 10.24075/medet.2025.021

Initiating lipid-lowering therapy in children with hereditary dyslipidemia presents a complex bioethical dilemma that operates at the intersection of the recommendations and regulatory prescriptions. Clinical recommendations based on long-term cardiovascular risks state that some lipid-lowering drugs should already be used in childhood. However, the official contraindications listed in the instructions of many drugs hinder the use of most statins in pediatric practice (with rare exceptions). Thus, a physician has to make a difficult choice by either following the approved instructions or considering the treatment that goes beyond them. This article is devoted to the bioethical analysis of this conflict.

MATERIALS AND METHODS

During the present study, a systematic comparative analysis of regulatory and clinical databases regulating the use of lipid-lowering therapy in pediatric practice was carried out. Special emphasis was made on finding and analyzing the contradictions between official patient information leaflets and updated clinical guidelines.

Preparations for analysis were selected based on their mentioning in modern clinical recommendations to treat inherited dyslipidemia in children, in particular homozygous and heterozygous familial hypercholesterolemia. The final sample included 11 medicinal preparations belonging to basic pharmacological groups such as statins (atorvastatin, rosuvastatin, pitavastatin, simvastatin), cholesterol absorption inhibitors (ezetimibe), fibrates (fenofibrate), omega 3 fatty acids, PCSK9 inhibitors (alirocumab, evolocumab) and inclisiran.

An official patient information leaflet registered in the Russian Federation was analyzed for every medicinal preparation. Regulatory guidance was examined as of August 2025 through official sources such as the State Register of

Medicines and Information Resources of Manufacturers of Pharmaceutical Products. When analyzing the instructions, the Contraindications and Pediatric Use subsections were given special attention. Wording about age restrictions, specific age thresholds, and justifications for the restrictions were of particular interest. The obtained data were included within a single base with a subsequent comparative analysis.

Relevant clinical recommendations were studied simultaneously. Differences in approaches to the age of initiating therapy, selection of first-line drugs and dosage schedules in pediatric practice were compared.

RESEARCH RESULTS

A bioethical contradiction occurring during selection of therapy for children with hereditary dyslipidemias, in particular familial hypercholesterolemia, was detected during the research. The contradiction consists in the gap between pressing clinical recommendations [1] and officially registered patient information leaflets [2–12] for the reviewed medicinal preparations.

The research is relevant due to high epidemiologic prevalence of inherited dyslipidemias. Heterozygous familial hypercholesterolemia (HeFH) is a moderately common genetic disease, which is present in 1 per 200–250 of the European population. Homozygous familial hypercholesterolemia (HoFH) is a rare genetic condition with an estimated frequency of 1 in 160,000 to 1 in 300,000, which is characterized by an extremely unfavorable outcome and early cardiovascular complications. The combination of the high population prevalence of heterozygous FH and the exceptional severity of homozygous FH shows the medical and social significance of the problem and the need to develop clear algorithms for managing pediatric patients, including early diagnosis and timely initiation of therapy [13].

Clinical recommendations based on data from numerous long-term studies and meta-analyses clearly demonstrate the need for early initiation of drug therapy to reduce lifelong cardiovascular risk. The use of lipid-lowering drugs is considered as a treatment strategy aimed at preventing early atherosclerosis and its complications.

Meanwhile, most official prescribing instructions contain direct age restrictions or lack data on the use of the medicinal agents in pediatric practice. This is how legal and regulatory concerns for physicians arise [14].

To provide for a detailed analysis of this conflict, a list of drugs mentioned in the current clinical guidelines for treatment of homozygous and heterozygous FH in children has been compiled:

- statins: atorvastatin, rosuvastatin, pitavastatin, simvastatin;
- cholesterol absorption inhibitors: ezetimibe;
- PCSK9 inhibitors: alirocumab, evolocumab;
- other lipid-lowering agents: bempedoic acid, omega-3 polyunsaturated fatty acids, fibrates, inclisiran

The results of the comparative analysis demonstrate a pronounced regulatory gap.

Analysis of basic prescribing information has shown as follows:

- five of the eleven drugs reviewed have formal age-related restrictions for pediatric patients. In the Contraindications or Pediatric Use sections it has been shown that safety and effectiveness of rosuvastatin, bempedoic acid, inclisiran, fenofibrate and omega 3 fatty acids are not established in children from 0 to 18 years old, whereas data on their use are limited [2–6]. The wording officially prohibits their use in minor children due to the lack of sufficient evidential base required to register the respective indications;
- four medicinal agents such as ezetimibe, evolocumab, simvastatin and atorvastatin are officially approved in children 10 years and older [7–10];
- alirocumab is contraindicated in children under 8, due to the lack of safety and effectiveness data for this age [11];
- pitavastatin is associated with the following age restrictions: it is contraindicated in children under 6 due to the lack of sufficient data for patients of this age [12].

Thus, a considerable part of medicinal agents registered in the Russian Federation have direct age-related limitations in patient information leaflets or lack sufficient clinical data hindering their use in pediatric practice. It forms a significant legal and regulatory barrier for a treating physician. According to par. 4 of article 37 of Federal Law dated November 21, 2011 No. 323-ФЗ (amended as of December 28, 2024) ‘On fundamental healthcare principles in the Russian Federation’ [14], medicinal agents should be prescribed and used based on the patient information leaflet only. Thus, a direct age-related limitation (‘contraindicated to children under 18’) or information on the lack of using the prescription drugs in pediatric populations makes legal prescription of the medicinal agent to pediatric population impossible thus creating a legal dilemma for a clinician when the medicinal agent is essential for therapeutic treatment.

CONCLUSIONS

The conducted research resulted in detection of a bioethical and regulatory contradiction associated with the use of lipid-lowering therapy among children with inherited dyslipidemias. The purpose of the study to detect and analyze a discrepancy between clinical recommendations and patient information leaflets has been achieved. According to the analysis, modern clinical practice recommends early initiation of therapy so that a long-term cardiovascular risk could be decreased, whereas patient information leaflets contain significant age-related restrictions and shortage of data that hinder the use of certain lipid-lowering agents in childhood.

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