

## Editorial

## Treatment of Heterozygous Familial Hypercholesterolemia in Children and Adolescents: An Unsolved Problem



## Tratamiento de la hipercolesterolemia familiar heterocigota en la infancia y la adolescencia: un problema no resuelto

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Familial hypercholesterolemia (FH) is a monogenic disease characterized by a defect in cellular uptake of plasma lipoproteins, particularly low-density lipoproteins (LDLs). Although the gene affected is ubiquitously expressed, the defect is functionally important in the liver because it is predominantly responsible for the catabolism of plasma LDL. The result is an accumulation of LDL particles in the plasma and their vascular and extravascular deposition. This build-up triggers premature atherosclerosis, which predominantly manifests as coronary disease, corneal arcus, tendon xanthomas, and xanthomas.<sup>1</sup> FH is one of the most common metabolic diseases in the general population, with estimated prevalences of its heterozygous form of between 1:250 and 1:500 and of its homozygous form of between 1:300 000 and 1:1 000 000.<sup>2,3</sup> Functional mutations in 4 different loci cause most FH cases: *LDLR*, *PCSK9*, and *APOB* and *APOE*, which respectively code for the LDL receptor; the enzyme proprotein convertase subtilisin/kexin type 9, which regulates the half-life of the LDL receptor, and the apolipoproteins (apo) B and E, which are the ligands for the LDL receptor.<sup>2,4</sup>

Lipid-lowering therapy is a medical priority for adults with FH because, according to registries from the pre-statin era, more than half of men with FH and about one-third of women will have a cardiovascular event before 60 years of age without lipid-lowering therapy. Statins have changed the natural history of FH and the latest studies indicate that death from coronary heart disease has highly significantly decreased in recent years, at least by 50%<sup>5</sup>; however, the rate is still higher than that of the general population.<sup>6</sup> Although there is no evidence from randomized clinical trials in patients with FH, all scientific societies recommend, with minor differences, that all adults with FH receive early and intensive treatment that is primarily based on high-potency statins.<sup>2,7–9</sup>

The evidence of the clinical benefit of lipid-lowering therapy in adults with FH, although based on observational studies, extrapolated from other populations, or derived from trials whose endpoints were not clinical events, but surrogates such as carotid intima-media thickness, can be considered solid or, at least, the best possible with the current approaches.<sup>2</sup> However, the situation for children and adolescents is markedly different because all of the recommendations are based on expert opinion and there is little information on the potential benefit of lipid-lowering therapy in this population.

The main arguments for the diagnosis and treatment of FH in childhood or adolescence to impede or delay cardiovascular disease can be summarized as follows:

- Atherosclerosis begins at an early age, and studies such as PDAY (Pathobiological Determinants of Atherosclerosis in Youth) show that the first lesions occur in the first decades of life and that their development can be predicted by the childhood concentration of cholesterol.<sup>10</sup>
- The cholesterol concentration in childhood is a good predictor of vascular disease in adulthood.<sup>11</sup>
- Mendelian randomization studies reveal that reductions in the concentration of LDL cholesterol that are maintained from birth and throughout life have a much greater benefit than more intensive reductions beginning in adulthood.<sup>12</sup>
- Statin therapy in children with FH prevents carotid wall thickening, which begins to develop in untreated children at 7 years of age.<sup>13</sup>
- Safe and well-tolerated drugs such as statins can be used to dramatically reduce LDL cholesterol in children and adolescents and considerable evidence shows that they reduce cardiovascular disease in adults.<sup>14</sup>

Prolonged drug therapy aimed at reducing the risk of a disease in the mid-to-long-term, at any age but especially in young people, should necessarily have evidence showing that the risk associated with the intervention is small, that the potential benefit is important, and that the intervention is cost-effective. With the currently available data, these prerequisites are met in a

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considerable proportion of children and adolescents, particularly those with a family history of premature cardiovascular disease, highly elevated levels of LDL cholesterol, or the presence of other associated cardiovascular risk factors, which is why the recent recommendations support the use of statins in this population. However, there are controversial aspects, such as the age of drug therapy initiation; what levels of LDL cholesterol indicate treatment initiation; what dose and type of statin to use in children; what LDL cholesterol targets should be established; and what role combination treatment should play in this population. The theoretical framework seems clear: we should initiate early treatment of hypercholesterolemia and aim to avoid future disease, but the practical application of this principle is still subject to many uncertainties.

The article by Saltijeral et al., published in *Revista Española de Cardiología*, reports the lipid-lowering therapy data of the SAFEHEART study pertaining to a group of 217 children and adolescents with genetic diagnosis of heterozygous FH who were younger than 18 years at the initiation of follow-up.<sup>15</sup> The results are important and reflect the uncertainties surrounding the field. The study, conducted in highly selected and well-motivated units, concerned children and adolescents (mean age at entry, 15 years) from families containing diagnosed progenitors who were sufficiently well-aware of the importance of their disease to include their children in the study. The participants also showed good adherence, important for the completion of clinical follow-up, and a considerable proportion of them were older than 18 years at the end of follow-up. Despite all of the factors favoring the intervention, at the end of follow-up, a third was not under treatment with statins, only 41% of children and adolescents achieved LDL cholesterol concentrations < 130 mg/dL, and only 23% of participants adhered to a lipid-lowering therapy capable of reducing LDL cholesterol by more than 50%. In addition, there was considerable heterogeneity in the treatments used. For example, 11% of the children and adolescents received ezetimibe monotherapy, a therapeutic approach that is difficult to explain, and the use of statins seemed to be highly variable, with more potent statins such as atorvastatin and rosuvastatin comprising 50% of the statins prescribed.

With some variations, the guidelines recommend LDL cholesterol reductions greater than 50% and/or concentrations < 130 mg/dL after about 10-year use of statins, preferably in monotherapy.<sup>7–9,14,16</sup> Although the recommendations are relatively recent and their practical application remains to be reflected in a study fitting these characteristics, it seems evident that there is some skepticism regarding the guidelines, a reflection of the uncertainties in the literature.

Due to the regular monitoring required, it is difficult to advocate a lifetime treatment to a 12-year-old girl without risk factors who attends the clinic with her 79-year-old grandmother who has the same mutation as her granddaughter but is perfectly healthy. Undoubtedly, it is much easier when there is a burden of premature cardiovascular disease in the family. Clinical judgment and treatment individualization are important in all areas of medicine; provision of information to patients and relatives is vital for the long-term prevention of diseases; and decisions should be made by patients and relatives in accordance with their expectations, worries, and life experience. If there is a supposed clinical paradigm of these statements, it is the treatment of children with FH, and the study presented in this issue reflects the variability caused by differences among families, the perceived severity of the disease by physicians, patients, and family members, and the absence of solid clinical evidence. The SAFEHEART study is a good example of how to approach scientific study to generate high-quality information that can improve the health and survival of this population in the future.

Meanwhile, we should adhere in a reasoned and reasonable manner to the guidelines because they are the best evidence available. Children tolerate statins much better than adults, long-term safety studies are available, most affected young people have unacceptably high cholesterol levels of > 190 mg/dL, treatment initiation in childhood and adolescence improves therapeutic adherence in adulthood, and many girls and young women will have to cease taking lipid-lowering agents for large periods of time due to motherhood, which is why some years of treatment beforehand would more than likely have a long-term beneficial effect. We should keep family members and patients informed, use cost-effective and safe drugs, avoid maximum doses in children, especially those younger than 14 years and at treatment initiation, ensure that monitoring is comfortable for patients and their family, with minimal follow-up appointments once treatment safety and effectiveness is confirmed, and keep them fully involved in decision making.

## CONFLICTS OF INTEREST

F. Civeria has received remuneration for consultancy work and presentations from Amgen, Sanofi, Pfizer, and MSD.

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