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Consensus

Clinical management of homozygous familial hypercholesterolemia: Perspectives from an expert panel

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Abstract

Introduction: Homozygous familial hypercholesterolemia (HoFH) is a rare but severe genetic disorder characterized by extremely elevated LDL-C levels from birth, leading to accelerated atherosclerosis and premature cardiovascular disease. Despite advances in lipid-lowering therapies, the evidence guiding clinical practice remains heterogeneous, highlighting the need for an expert consensus to synthesize available data and provide practical recommendations.

Objective: This narrative review aims to unify current medical evidence to guide the management of homozygous familial hypercholesterolemia (HoFH). Through a multidisciplinary expert consensus, the panel seeks to synthesize the available scientific information on HoFH. The main objective is to provide the medical community with practical, clear recommendations to optimize patient care, emphasizing three fundamental areas: improving the accuracy of early diagnosis, structuring comprehensive clinical management, and evaluating the effectiveness of emerging therapies. Ultimately, the panel's goal is

Highlights

- HoFH is a rare, life-threatening disorder requiring early diagnosis and intervention.
- This review integrates expert consensus with evidence on diagnostic and therapeutic strategies.
- It provides practical recommendations for clinicians managing HoFH in both adult and paediatric populations.

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to support actions to reduce the risk of premature cardiovascular disease, as well as to standardize the care of HoFH.

Methodology: This narrative review was developed through a multidisciplinary consensus process. Experts in internal medicine, cardiology, endocrinology, paediatrics, and medical genetics defined key topics, drafted sections according to their expertise, and iteratively refined the content through collaborative discussions. Evidence was selected pragmatically, based on clinical relevance and applicability, to inform diagnosis, management, and emerging therapies for HoFH.

Results: The review addresses major domains in the care of HoFH, including clinical and genetic diagnosis, differential diagnosis, cascade screening, cardiovascular risk assessment, and therapeutic approaches. Both non-pharmacological and pharmacological interventions are discussed, from statins and ezetimibe to lomitapide, evinacumab, and novel emerging therapies. Special populations such as paediatric patients and pregnant women are also considered. Additionally, the review highlights the social and public health impact of HoFH, emphasizing the importance of early detection and equitable access to advanced therapies.

Conclusions: HoFH is more prevalent than previously recognised and requires early diagnosis and comprehensive management. This consensus synthesizes expert experience and current evidence to provide practical guidance for clinicians. By integrating pharmacological, non-pharmacological, and genetic strategies, it aims to improve outcomes and reduce the cardiovascular burden of HoFH.

Keywords: Familial hypercholesterolemia, LDL cholesterol, Cascade screening, Lipid-lowering therapy, Lomitapide, Evinacumab.

Manejo clínico de la hipercolesterolemia familiar homocigótica: perspectivas de un panel de expertos

Resumen

Introducción: la hipercolesterolemia familiar homocigota (HFHo) es un trastorno genético raro pero grave, caracterizado por niveles extremadamente elevados de cLDL desde el nacimiento, lo que conduce a aterosclerosis acelerada y enfermedad cardiovascular prematura. A pesar de los avances en las terapias hipolipemiantes, la evidencia que guía la práctica clínica sigue siendo heterogénea, lo que resalta la necesidad de un consenso de expertos que sintetice la información disponible y ofrezca recomendaciones prácticas.

Objetivo: esta revisión narrativa tiene como fin unificar la evidencia médica actual para guiar el manejo de la hipercolesterolemia familiar homocigota (HFHo). Mediante un consenso multidisciplinario de expertos, el panel busca sintetizar la información científica disponible sobre la HFHo. El objetivo principal es ofrecer a la comunidad médica recomendaciones prácticas y claras que optimicen el cuidado de los pacientes, con énfasis en tres áreas fundamentales: mejorar la precisión del diagnóstico temprano, estructurar un manejo clínico integral y evaluar la efectividad de las nuevas terapias emergentes. El panel aspira a apoyar acciones para reducir el riesgo de enfermedad cardiovascular prematura, así como a estandarizar la atención de la HFHo.

Métodos: esta revisión narrativa se desarrolló mediante un proceso de consenso multidisciplinario. Expertos en medicina interna, cardiología, endocrinología, pediatría y genética médica definieron los temas clave, elaboraron secciones de acuerdo con su experiencia y refinaron el contenido de manera iterativa a través de discusiones colaborativas. La selección de evidencia se basó en la relevancia clínica y su aplicabilidad para informar el diagnóstico, el manejo y las terapias emergentes de la HFHo.

Destacados

- La HFHo es un trastorno raro y potencialmente letal que requiere diagnóstico temprano.
- Esta revisión integra el consenso de expertos y la evidencia actual sobre diagnóstico y tratamiento.
- Proporciona recomendaciones prácticas para el manejo de la HFHo en adultos y la población pediátrica.

Resultados: la revisión aborda los principales aspectos del manejo de la HFHo, incluyendo el diagnóstico clínico y genético, el diagnóstico diferencial, la detección en cascada, la evaluación del riesgo cardiovascular y las estrategias terapéuticas. Se discuten intervenciones no farmacológicas y farmacológicas, desde estatinas y ezetimiba hasta lomitapide, evinacumab y nuevas terapias en investigación. También se consideran poblaciones especiales como niños y mujeres embarazadas. Además, se destaca el impacto social y en salud pública de la HFHo, subrayando la importancia de la detección temprana y del acceso equitativo a terapias avanzadas.

Conclusiones: la HFHo es más prevalente de lo previamente estimado y requiere diagnóstico temprano y manejo integral. Este consenso sintetiza la experiencia clínica y la evidencia actual para ofrecer orientaciones prácticas a los profesionales de la salud. Al integrar estrategias farmacológicas, no farmacológicas y genéticas, busca mejorar los desenlaces y reducir la carga cardiovascular de la HFHo.

Palabras clave: hipercolesterolemia familiar, colesterol LDL, detección en cascada, terapia hipolipemiante, lomitapide, evinacumab.

Introduction

Dyslipidemias are metabolic disorders characterised by abnormalities in the levels of cholesterol, triglycerides, or both, and represent a major risk factor for cardiovascular disease and overall health (1). From a genetic perspective, they can be classified into two broad categories: polygenic dyslipidemias, which result from the combined effect of multiple common DNA variants, and monogenic dyslipidemias, which are caused by rare pathogenic variants that disrupt the function of key proteins, thereby producing distinct clinical phenotypes (2). To date, 25 forms of monogenic dyslipidemias have been described, each associated with characteristic alterations in plasma lipid fractions, including elevated low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides, or other lipid parameters.

Among these, familial hypercholesterolemia (FH) is one of the most prevalent and clinically significant. FH is a genetic disorder defined by persistently elevated LDL-C levels that lead to a 20-fold increase in cardiovascular risk compared with the general population. Patients frequently develop premature atherosclerosis, sometimes manifesting before the age of 20 (3-4). FH exists in two main forms: heterozygous FH (HeFH), with an estimated prevalence of 1 in 300 individuals, typically caused by a pathogenic variant in one allele of an FH-related gene; and the rarer homozygous FH (HoFH), affecting fewer than 1 in 300.000 individuals, in which both alleles harbour pathogenic variants. HoFH is associated with a markedly severe phenotype, LDL-C levels often exceeding 500 mg/dL, and dramatically increased risk of premature cardiovascular disease compared with HeFH (3, 5).

Given the severity and complexity of HoFH, its early recognition and aggressive management are essential to reduce morbidity and mortality. However, major challenges remain, including underdiagnosis, delayed initiation of therapy, limited access to advanced treatments, and significant regional disparities in care. This review provides an updated and comprehensive synthesis of the genetic basis, clinical features, diagnostic approaches, and current therapeutic strategies for HoFH, with a particular focus on evidence relevant to Latin America. By integrating clinical, molecular, and therapeutic perspectives, we aim to support clinicians in improving the detection, management, and long-term outcomes of patients affected by this life-threatening condition.

Methodology

This narrative review was developed through a structured, multidisciplinary expert consensus process with a specific focus on its applicability to Latin American healthcare settings. The author group included specialists in internal medicine,

cardiology, endocrinology, paediatrics, and medical genetics, all with extensive experience in the diagnosis and management of familial hypercholesterolemia in the region.

An initial consensus meeting defined the scope, key clinical questions, and thematic structure of the manuscript. Subsequently, relevant literature was identified through targeted searches of major biomedical databases (including PubMed/MEDLINE and Scopus), complemented by a manual review of reference lists from key guidelines, consensus statements, and landmark clinical trials. No formal date or language restrictions were applied.

Evidence was selected pragmatically based on methodological quality, clinical relevance, and potential applicability to Latin American contexts. Given the rarity of homozygous familial hypercholesterolemia and the limited number of region-specific studies, international evidence was prioritized when robust and was critically interpreted in consideration of regional factors such as healthcare system heterogeneity, access to advanced therapies, diagnostic availability, and socioeconomic constraints.

Draft sections were prepared by expert subgroups according to their areas of expertise and were subsequently reviewed in iterative rounds by the full author panel. Discrepancies were resolved through discussion until consensus was achieved. This approach allowed the integration of global evidence with expert clinical experience from Latin America to generate context-sensitive recommendations.

Epidemiology

Early epidemiological studies, based solely on clinical and laboratory criteria, and without genetic or molecular testing, estimated the prevalence of familial hypercholesterolemia (FH) at approximately 1 in 500 individuals in the general population. Clinical diagnosis relied on elevated low-density lipoprotein cholesterol (LDL-C), family history, and typical clinical manifestations (6-7).

With the introduction of molecular diagnosis, recent studies have demonstrated higher prevalence rates. For heterozygous FH (HeFH), prevalence has been reported at around 1 in 208 individuals (8-9). A meta-analysis including over 11 million participants found, based on genetic criteria, a prevalence of 1 in 300 in the general population (10). Diagnosis based solely on clinical features shows low sensitivity, as tendon or cutaneous xanthomata, highly specific signs, are present in only 5–60% of patients depending on age. This discrepancy accounts for the differences between clinically and genetically derived prevalence estimates (table 1), with genetic testing revealing cases even in individuals without typical phenotypic features (8-9, 11).

Genetic testing for FH has an estimated sensitivity of 60–80%, suggesting that the true prevalence may be even higher. Globally, the prevalence of HeFH and homozygous FH (HoFH) has been estimated at 1:300 and 1:360.000, respectively, with higher frequencies in populations with founder effects, such as French Canadians, Afrikaners in South Africa, and Lebanese Christians (12-13).

The true prevalence of HoFH varies according to the diagnostic approach, given the wide phenotypic spectrum. Molecular criteria may increase case detection, including individuals with milder phenotypes. Notably, the absence of pathogenic variants does not exclude the diagnosis when clinical features are compatible (13-14). Assuming a prevalence of 1 in 300.000 in a global population of 7 billion, approximately 23.000 cases would be expected worldwide; most are likely concentrated in less affluent regions with high rates of consanguinity or founder effects, where the disease remains largely underdiagnosed or untreated (15-16).

The updated *European Atherosclerosis Society (EAS) Consensus Statement* on HoFH estimated that about 30.000 people worldwide were living with the condition in 2020, with a prevalence ranging from 1:250.000 to 1:360.000. For Latin America and the Caribbean, estimates range between 1.818 and 2.615 patients (17). Major challenges include: (i) underdiagnosis, with recognition of fewer than 5% of cases; (ii) delayed diagnosis, with a mean age of 12 years; (iii) cardiovascular or valvular involvement already present in about 10% of patients at the time of detection; and (iv) insufficient treatment,

with LDL-C targets achieved in fewer than 5% of cases. In light of this scenario, the EAS has emphasised the urgent need to strengthen detection, recognition, and treatment strategies through clinical guidelines and comprehensive care models (17).

Table 1. Estimated prevalence of familial hypercholesterolemia according to diagnostic criteria

Diagnostic approach	Population studied	Estimated prevalence	Comments
Clinical (biochemical and family history criteria)	General population	1:500	Underestimates prevalence; low sensitivity and depends on physical findings (xanthomata present in 5–60% of cases).
Genetic (molecular testing)	General population	1:300	Higher diagnostic accuracy and identifies individuals without a classical phenotype.
Heterozygous FH (HeFH)	General population	1:208 – 1:300	Varies by region and diagnostic criteria.
Homozygous FH (HoFH)	Global population	1:250.000 – 1:360.000	Higher frequency in founder populations (French Canadians, Afrikaners, Lebanese Christians).
Expected HoFH cases (global estimate)	~7 billion inhabitants	~23.000	Mostly concentrated in regions with high rates of consanguinity and limited access to diagnosis/ treatment.

Source: Own elaboration.

Genetic basis

Familial hypercholesterolemia (FH) is an autosomal semidominant disorder. Individuals carrying a pathogenic variant in a single allele—i.e., those with monoallelic or heterozygous FH—exhibit an abnormal biochemical phenotype and, in some cases, clinical features suggestive of the condition (17). Conversely, carriers of biallelic or homozygous variants show a more severe elevation of LDL-cholesterol (LDL-C) and earlier, more pronounced clinical manifestations (17).

To date, four genes have been confirmed as causative: *LDLR* (LDL receptor), *APOB* (apolipoprotein B), *PCSK9* (proprotein convertase subtilisin/kexin type 9), and *LDLRAP1* (LDL receptor adaptor protein 1). Pathogenic variants in *LDLR* account for the majority of cases (11, 18), followed by *APOB*, *PCSK9* and, less frequently, *LDLRAP1* (14) (table 2).

Table 2. Genotype–phenotype correlation in familial hypercholesterolemia

Gene	Type	Phenotype
LDLR	Heterozygous	▪ LDL-C elevation >190 mg/dL. ▪ Increased risk of premature coronary heart disease. ▪ Progressive development of xanthomas and xanthelasmata.
	Homozygous	▪ Untreated adults may exhibit LDL-C levels >500 mg/dL. ▪ Early appearance of xanthelasmata, tendon and interdigital xanthomas. ▪ Severe coronary artery disease, often manifesting during the third decade of life. ▪ Limited statin efficacy, as treatment relies on the upregulation of functional hepatic LDL receptors.
APOB	Heterozygous	▪ Associated with lower LDL-C levels and a milder phenotype than LDLR-related HeFH.
	Homozygous	▪ Clinical presentation resembles LDLR-related HeFH. ▪ Less severe phenotype than LDLR-related HoFH, with lower LDL-C levels and later onset of coronary heart disease.
PCSK9	Heterozygous	▪ Associated with lower LDL-C levels and a milder phenotype than LDLR-related HeFH. ▪ Severe, early-onset FH may occur in individuals with a whole-gene duplication.
	Homozygous	▪ Presentation is similar to LDLR-related HeFH. ▪ Less severe phenotype than LDLR-related HoFH, with lower LDL-C levels and later onset of coronary heart disease.
LDLRAP1	Homozygous	▪ Clinical features resembling LDLR-related HoFH: LDL-C >500 mg/dL, early-onset coronary heart disease, aortic valve stenosis, and childhood development of planar, tuberous or tendon xanthomas. ▪ Variable response to treatment; advanced therapies or LDL apheresis may be required.

Source: Own elaboration.

Most patients carry two pathogenic variants, either within the same gene (monogenic) or across two different genes (digenic). Based on their genetic configuration, the following categories are recognised:

- **Homozygotes:** Identical variants in both alleles of the same gene.
- **Compound heterozygotes:** Distinct variants in both alleles of the same gene.

- **Double heterozygotes:** Variants in two different FH-associated genes.

A rare form, termed autosomal recessive FH, results from biallelic variants in LDLRAP1, representing <1% of cases (13, 18-20) (table 3).

Table 3. Genetic nomenclature of familial hypercholesterolemia (FH)

Traditional clinical terminology	Precise genetic nomenclature	Comments
Homozygous familial hypercholesterolemia (HoFH): A general term encompassing a spectrum of genetic diagnoses	**1. Biallelic semidominant monogenic FH (single gene)** (a) Defined by causal genes: · *LDLR*-related → accounts for 85–90% of variants · *APOB*-related → accounts for 5–10% of variants · *PCSK9*-related → accounts for 1–3% of variants (b) Defined by the nature of the variants: · Two identical variants → formerly "true/simple HoFH" · Two different variants in the same gene → formerly "compound heterozygous HoFH"	Represents the most frequent form of HoFH.
	2. Biallelic semidominant digenic FH (two causal genes) (a) Defined by causal genes: · *LDLR* + *APOB* → 90–95% of digenic cases · *LDLR* + *PCSK9* → 2–5% of digenic cases · *APOB* + *PCSK9* → <2% of digenic cases (b) Defined by the nature of the variants: · Two different variants in two different genes → formerly "double heterozygous FH"	Rare compared with monogenic HoFH; phenotype can vary according to gene combination.
	3. Autosomal recessive biallelic FH (single gene, recessive inheritance) Parents are true heterozygous carriers with normal biochemical and clinical phenotypes. (a) Defined by causal genes: · *LDLRAP1*-related → accounts for all cases and represents <1% of all HoFH cases (b) Defined by the nature of the variants: · Two identical variants → formerly "true/simple ARH" · Two different variants in the same gene → formerly "compound heterozygous ARH"	Extremely rare form; all patients have *LDLRAP1*-related variants.

Source: Own elaboration.

LDLR gene

The *LDLR* gene, located on chromosome 19p13.2, encodes the LDL receptor. Approximately 90% of FH cases are attributed to pathogenic variants in *LDLR*, with over 1.700 mutations identified (21-22).

Brown and Goldstein demonstrated that LDL binding to fibroblasts suppresses cholesterol synthesis through HMG-CoA reductase inhibition (23-24). They later described receptor-mediated endocytosis using *LDLR* as a prototypical model (25).

Pathogenic variants are conventionally classified according to residual receptor activity:

- **Null mutations:** <2% activity.
- **Defective mutations:** 2–25% activity (26).

Homozygous carriers of null mutations typically present with extremely high LDL-C levels and poor clinical outcomes (27). In HeFH, clinical expression depends on the type of mutation and the residual receptor activity provided by the healthy allele (27).

APOB gene

Located on 2p24.1, and comprising 12 exons, APOB encodes the main apolipoprotein of chylomicrons and LDL. Two isoforms exist: apoB48 (intestine) and apoB100 (liver) (28). Pathogenic variants in APOB account for 5–10% of FH cases (28). These mutations produce apoB molecules with impaired LDLR binding capacity, leading to reduced LDL-C clearance and hypercholesterolemia (29-30).

PCSK9 gene

Located on 1p32.3, *PCSK9* encodes a serine protease that promotes LDL receptor degradation, thereby increasing circulating LDL-C levels (31).

Overexpression of PCSK9 reduces LDLR availability, while inactivating mutations prevent receptor degradation (32).

- **Gain-of-function mutations:** Account for 1–3% of FH cases, markedly elevating LDL-C.
- **Loss-of-function mutations:** Significantly reduce LDL-C and confer cardiovascular protection (6, 33).

LDLRAP1 gene

Located on 1p36.11, *LDLRAP1* encodes the LDL receptor adaptor protein 1, required for clathrin-mediated internalisation of LDLR (36). Biallelic variants cause autosomal recessive FH, a very rare form (<1% of cases) (34).

Defective *LDLRAP1* function impairs LDLR trafficking in hepatocytes, resulting in elevated LDL-C (35).

Other genes

Occasional mutations have been described in *STAP1*, *APOE*, and *PNPLA5*, although their contribution to FH appears to be less significant (8).

Clinical presentation

The phenotype of HoFH typically manifests early in life. Clinical features can be categorised into clinical stigmata, laboratory findings, and cardiovascular complications. The classical triad consists of markedly elevated cholesterol, xanthomas, and premature cardiovascular disease (36).

Clinical stigmata: Patients may present with premature corneal arcus (generally before 45 years of age), cutaneous xanthomas, and tendon xanthomas located on extensor surfaces such as the elbows, wrists, knees, and buttocks. Compared with HeFH, xanthomas are more prevalent in HoFH. Achilles tendon hypertrophy, detectable by palpation, is highly suggestive; a thickness >9 mm on radiography is included among the diagnostic criteria of some societies. Xanthomas may regress with lipid-lowering therapy. In a Colombian study of 36 HoFH patients, tendon xanthomas were reported in 26 cases, corneal arcus in 19, and xanthelasmata in 7. Regarding cardiovascular severity, 14 patients developed coronary artery disease, followed by aortic and carotid stenosis in 9 and 8 cases, respectively, and 2 patients experienced a stroke (37) (figures 1 and 2).

Laboratory findings: HoFH is usually characterised by LDL-C >500 mg/dL. However, fasting LDL-C >370 mg/dL is considered highly suggestive and warrants further diagnostic evaluation (36).

Complications: The persistent elevation of LDL-C results in early-onset coronary artery disease and aortic valve stenosis. Additional manifestations of atherosclerosis include aortic aneurysm, peripheral arterial disease, and cerebrovascular disease. According to the LDL-C accumulation hypothesis, the mean age of coronary artery disease onset in HoFH patients is approximately 11 years, with cases documented even in the first decade of life (36, 38).

Figure 1. Clinical stigmata of familial hypercholesterolemia (FH)

Note. A. Corneal arcus. B. Bilateral Achilles tendon xanthoma. C–E. Cutaneous xanthomas in different locations.

Source: Own elaboration.

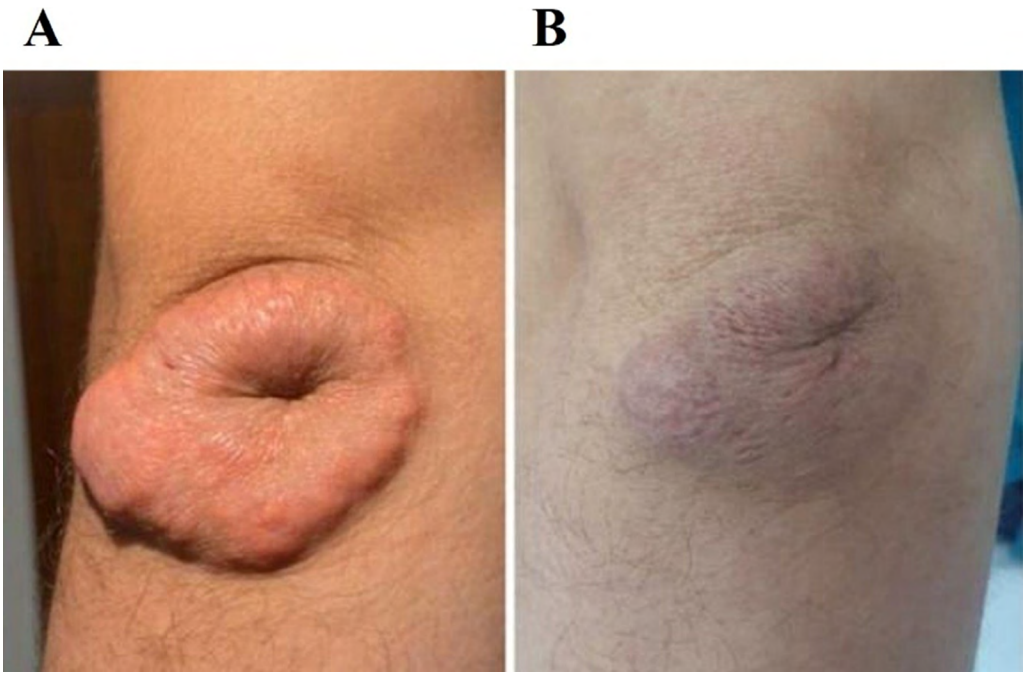

Figure 2. Clinical stigmata of familial hypercholesterolemia (FH)

Note. A. Tendinous xanthoma of the elbow. B. Regression of the xanthoma following LDL-C reduction with pharmacological therapy.

Source: Own elaboration.

Clinical diagnosis

Familial hypercholesterolemia (FH) can be diagnosed through standardised clinical scoring systems and genetic confirmation. The most widely used scoring tool is the Dutch Lipid Clinic Network (DLCN) Criteria (36) (table 4).

This system allocates points according to:

- LDL-cholesterol (LDL-C) levels.
- Personal or family history of hypercholesterolemia or premature atherosclerotic disease.
- Physical stigmata such as tendon xanthomas or corneal arcus.

Interpretation of the score is as follows:

- 3–5 points: possible FH.
- 6–8 points: probable FH.
- ≥8 points: definite FH

Table 4. Dutch Lipid Clinic Network (DLCN) criteria for the clinical diagnosis of familial hypercholesterolemia

Criterion	Points
Family history	
First-degree relative with premature coronary artery disease (men <55 years; women <60 years), or LDL-C above the 95th percentile.	1
First-degree relative with tendon xanthomas and/or corneal arcus, or a child <18 years with LDL-C >95th percentile.	2
Clinical history	
Patient with premature coronary artery disease (men <55 years; women <60 years).	2
Patient with premature cerebral or peripheral vascular disease.	1
Physical examination	
Tendon xantomas.	6
Corneal arcus before age 45.	4
LDL-C levels (mg/dL)	
≥330	8
250–329	5
190–249	3
155–189	1
DNA analysis	
Functional pathogenic variant in LDLR, APOB, or PCSK9	8

Source: Own elaboration based on published DLCN criteria.

Updated diagnostic criteria (EAS 2023)

The European Atherosclerosis Society (EAS) Consensus Statement on HoFH, published in 2023, proposed updated diagnostic criteria that integrate clinical and genetic findings (17) (table 5).

Clinical criteria:

- LDL-cholesterol (LDL-C): untreated LDL-C levels >400 mg/dL are suggestive of HoFH and warrant further diagnostic evaluation.
- Additional criteria: presence of cutaneous and tendon xanthomas before the age of 10 years, or untreated LDL-C levels consistent with HeFH in both parents.
- In digenic forms, one parent may exhibit normal LDL-C levels while the other may present with values consistent with HeFH.

Genetic criteria:

- Confirmation of biallelic pathogenic/likely pathogenic variants located on different chromosomes in *LDLR, APOB, PCSK9,* or *LDLRAP1*, or identification of ≥2 variants in different loci.

Table 5. Updated diagnostic criteria for homozygous familial hypercholesterolemia (EAS 2023)

Category	Criteria
Clinical criteria	▪ Untreated LDL-C >400 mg/dL (suggestive, requires confirmation). ▪ Cutaneous/tendon xanthomas before age 10. ▪ Untreated LDL-C levels consistent with HeFH in both parents. ▪ In digenic forms, one parent may have normal LDL-C levels, and the other may have LDL-C levels consistent with HeFH.
Genetic criteria	▪ Biallelic pathogenic/likely pathogenic variants in LDLR, APOB, PCSK9, LDLRAP1 on different chromosomes. ▪ Presence of ≥2 pathogenic variants at different loci.

Source: Own elaboration based on the 2023 EAS Consensus Statement.

Differential diagnosis

The marked elevation of LDL-cholesterol (LDL-C) in HoFH often facilitates clinical suspicion. Nevertheless, other conditions may present with equally high LDL-C levels, including uncontrolled hypothyroidism, primary biliary cirrhosis, anorexia, nephrotic syndrome, and the use of certain medications (17, 36).

The main differential diagnoses involve rare autosomal recessive disorders with overlapping phenotypes:

Sitosterolemia (phytosterolemia): Caused by mutations in ABCG5 or ABCG8, encoding sterol transporters that limit phytosterol absorption and promote biliary excretion. Often diagnosed in childhood, it is characterised by markedly elevated cholesterol, tendon/tuberous xanthomas, and premature cardiovascular disease. Unlike HoFH, it shows a dramatic response to dietary phytosterol restriction, ezetimibe, or bile acid sequestrants (17, 39-40).

Cerebrotendinous xanthomatosis (CTX): An autosomal recessive disorder due to mutations

in *CYP27A1*, resulting in reduced activity of mitochondrial sterol 27-hydroxylase. This leads to impaired bile acid synthesis and accumulation of cholestanol and cholesterol in the tendons, lens, and the central nervous system. Clinical manifestations include ataxia, cognitive impairment, cataracts, and tendon xanthomas, along with gastrointestinal symptoms, jaundice, and coronary artery disease (13, 17, 36, 41).

Lysosomal acid lipase deficiency (LAL-D): Caused by *LIPA* gene mutations, impairing lysosomal lipid metabolism. It is characterised by cholesteryl ester and triglyceride accumulation in the liver, spleen, and other tissues, leading to hypercholesterolemia, accelerated atherosclerosis, and progressive liver disease. Clinical severity depends on residual enzymatic activity (36, 42-43).

Genetic diagnosis in HoFH

The introduction of nucleic acid sequencing in the late 20th century, followed by the development of next-generation sequencing (NGS), has revolutionised the diagnosis of genetic disorders, including cardiovascular, immunological, neurological, and metabolic diseases. Today, nearly 7000 diseases—representing ˜80% of rare and Mendelian conditions—can be diagnosed through genetic testing (44-46).

Genetic disorders can be classified as:

- **Monogenic:** caused by variants in a single gene.
- **Polygenic/multifactorial:** the result of multiple low-effect variants combined with environmental factors.
- **Chromosomal:** involving structural or numerical chromosomal abnormalities.

The main genetic tools include the following (47-52).

- Karyotyping (numerical/structural abnormalities).
- Sanger sequencing (up to 900 bp).
- **NGS (next-generation sequencing):** gene panels, whole exome, or whole genome sequencing.
- **MLPA (Multiplex Ligation-dependent Probe Amplification):** detection of copy number variations.

An international expert panel convened by the Familial Hypercholesterolemia Foundation concluded that genetic testing in FH (53):

1. Enables a definitive diagnosis.
2. Identifies pathogenic variants linked to higher cardiovascular risk, requiring more aggressive lipid-lowering therapy.
3. Supports earlier initiation of therapy and improved adherence.
4. Facilitates cascade screening of at-risk relatives.

Therefore, the Expert Consensus Panel recommends that genetic testing should be considered the standard of care in patients with definite or probable FH, as well as in their at-risk relatives. Core genes include *LDLR, APOB, PCSK9*, and *LDLRAP1*, with extension to other genes if the phenotype warrants.

Clinical evaluation begins with suspicion based on lipid profile, physical stigmata (tendon xanthomas, xanthelasma, corneal arcus), and premature cardiovascular disease in the patient or relatives (14). Once genetic testing is indicated, informed consent must be obtained. The approach may include:

- Targeted *LDLR* sequencing (Sanger method).
- Gene panels for dyslipidemias (e.g., LipidSeq, including 23 genes associated with monogenic and polygenic dyslipidemias) (54).
- MLPA for *LDLR* if initial testing is negative.
- Whole-exome or genome sequencing, depending on availability and clinical context.

The current consensus proposes a stepwise diagnostic algorithm, starting with gene panels or targeted sequencing, followed by MLPA, and proceeding to exome/genome sequencing if results are negative (figure 3).

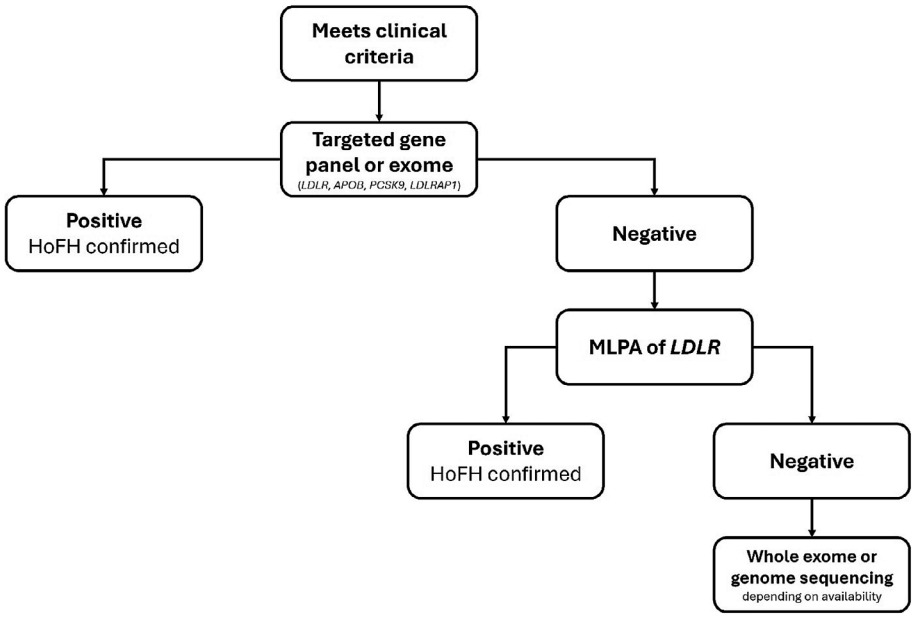

Figure 3. Genetic diagnostic algorithm for homozygous familial hypercholesterolemia (HoFH)

Source: Own elaboration based on international consensus recommendations.

Cascade screening in HoFH

Genetic testing for hereditary dyslipidemias, particularly FH, enables diagnostic confirmation, guides management strategies, and provides genetic counselling for patients and their relatives. Given that HoFH presents with more severe and early-onset phenotypes, including premature atherosclerotic cardiovascular disease, and considering its semidominant inheritance pattern, cascade screening of family members is essential.

Clinical guidelines from the European Atherosclerosis Society (EAS) and the National Institute for Health and Care Excellence (NICE) recommend cascade testing in all patients diagnosed with FH, especially in homozygous cases, since parents are typically heterozygous, even when LDL levels are near normal (4, 17, 55-56).

Cascade screening involves the evaluation of first-, second-, and third-degree relatives of the index case through LDL-C measurement and/or genetic testing for the identified pathogenic variant. Relatives testing positive—either for a pathogenic variant or with an LDL-C level >190 mg/dL—become new index cases, triggering further cascade screening within their own families (17, 57-58).

Although LDL-C measurement is less costly than genetic testing, it may yield false negatives, as some carriers can present with near-normal lipid levels. Therefore, genetic testing should be included whenever possible (4, 58).

In patients with HoFH, specialised genetic counselling is essential to identify other affected individuals and heterozygous carriers. Detecting the disease in parents and other relatives enables appropriate counselling, supports informed reproductive decisions, and allows early diagnosis in neonates, thereby reducing disease burden through timely treatment (4).

Evidence shows that cascade screening in FH is cost-effective: approximately 45% of screened relatives are positive (range 30–61%), with an average of 1.65 affected relatives identified per index case (range 0.22–8) (59). On this basis, the Centers for Disease Control and Prevention (CDC) has classified FH cascade screening as a Tier 1 genomic application, indicating a proven public health benefit supported by strong evidence and clinical guidelines (2).

Social impact of the disease

Rare diseases, including HoFH, are chronic and uncommon disorders with a profound impact on the quality of life of patients and their families (60). HoFH may cause significant disability and compromise the psychosocial, emotional, economic, educational, and occupational dimensions of life. Therefore, patient care must adopt an interdisciplinary approach, addressing both biomedical and psychosocial dimensions, to improve the quality of life of affected individuals and their families (17).

Research conducted at the Institute of Human Genetics of the Pontificia Universidad Javeriana (Bogotá, Colombia) has explored the social and occupational consequences of chronic rare diseases. Although not focused exclusively on FH, the findings can be extrapolated to this population. Similar findings were reported in the Study on the Situation of Health and Social Needs of People with Rare Diseases in Latin America (ENSERio LATAM), conducted by the Ibero-American Alliance for Rare Diseases. The main results are summarised in table 6:

- Educational and occupational impact: 58% of patients with advanced disease reported negative consequences in their work and academic life, including job loss and reduced opportunities, mainly due to hospitalisations and medical appointments.
- Socio-familial impact: 48% experienced deterioration in family relationships, and up to 39% reported the loss of friendships or social isolation.
- Daily activities: 28% were unable to manage finances or administrative tasks; 23% had motor and sensory difficulties; 21% faced limitations in self-care.
- Emotional and psychological impact: Patients frequently reported anxiety, stress, and depression. One-third (33%) reported being constantly unhappy, and 66% reported feeling unhappy frequently. Women were disproportionately affected, as they often assumed additional burdens, and were at higher risk of caregiver overload.

Furthermore, patients with FH face a 5- to 22-fold increased risk of atherosclerotic cardiovascular disease, owing to lifelong exposure to markedly elevated LDL-C levels, which may further amplify conventional cardiovascular risk factors (61).

Table 6. Social impact of homozygous familial hypercholesterolemia (HoFH), adapted from ENSERio LATAM and extrapolated rare disease data

Affected domain	Main findings	Reported percentage
Educational and occupational	Loss of job and academic opportunities; absenteeism due to medical care.	58%
Socio-familial	Deterioration of family relationships; social isolation and loss of friendships.	48% (family) / 39% (friendships)
Daily activities	Difficulty managing finances, administrative tasks, or personal care.	28% (finances/administration), 23% (motor and sensory limitations), 21% (self-care)
Emotional and psychological	Anxiety, depression, stress; constant or frequent unhappiness; caregiver burden (higher in women)	33% always unhappy / 66% frequently

Source: Own elaboration based on the ENSERio LATAM study and extrapolated evidence from rare disease populations.

Cardiovascular risk calculators

Commonly used cardiovascular risk calculators —the Framingham Risk Score, Systematic COronary Risk Evaluation (SCORE), and the ASCVD risk estimator— have not been validated in patients with FH (61, 65).

To overcome this limitation, FH-specific risk scoring systems have been proposed, such as the Montreal-FH-SCORE and SAFEHEART-RE (62-63).

The SAFEHEART study (*The SpAnish Familial HypErcHolEsterolemiA CohoRt STudy*) is a long-term, prospective, multicentre registry initiated in 2004, involving more than 30 centres in Spain and following families with genetically confirmed FH over time. Its primary aim has been to identify prognostic factors for cardiovascular morbidity and mortality in this population.

Based on this cohort, a risk equation (SAFEHEART-RE) was developed to estimate the likelihood of fatal and non-fatal cardiovascular events at 5 and 10 years. The model incorporates eight variables: sex, age, body mass index (BMI), smoking status, blood pressure, history of atherosclerotic cardiovascular disease, LDL-C levels, and lipoprotein(a) levels. This tool has shown a predictive accuracy of approximately 85% (64-65).

Preclinical cardiovascular involvement assessment

The evaluation of preclinical cardiovascular involvement in patients with familial hypercholesterolemia (FH), particularly in HoFH, remains a major clinical challenge. A variety of imaging and laboratory tools can facilitate the early detection of subclinical atherosclerosis and valvular alterations, enabling timely interventions.

Coronary computed tomography (CT) and coronary calcium score: Coronary CT with calcium scoring is a well-established marker of subclinical atherosclerosis (66). The absence of coronary calcification in FH is associated with lower cardiovascular event rates, whereas a calcium score > 100 Agatston units is linked to a 32-fold higher risk compared to a score of 0 (67). The EAS consensus recommends coronary CT every five years, starting in early childhood (4, 17).

Carotid ultrasonography (CUS): CUS enables the detection of atherosclerotic plaques (luminal protrusion > 0.5 mm) and measurement of carotid intima–media thickness (IMT), considered abnormal when > 0.9 mm (68). Both are surrogate markers of coronary atherosclerosis and correlate with cardiovascular events, although recent evidence suggests that carotid plaque burden is a stronger predictor than IMT (64-65).

Cardiac magnetic resonance (CMR): In addition to coronary atherosclerosis, valvular and supravalvular aortic stenosis represent life-threatening complications in FH. CMR allows assessment of aortic morphology and characterisation of atheromatous plaques, aiding in the timely identification of patients requiring intervention (69-70).

Transthoracic echocardiography (TTE) and transoesophageal echocardiography (TEE): TTE is fundamental for the evaluation of valvular involvement (aortic and mitral calcification, insufficiency, stenosis) and detection of atheromatous plaques in the ascending aorta. Annual examinations are recommended (4, 61, 69-70). Speckle-tracking echocardiography provides additional sensitivity for detecting early segmental or global myocardial dysfunction (71). TEE is reserved for cases with inconclusive or suspicious findings on TTE.

Stress echocardiography and myocardial perfusion imaging: These modalities are valuable when coronary calcium scoring is unavailable or abnormal. They are particularly indicated in symptomatic patients, those with a late diagnosis or delayed treatment initiation, and in athletes undergoing intensive training, given the high prevalence of silent ischemia (4, 61, 69, 72).

Lipoprotein(a) [Lp(a)]: Even modest increases in Lp(a) confer an independent risk for cardiovascular disease in FH, justifying its inclusion in the current risk stratification approach (17, 72-73).

Coronary angiography: As an invasive procedure, coronary angiography is reserved for patients with positive ischaemia testing or with clinical features strongly suggestive of angina (74).

Table 7. Tools for the assessment of preclinical cardiovascular involvement in familial hypercholesterolemia

Tool	Key findings	Clinical recommendations / utility
Coronary CT and calcium score	Score >100 = 32-fold ↑ risk	Repeat every 5 years from childhood (EAS)
Carotid ultrasonography	Plaques (>re0.5 mm) or IMT > 0.9 mm	Plaque burden is more predictive than IMT
Cardiac magnetic resonance	Atheromatous plaques, valvular/aortic stenosis	Guides surgical intervention decisions
Transthoracic echocardiography	Valvular involvement, plaques in the ascending aorta	Annual; speckle tracking for early dysfunction
Stress echocardiography / perfusion imaging	Silent ischaemia, exercise-induced risk	For late diagnosis, adults, or athletes
Lipoprotein(a)	Small increases = independent risk	Recommended for risk stratification
Coronary angiography	Direct assessment of the coronary tree	Reserved for positive ischaemia or angina

Source: Own elaboration based on evidence from scientific literature.

Management of HoFH

Non-pharmacological treatment of HoFH

Familial hypercholesterolemia (FH) is recognized as a modifiable risk factor for atherosclerosis and cardiovascular disease (CVD). Patients with FH are at high cardiovascular risk, and those with additional comorbidities are considered at very high risk (75-76). The likelihood of premature CVD is determined not only by the genetic basis of the disease but also by additional environmental and metabolic risk factors (75).

Several studies have demonstrated that male sex, older age, smoking, increased body mass index (BMI), hypertension, diabetes, low HDL-C levels, and elevated lipoprotein(a) [Lp(a)] contribute to the development and prognosis of CVD in FH patients (75, 77). Obesity, particularly visceral adiposity, promotes an altered metabolic and proinflammatory milieu that enhances the atherogenicity of LDL particles, favouring endothelial dysfunction and early atherosclerosis (78).

Although statins are the cornerstone of therapy, non-pharmacological interventions remain essential for reducing overall cardiovascular risk and are strongly recommended by international guidelines (79). These include the following strategies:

Dietary interventions

Referral to a nutrition specialist is indispensable for long-term management. General recommendations include:

- Reducing saturated fats, trans fats, and dietary cholesterol.
- Increasing fish intake (≥1 serving/week), fruits, and vegetables.
- Restricting processed meats and full-fat dairy products.

Specific recommendations:

- Total daily fat intake: 25–35%.
- Saturated fat: <7% of total calories.
- Dietary cholesterol: <200 mg/day.
- Fibre intake: 10–20 g/day.

A diet low in saturated fat reduces LDL-C by 8–10%, while restricting dietary cholesterol alone decreases LDL-C by 3–5% (75, 80-82).

Mediterranean diet: Characterised by a high intake of fruits, vegetables, monounsaturated fats (olive oil, nuts, avocado), oily fish, and complex carbohydrates, it reduces the incidence of major cardiovascular events by ˜30% compared with a low-fat diet (75, 80, 81, 83).

Phytosterols and stanols: Particularly relevant in paediatric patients, supplementation can reduce LDL-C by up to 15% (75, 79–80). A double-blind crossover trial in 41 children with FH showed reductions of 11% in total cholesterol and 14% in LDL-C after 4 weeks of sterol-enriched margarine (84). The Portfolio diet (phytosterols, soy protein, fibre, nuts) demonstrated a 13.1% LDL-C reduction compared with 3% with a low-fat diet (85). In addition, individuals with healthy lifestyle habits had up to a 50% lower risk of cardiovascular disease, even when carrying high-risk genetic variants such as those associated with FH (86).

Despite these benefits, diet alone is insufficient to halt CVD progression in most FH patients. However, it plays a vital role in controlling additional risk factors such as hypertension, diabetes, obesity, oxidative stress, and endothelial dysfunction (79-80).

Physical activity

Daily aerobic exercise is recommended for all FH patients: ≥150 minutes/week for normal-weight patients and ≥300 minutes/week for those with overweight or obesity (75). Aerobic activity (e.g., walking, cycling) should be complemented with muscle-strengthening exercises twice weekly. Experimental studies suggest that exercise protects against early endothelial dysfunction and oxidative stress (80).

A study by Pitsavos et al. found that exercise capacity <7 METs was associated with a threefold increase in cardiovascular events, while each 1-MET improvement reduced event risk by 18% (78, 87).

Pre-exercise evaluation is mandatory, including ECG, TTE, and stress testing, since most patients may develop ischaemic heart disease or aortic stenosis before age 20, with exercise-related angina, syncope, or sudden death occurring in untreated cases (17, 88).

Weight management

Weight control is another cornerstone of non-pharmacological therapy. Visceral adiposity promotes small dense LDL particles, proinflammatory adipokines, and insulin resistance, all of which contribute to increased CVD risk (80).

Waist circumference is a stronger predictor of CVD than BMI, as it reflects intra-abdominal fat and correlates with ectopic fat accumulation in the liver, muscle, heart, and pancreas (78). In FH patients, visceral fat assessed by CT has been associated with coronary stenosis severity (89), while epicardial fat volume correlates with subclinical coronary atherosclerosis (90).

Smoking cessation

Smoking accelerates atherogenesis and increases cardiovascular risk in FH patients. Smoking cessation is strongly recommended, regardless of potential weight gain (78, 80-81). In a Dutch FH cohort, excess cardiovascular risk attributable to smoking decreased linearly after 6–9 years of cessation, supporting the role of smoking as a key modifiable determinant of risk (91). Passive smoking should also be discouraged within families (75).

Alcohol moderation

Alcohol intake should be limited to ≤100 g per week. Stricter control is warranted in patients with hypertension or diabetes due to their higher baseline cardiovascular risk (75, 80-81).

Overall impact

Lifestyle interventions alone may produce modest reductions in LDL-C and should not be considered a substitute for pharmacological therapy. Patients must be counselled that these measures complement, but do not replace, lipid-lowering drugs (75). A meta-analysis by the

Cholesterol Treatment Trialists' (CTT) Collaboration demonstrated that a reduction of 39 mg/dL in LDL-C translates into a 22% reduction in cardiovascular risk (92). This highlights the importance of combining non-pharmacological strategies with pharmacological therapy to achieve treatment goals and reduce the long-term cardiovascular risk.

Pharmacological management of HoFH

The pharmacological management of HoFH remains a major clinical challenge. Conventional lipid-lowering therapies are less effective due to impaired LDL receptor function, which limits LDL-C reduction compared with patients with polygenic or heterozygous hypercholesterolemia.

Patients with HoFH experience lifelong exposure to markedly elevated LDL-C and ApoB levels, often from birth, resulting in premature and accelerated atherosclerosis. This underscores the need for early diagnosis and aggressive therapy to reduce cumulative risk. Importantly, the high cost of advanced therapies represents a significant barrier to optimal management in many healthcare settings.

Statins

Statins remain the cornerstone of treatment. Their mechanism of action involves upregulation of LDL receptor (LDLR) expression via sterol regulatory element-binding proteins (SREBPs). Therefore, their efficacy depends on residual receptor activity.

- In patients with <2% residual LDLR activity, LDL-C reduction is typically 10–25%.
- In those with partial receptor function, the response remains modest, even at maximal tolerated doses (17, 93-94)

Statins significantly reduce cardiovascular risk in FH (95). A landmark 20-year follow-up study by Luirink et al. demonstrated that early initiation of statins in childhood (age 8–18 years) was associated with fewer cardiovascular events compared with their untreated parents, highlighting the benefit of reducing lifetime LDL-C exposure (96). Similarly, Kusters et al. showed that statin therapy in children attenuated carotid intima–media thickness progression to levels comparable with those of unaffected siblings (97).

Guidelines recommend early, high-intensity statin therapy at the maximal tolerated dose, initiated as soon as possible and maintained lifelong, to improve outcomes and reduce cardiovascular morbidity and mortality.

Ezetimibe

Ezetimibe inhibits intestinal absorption of dietary and biliary cholesterol via the Niemann-Pick C1-like 1 (NPC1L1) protein. Its efficacy is independent of residual LDLR function (1).

- Provides an additional 15–20% LDL-C reduction when combined with statins (98-100).
- Approved for use from age 10 years (101-102).
- Particularly useful in sitosterolemia, where dramatic reductions in cholesterol levels with monotherapy support its diagnostic role (103).

Bile acid sequestrants

Bile acid sequestrants, such as cholestyramine, increase fecal cholesterol excretion by interrupting enterohepatic circulation (1, 104).

- LDL-C reduction of ~15% when combined with statins.
- Limited efficacy in HoFH patients without functional LDLR.
- Poor adherence due to gastrointestinal side effects and frequent dosing (every 6–8 hours).
- May reduce fat-soluble vitamin and folate absorption.

PCSK9 inhibitors

Monoclonal antibodies (evolocumab, alirocumab) inhibit PCSK9, increasing LDLR recycling and surface availability, with the following reported effects:

- LDL-C reductions up to 60% in general populations (105-107).
- Efficacy in HoFH depends on residual LDLR function; patients with null–null mutations show minimal response (108-109).
- Statins increase PCSK9 expression, which has been proposed as one of the

mechanisms underlying the "therapeutic ceiling effect" observed in FH (110).

Evolocumab has been extensively evaluated in patients with HoFH. In the TESLA Part B trial (phase 3, 49 patients), monthly administration of evolocumab 420 mg resulted in a mean 32% reduction in LDL-C after 12 weeks of treatment (108, 111). The long-term TAUSSIG open-label study followed HoFH and severe HeFH patients for more than four years, showing a sustained 24% reduction in LDL-C at week 48, with continued efficacy at week 216. Importantly, 26% of patients were able to discontinue LDL apheresis during follow-up, and the annualised cardiovascular event rate was 2.7 per year (112). In paediatric populations, the HAUSER-OLE extension trial included 12 adolescents with HoFH (aged 10–18 years), who achieved a 14% reduction in LDL-C after 80 weeks of monthly treatment, confirming its potential role in children and adolescents, although with more modest efficacy than in adults (113).

Alirocumab has also demonstrated efficacy in HoFH. In the ODYSSEY HoFH trial (69 patients on background statin, ezetimibe, lomitapide, or apheresis therapy), biweekly injections of alirocumab 150 mg reduced LDL-C levels by a mean of 35.6% after 12 weeks (114). However, results in younger populations were less pronounced: in a paediatric study including 18 patients with a mean baseline LDL-C of 373 mg/dL, the LDL-C reduction after 12 weeks was only 4.1%, largely reflecting the heterogeneity of genetic backgrounds and residual LDLR activity (115, 154)

Taken together, these data show that PCSK9 inhibitors can substantially lower LDL-C in many patients with HoFH, but the magnitude of response depends strongly on the underlying genotype and residual LDLR function. For this reason, they should be used at the maximum recommended doses in adults with HoFH: evolocumab 420 mg monthly or alirocumab 150 mg every two weeks.

siRNA therapy (inclisiran)

Inclisiran is a small interfering RNA (siRNA) that silences hepatic PCSK9 expression and is administered twice yearly. In patients with HoFH, early proof-of-concept studies showed variable LDL-C responses ranging from −37% to +3% after 180 days of treatment (116-121).

In a proofofconcept study in HoFH (ORION2, n=4), inclisiran produced a consistent fall in circulating PCSK9 and highly variable LDLC responses at day 180, ranging from +3% to −37%; a sustained LDLC reduction was observed in three of four patients (116). The randomised ORION5 trial (n=59) compared inclisiran 284 mg with placebo in HoFH patients receiving maximal lipidlowering therapy with or without LDL apheresis. Although PCSK9 levels fell by 60.6% with inclisiran, the placeboadjusted change in LDLC at day 150 was only +1.68%, with no significant difference versus placebo (122). Taken together, these findings indicate robust target engagement but inconsistent LDLC lowering in HoFH, likely reflecting the heterogeneity of LDLR mutations and dependence on residual receptor activity.

Lomitapide

Lomitapide is an oral agent specifically approved for the treatment of HoFH. Its major advantage is that its mechanism of action is independent of residual LDLR function, making it particularly useful in patients with null–null mutations, who represent the most severe phenotype and are typically unresponsive to conventional lipid-lowering therapy (123-125).

Lomitapide acts by inhibiting microsomal triglyceride transfer protein (MTP), which is required for the assembly of ApoB-containing lipoproteins in both hepatocytes (ApoB100, VLDL) and enterocytes (ApoB48, chylomicrons). By blocking this process, lomitapide reduces VLDL secretion and consequently lowers plasma levels of VLDL-C and LDL-C (126-129).

The pivotal phase 3 HoFH Lomitapide Study (29 patients, mean dose 40 mg/day) demonstrated a 50% reduction in LDL-C at week 26, which was sustained at 38% by week 56 (130). A subsequent Japanese study (n=9) using titrated doses up to 20 mg/day reported a 42% reduction in LDL-C at week 26, with more than half of the patients achieving LDL-C <100 mg/dL (131). An extension of this cohort (n=8) confirmed a sustained 50% reduction in LDL-C after 60 weeks (132). Real-world registries, including the LOWER registry,

have confirmed lomitapide's effectiveness, showing that substantial LDL-C reductions can be achieved at lower doses (e.g., 10–20 mg) with improved tolerability compared with the pivotal trial (133-136)

Lomitapide is taken orally once daily, preferably two hours after the evening meal. Treatment should begin at 5 mg/day, followed by gradual titration to 10, 20, 40, and up to a maximum of 60 mg/day, depending on tolerance (137). Capsules are available in 5, 10, and 20 mg formulations. When treatment is initiated at 5 mg/day, slow titration is recommended, with an increase to 10 mg after at least 2 weeks and subsequent dose increases every 4 weeks (138, 139). Dose increases should be spaced at least every 2–4 weeks.

Because lomitapide undergoes extensive hepatic metabolism via CYP3A4, it is contraindicated in patients with moderate-to-severe hepatic impairment and should not exceed 40 mg/day in end-stage renal disease. Grapefruit juice and strong CYP3A4 inhibitors (e.g., ketoconazole, ritonavir) are contraindicated; moderate inhibitors require limiting lomitapide to ≤30 mg/day.

The main adverse effects are gastrointestinal (up to 90% at treatment initiation), including diarrhoea, nausea, dyspepsia, and anorexia, which are the leading cause of treatment discontinuation (133). Hepatic steatosis and transaminase elevations are also common, related to impaired triglyceride secretion. These adverse events can be mitigated by a strict low-fat diet (<20% of total calories from fat) and slow dose titration (137-138, 140). Long-term follow-up (mean 5.1 years) did not reveal additional safety signals beyond the known risks of steatosis and transaminase elevations (133). Importantly, registry data suggest that liver fat accumulation is reversible with drug discontinuation, although long-term monitoring is required. Patients should receive supplementation with vitamin E and omega-3 fatty acids, and levels of fat-soluble vitamins should be regularly monitored.

Special populations and contraindications

- Pregnancy: Lomitapide is teratogenic and contraindicated; women of childbearing potential should use effective contraception. If combined with oral contraceptives, the maximum recommended dose is 30 mg/day.
- Paediatrics: Although approved for adults (≥18 years), increasing case series have reported safe and effective use in adolescents and children, pending more robust long-term data (138).
- Prescriber requirements: Given the complexity of dosing, monitoring, and potential toxicities, lomitapide should only be prescribed by clinicians with prior training and experience in lipid disorders.

Overall, lomitapide represents a highly effective therapy for HoFH, capable of achieving substantial LDL-C reductions even in receptor-negative patients, but its use requires strict adherence to dietary measures, careful dose escalation, and close safety monitoring.

Evinacumab

Angiopoietin-like 3 (ANGPTL3) is a protein that acts as a dual inhibitor of lipoprotein lipase and endothelial lipase, thereby regulating triglyceride clearance in adipose tissue. Its biological effect is to increase plasma HDL-C and, more importantly, triglyceride levels, which serve as substrates for VLDL-C and LDL-C production (132, 141). Registry data from patients with loss-of-function mutations in *ANGPTL3* show markedly reduced triglyceride, LDL-C, and HDL-C levels. Large population studies with *ANGPTL3* exon sequencing have confirmed a significantly lower cardiovascular risk in these individuals (142-143).

Evinacumab is a fully human monoclonal antibody against ANGPTL3, developed for the treatment of HoFH and severe hypertriglyceridemia (144). The pivotal ELIPSE HoFH trial, a phase 3, placebo-controlled study, included 65 patients with HoFH receiving maximal lipid-lowering therapy. Patients treated with evinacumab 15 mg/kg intravenously every four weeks achieved a 47% reduction in LDL-C at 24 weeks, irrespective of genotype (null vs. defective alleles) (145).

An open-label extension study enrolled 116 patients (14 adolescents ≥12 years; mean age 39 years), comprising two cohorts: treatment-naïve patients (n=46) and rollover participants from prior trials (n=70). Concomitant lomitapide was used

in 19% and LDL apheresis in 39%. At 24 weeks, evinacumab produced a 43.6% reduction in LDL-C, with an acceptable safety profile despite a higher rate of treatment-emergent adverse events (146).

More recently, an open-label paediatric study evaluated 14 children aged 5–11 years with genetically confirmed HoFH. Inclusion required LDL-C ≥130 mg/dL despite maximal therapy including lomitapide and apheresis. Evinacumab achieved a 48% LDL-C reduction at 24 weeks, with a rapid decline from week 1 that was sustained over time. The treatment was generally well tolerated, with gastrointestinal symptoms being the most common adverse events; immunogenicity was minimal (147).

Evinacumab has been approved by the FDA and EMA since 2021 for patients aged ≥12 years, with the indication expanded to children ≥5 years in 2023. It is administered intravenously every four weeks (148).

Mipomersen

Mipomersen is an antisense oligonucleotide targeting ApoB-100 mRNA, thereby reducing ApoB-containing lipoproteins (VLDL and LDL). It is administered subcutaneously and has shown significant LDL-C and VLDL-C reductions in HoFH patients. However, its clinical use is limited due to hepatotoxicity, including hepatic steatosis and transaminase elevations (149). Although approved for HoFH in some regions, mipomersen is not widely available and is not marketed in Colombia.

Emerging therapies

Several innovative therapeutic approaches are under investigation for HoFH. These include:

- Gene therapy and CRISPR-based genome editing, targeting PCSK9 (Verve-101, Verve-102) or *ANGPTL3* (Verve-201). Given that PCSK9 inhibition still depends on residual LDLR function, *ANGPTL3*-directed therapies (e.g., Verve-201) may be more promising for null–null patients (150).
- Antisense oligonucleotides targeting *ANGPTL3*: vupanorsen development was halted due to hepatic enzyme elevations in the TRANSLATE trial (151).
- Monoclonal antibodies against *ANGPTL3*, such as SHR-1918, are currently being evaluated in phase 2 studies for efficacy and safety in patients with dyslipidemia.
- siRNA therapies targeting *ANGPTL3*: zodasiran, solbinsiran, and ALN-ANG3. In an open-label trial, zodasiran reduced LDL-C by up to 48% in 18 HoFH patients; however, its phase 3 program was discontinued for commercial reasons (150, 157).

Another promising agent is lerodalcibep, a recombinant fusion protein consisting of a PCSK9-binding adnectin linked to human albumin. The LIBerate-HoFH trial (phase 3, randomized, open-label) evaluated monthly subcutaneous lerodalcibep (300 mg) versus evolocumab (420 mg) in 66 genetically confirmed HoFH patients aged ≥10 years (30% of whom were paediatric). Lerodalcibep was non-inferior to evolocumab, with LDL-C lowering largely determined by residual LDLR function (152-153).

LDL Apheresis

LDL apheresis remains the cornerstone of non-pharmacological therapy for HoFH, offering efficacy independent of LDLR function, making it essential in null–null patients. Per session, LDL-C can be reduced by 73–80%, with additional benefits including regression of xanthomas, improved exercise tolerance, reduced angina, decreased inflammatory markers, and enhanced response to pharmacological therapy (154).

Typically performed every two weeks, apheresis should be initiated as early as possible—ideally between the ages of 3 and 8 years. However, the therapy has major limitations: it requires vascular access, specialized lipid clinics, and trained personnel, and availability is uneven across regions, often restricted by healthcare coverage. Moreover, LDL-C levels rebound progressively after each session, and non-selective removal affects other lipoproteins, including ApoE, HDL, and pre-β1 HDL (146). Adverse events include allergic reactions, hypotension, and catheter-related complications.

Liver transplantation

Liver transplantation offers a potential metabolic cure for HoFH by introducing a donor

liver with functional LDLR activity. However, it is reserved for a small subset of refractory patients, particularly those with biallelic null mutations or progressive coronary disease despite maximal therapy (LDL-C >500 mg/dL) (17).

Special considerations include perioperative risks, donor organ scarcity, lifelong immunosuppression, and competition for organs with patients suffering from acute or advanced primary liver disease. In some cases, combined liver–heart transplantation may be indicated for patients with severe cardiopathy requiring surgical intervention.

Reported outcomes vary:

- A Chinese cohort (2014–2022) of six paediatric HoFH patients reported 100% survival at a mean follow-up of 37.4 months, with marked LDL-C reduction and clinical improvement (155).
- A European–Middle Eastern consortium (n=9 patients; mean age 10.8 years, youngest patient aged 2 years) reported survival up to 28 years, though 33% mortality was related to perioperative complications, and several patients required ongoing lipid-lowering therapy or repeat transplantation (156).

In conclusion, while liver transplantation is not curative, it may be considered in carefully selected HoFH patients with refractory disease, progressive ASCVD, or uncontrolled LDL-C, particularly when performed in experienced centres (figure 4).

Special populations

HoFH in children and adolescents: HoFH is a rare condition in the general population, with its prevalence varying depending on the population studied. Its clinical importance lies in the early onset of atherosclerosis and premature cardiovascular disease, which can become life-threatening in the first decades of life (149, 157-161).

Diagnosis in children should be suspected when there is a family history of premature cardiovascular disease, parents with total cholesterol >240 mg/dL, or when the patient presents with extravascular cholesterol deposits such as tendon xanthomas, tuberous xanthomas, and xanthelasma, particularly after the age of 5. The most frequent sites are the Achilles tendon, popliteal fossa, antecubital region, gluteal area, and interdigital spaces. Polyarthralgia and supravalvular aortic stenosis may also occur, the latter being responsible for chest pain and early myocardial infarction. Some patients are identified through universal lipid screening, currently recommended at ages 9–11 and again at 17–21, or earlier in children with a family history of hypercholesterolemia or other risk factors such as hypertension, obesity, or diabetes. Early identification of children with homozygous variants is crucial to ensure the prompt initiation of therapy (93, 162-164). Table 8 shows reference lipid values in the pediatric population.

For diagnostic confirmation, the Dutch Lipid Clinic Network (DLCN) criteria are applied: >8 points indicate definite FH, 5–8 points probable FH, and 3–5 points possible diagnosis, with good sensitivity and specificity in pediatric cohorts (36). Molecular studies should be considered in all suspected cases, after obtaining informed consent. Cascade testing is essential, as parents are frequently heterozygous carriers and siblings may also carry the same variants, potentially resulting in HoFH.

Non-pharmacological therapy should begin from age 2, including a diet with <30% total fat, 7–10% saturated fat, <200 mg/day of cholesterol, and high dietary fiber intake (4–5 servings of fruits and vegetables daily).

While statin therapy in heterozygous FH is usually recommended only after age 8, HoFH is an exception. Pharmacological therapy should start as soon as the diagnosis is established, although the response is often limited due to its dependence on residual LDLR function (17, 149, 158).

Statin use in children with FH has been associated with a decline in the cumulative incidence of cardiovascular disease from 26% to 1%, as well as regression of carotid intima-media thickness compared with untreated individuals (96). LDL-C treatment goals in children and adolescents are <115 mg/dL, ideally achieved before age 18, though they may be re-evaluated in cases of documented atherosclerosis.

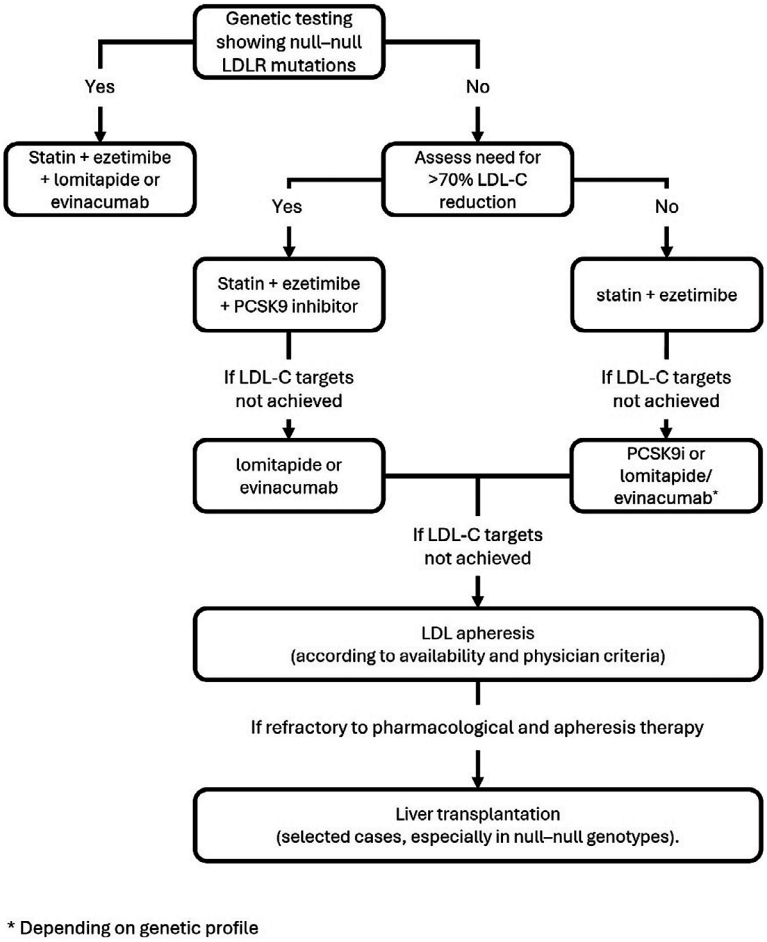

Figure 4. Proposed management algorithm for homozygous familial hypercholesterolemia (HoFH)

Note. The algorithm emphasizes treatment stratification according to genetic profile (null–null mutations vs. other variants), required LDL-C reduction, and therapeutic response.

LDL-C targets: <55 mg/dL in adults; <115 mg/dL in children. PCSK9 inhibitors: Evolocumab 420 mg SC monthly or Alirocumab 150 mg SC every 2 weeks. PCSK9 response: Defined as >15% LDL-C reduction; discontinue if not achieved. Lifestyle measures: Strict low-fat diet, adherence, and persistence should be implemented in all patients. *Mandatory notification as a rare disease to the national health surveillance registry (e.g., SIVIGILA in Colombia).*

Source: Own elaboration.

Table 8. Reference values for lipid fractions in children and adolescents

Parameter	Ideal (mg/dL)	Borderline (mg/dL)	Elevated/Low (mg/dL)
Total cholesterol	<170	170–199	≥200
LDL-C	<110	110–129	≥130
Non–HDL-C	<120	120–144	≥145

Triglycerides (0–9 years)	<75	75–99	≥100
Triglycerides (10–19 years)	<90	90–129	≥130
HDL-C	>45	40–45	<40

Source: Own elaboration.

These goals usually require combination therapy or LDL apheresis, which remains the cornerstone of treatment in paediatric HoFH, especially given the limited access to novel therapies in low- and middle-income countries. Apheresis should be initiated as early as possible, ideally before age 8 (17).

Liver transplantation is an invasive alternative requiring lifelong immunosuppression and associated with surgical risks, with additional challenges related to organ availability for pediatric patients (165-169). It should be performed only in experienced pediatric transplant centers.

Lomitapide has been increasingly studied in paediatric populations. An international multi-center cohort of 11 patients (mean age 11.6 years) reported a mean baseline LDL-C of 422 mg/dL. Initiated at 2.5 mg daily, lomitapide reduced LDL-C by 56.7% ± 21.7%, allowing for longer apheresis intervals. Gastrointestinal adverse events were common, mostly at treatment initiation, with a safety profile similar to that seen in adults (170). More recently, the APH-19 phase 3 open-label multicenter trial enrolled 43 patients aged 5–17 years across 12 centers in Europe and the Middle East. At 24 weeks, LDL-C was reduced by 53.5%, with continued safety follow-up for 70 weeks. Adverse events were mostly mild, with 12% of patients experiencing gastrointestinal or hepatic complications (171).

Evinacumab has provided robust evidence in pediatric HoFH. Initially approved for patients aged ≥12 years, an expanded-use study included 14 patients aged 5–11 years with genetically confirmed HoFH. At week 24, evinacumab reduced LDL-C by −48.3%, ApoB by −41.3%, non-HDL cholesterol by −48.9%, and total cholesterol by −49.1% (145, 147).

Pregnancy: Genetic counseling is recommended for all women with HoFH considering pregnancy, as affected individuals will invariably transmit one defective allele.

Pregnancy itself increases multiple lipid fractions, including ApoB, LDL-C, and triglycerides. In heterozygous FH, percentage increases are similar to those of unaffected pregnant women, although absolute cholesterol values are much higher (172).

Women with HoFH should discontinue potentially teratogenic lipid-lowering drugs (statins, ezetimibe, lomitapide) at least four weeks before conception, or immediately upon recognition of pregnancy if unplanned. The safety of monoclonal antibodies during pregnancy remains unknown; therefore, their use is not recommended.

Bile acid sequestrants represent the safest pharmacological option during pregnancy (160, 173). LDL apheresis is another effective intervention and, when necessary, may be performed weekly (174-175).

Pregnancy in HoFH is associated with increased cardio-obstetric risk, due to elevated ApoB and a pro-coagulant state, which together exacerbate cardiovascular risk. Careful pre-pregnancy risk assessment is essential, particularly in women with coronary disease or moderate-to-severe aortic stenosis.

Importantly, the FDA recently revised its contraindication for statins in pregnancy, now allowing an individualized risk–benefit assessment in select cases of HoFH, particularly when apheresis is not feasible (see FDA safety communication).

Conclusions

Homozygous familial hypercholesterolemia (HoFH) is more prevalent than previously believed. Clinical suspicion must be raised early in life to mitigate the substantial cardiovascular risk inherent to this condition. Once HoFH is suspected, molecular studies are essential to confirm the diagnosis and to enable cascade screening of family members. However, initiation of treatment should not be delayed while awaiting genetic confirmation, particularly when access to testing is limited or delayed.

Therapy must begin as early as possible, ideally before the age of 8 years. Both pharmacological and non-pharmacological strategies are required, tailored to the individual patient. Statins and ezetimibe should generally be prescribed, even though their efficacy is limited in patients with null variants, as they may still contribute to the reduction of vascular inflammation. LDL apheresis remains an important therapeutic tool in settings where it is available, and its combination with pharmacological therapy and dietary measures may further enhance clinical outcomes. Finally, liver transplantation represents a last-resort intervention for patients with refractory disease, uncontrolled LDL-C, or progressive cardiovascular involvement despite maximal therapy.

In summary, early identification and aggressive management of HoFH—through a combination of lifestyle measures, pharmacological therapies, apheresis, and, in selected cases, transplantation—are essential to improve survival and quality of life in this high-risk population.

Authors' contributions

Álvaro J Ruiz: conceptualization, writing – original draft, writing – review & editing; Rafael Campo-Torrenegra: investigation, writing – original draft, writing – review & editing; Claudia Monsalve-Arango: investigation, writing – original draft, writing – review & editing; Mauricio Coll-Barrios: investigation, writing – original draft, writing – review & editing; Julián Gil-Forero: investigation, writing – original draft, writing – review & editing; Juan E. Gómez-Mesa: investigation, writing – original draft, writing – review & editing; Harry Pachajoa: investigation, writing – original draft, writing – review & editing; Carolina Rivera: investigation, writing – original draft, writing – review & editing; Alejandro Roman-Gonzalez: investigation, writing – original draft, writing – review & editing; Martha L. Tamayo: investigation, writing – original draft, writing – review & editing; Hernando Vargas-Uricoechea: investigation, writing – original draft, writing – review & editing.

Ethical statement

The authors declare that the present manuscript does not have any significant ethical implications, due to its nature as an expert panel perspective. Therefore, neither informed consent nor approval by ethics committees were required.

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Conflicts of interest

The authors declare no conflicts of interest regarding the subject of this work.

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The authors declare that no AI tools were used at any stage of the article's production.

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The authors declare that there are no available data published in open access repositories. For any inquiry or request related to the article, the corresponding author should be contacted.

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