Archives of Cardiovascular Disease 119 (2026) 182–184

Disponible en ligne sur
ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com

Scientific editorial

Homozygous familial hypercholesterolemia: New therapeutic approach and a call for action!

Antonio Gallo [a,*], Franck Boccara [b,c], Sophie Béliard [d]

[a] Sorbonne Université, Inserm UMR1166, Lipidology and Cardiovascular Prevention Unit, Department of Nutrition, AP–HP, Hôpital Pitié-Salpètrière, 47/83, boulevard de l'Hôpital, 75013 Paris, France
[b] Department of Cardiology, Saint-Antoine and Tenon Hospital, AP–HP, 75012 Paris, France
[c] Sorbonne université, GRC nº 22 (C2MV-Complications Cardiovasculaires et Métaboliques chez les patients vivant avec le Virus de l'immunodéficience humaine), Inserm UMR_S 938, centre de recherche Saint-Antoine, institut Hospitalo-Universitaire de cardio-métabolisme et nutrition (ICAN), 75571 Paris, France
[d] AP–HM, Endocrinology Department, Inserm, INRAE, Aix-Marseille University, Department C2VN, Marseille, France

ARTICLE INFO

Article history:
Received 4 August 2025
Received in revised form
13 September 2025
Accepted 16 September 2025
Available online 27 September 2025

Keywords:
Homozygous familial
hypercholesterolaemia
Lipoprotein apheresis
cardiovascular risk ;

1. Abbreviations

HoFH	homozygous familial hypercholesterolaemia
LA	lipoprotein apheresis
PCSK9	proprotein convertase subtilisin kexin-9

Homozygous familial hypercholesterolaemia (HoFH) is a rare inherited disease of lipid metabolism with an estimated prevalence of around 1/400,000 subjects [1]. It results from markedly reduced or absent activity of the low-density lipoprotein receptor (LDLR), most often due to biallelic variants in the *LDLR* gene. Less commonly, variants in *APOB*, *PCSK9* or *LDLRAP1* are implicated [2]. The consequent lifelong exposure to extremely high low-density lipoprotein cholesterol (LDL-C) from birth drives rapid and severe atherosclerotic cardiovascular disease, occurring as early as before the age of 3 years in the most severe forms in the absence of treatment. Aortic valve stenosis due to aortic valve disease occurs early in the life of subjects living with HoFH, often requiring valvular replacement interventions. Sometimes coronary artery bypass graft is also required due to the specific involvement of coronary ostia, responsible for sudden deaths in children or young adults with HoFH.

Since the introduction of lipid-lowering treatments such as statins, the average survival of patients living with HoFH has significantly improved [3]. Medical care is highly challenging as statin therapy and ezetimibe cannot reduce sufficiently the cholesterol burden, which prompts further atherosclerotic cardiovascular disease events. Lipoprotein apheresis (LA), when available, has been the standard of care, lowering LDL-C levels by 30–40% [4]. However, LA is invasive, resource-intensive, and accessible to only a minority of patients worldwide [5]. Data from the largest worldwide database on HoFH show that barely 30% of subjects with HoFH are treated with LA [1]. Adherence to LA is influenced by its frequency, distance from the LA centre and costs [5] (Table 1).

Surgical approaches (i.e. post-ileal bypass, liver transplantation) are now rarely considered [6]. Recently, proprotein convertase subtilisin kexin-9 (PCSK9) inhibitors were found to provide additional LDL-C lowering in some HoFH patients, but their efficacy depends on residual LDLR activity: patients with two null LDLR variants typically show no response [7–9]. The diminished efficacy of these lipid-lowering treatments, all LDLR dependent, has led to focus

* Corresponding author.
E-mail address: antonio.gallo@aphp.fr (A. Gallo).

https://doi.org/10.1016/j.acvd.2025.09.001
1875-2136/© 2025 The Authors. Published by Elsevier Masson SAS. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

Table 1
Available lipid-lowering drugs for HoFH.

Treatment	Pros	Cons
Statins/ezetimibe	Safe, well tolerated Cheap	Insufficient LDL-C lowering LDLR-dependent response to treatment
Lipoprotein apheresis	Acute extreme LDL-C lowering Pleiotropic properties	Invasive treatment Unease of access Expensive
PCSK9 inhibitors	Non-daily, non-invasive treatment	LDLR-dependent response to treatment
Lomitapide	Drastic LDL-C lowering Non-invasive treatment LDLR-independent therapy	Requires low-fat diet Not indicated in the presence of liver steatosis Expensive
Evinacumab	Drastic LDL-C lowering LDLR-independent therapy No dietary constraint	Monthly (intravenous) Expensive

HoFH: homozygous familial hypercholesterolaemia; LDL-C: low-density lipoprotein-cholesterol; LDLR: low-density lipoprotein receptor; PCSK9: proprotein convertase subtilisin/kexin type 9.

attention on drugs that lower LDL-C by LDLR-independent mechanisms.

Two new drugs have transformed the therapeutic landscape of HoFH. Lomitapide is an inhibitor of microsomal triglyceride transfer protein, involved in the triglyceride-rich lipoprotein constitution in the intestine and the liver. In a phase 3 study, a mean dose of 40 mg/day of lomitapide was reported to reduce plasma levels of LDL-C by ~50% in a cohort of subjects with HoFH [10]. Based on these results, lomitapide has been approved in Europe and the US for the treatment of adults living with HoFH. Real-world data have confirmed its efficacy, with an overall reduction of LDL-C by 60%, with 32% of patients achieving LDL-C < 100 mg/dL, 18.7% achieved LDL-C < 70 mg/dL, and almost 40% of subjects ceased LA after the introduction of lomitapide [11]. Potential drawbacks of this treatment are represented by the risk of gastrointestinal effects, and slight progression of liver steatosis. The first is related to the need for a low-fat dietary plan, as dietary fat is not being absorbed at the intestinal level; the latter is mostly related to the reduced formation and secretion of triglyceride-rich lipoproteins from the liver. A good adherence to a low-fat dietary plan is key for good adherence and tolerance of this treatment.

Evinacumab is a monoclonal antibody targeting angiopoietin-like 3, a protein involved in the metabolism of triglyceride-rich lipoproteins, once again exerting an LDLR-independent action. Recently, a phase 3, double-blind, placebo-controlled international trial in 65 subjects with HoFH who underwent evinacumab/placebo treatment for 24 weeks, showed a ~50% reduction in LDL-C levels in the evinacumab group versus placebo [12]. Subjects with null/null variants exhibited the same significant reductions as LDLR-defective mutation carriers, compared with placebo. Nasopharyngitis and flu-like symptoms of mild intensity were the most frequently reported adverse events, occurring in the same amount in drug and placebo groups. These results and safety profiles have been confirmed in real-world cohorts [13].

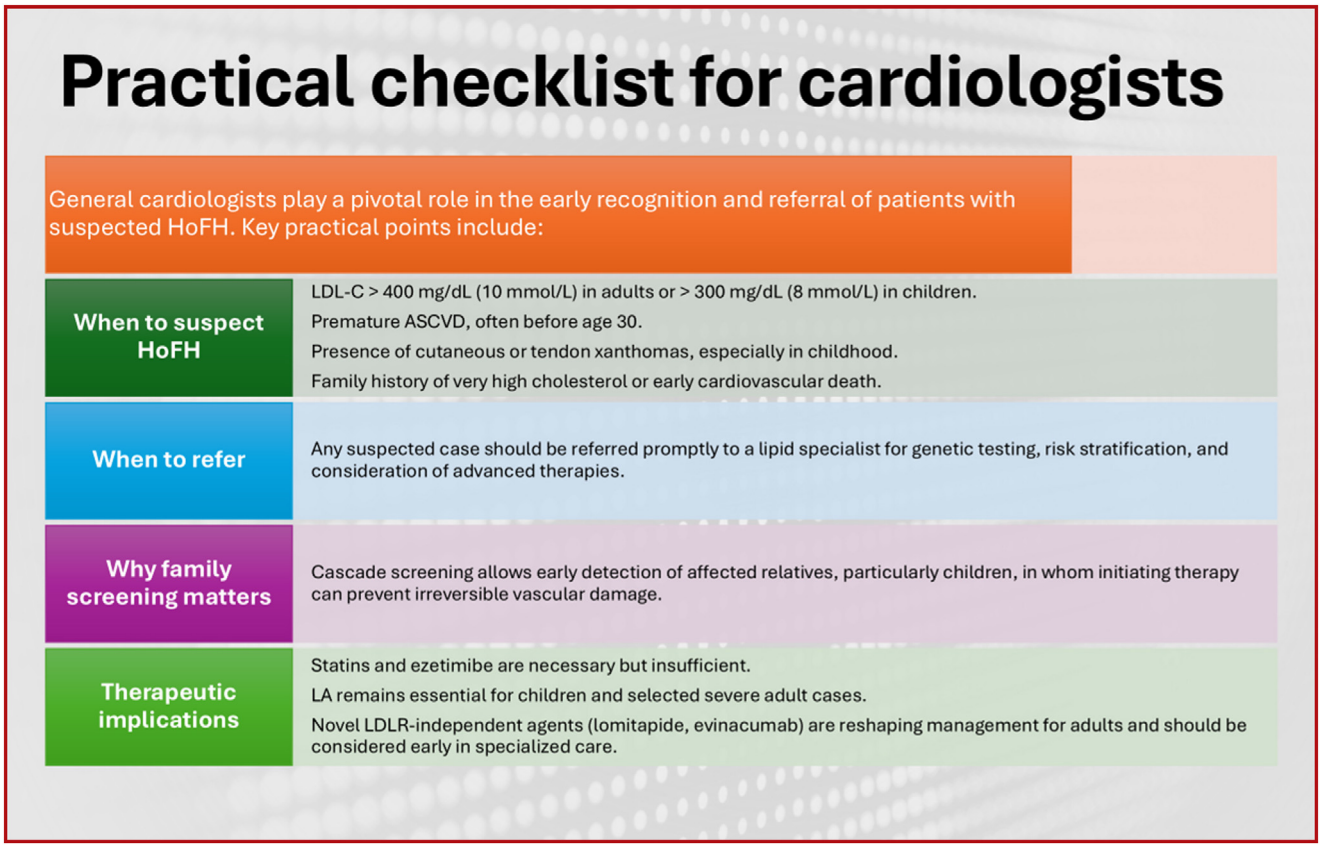
In clinical trials, no differences in cardiovascular outcomes were observed over the relatively short follow-up periods. Nevertheless, the substantial reduction in cholesterol burden strongly suggests that long-term use of these therapies will translate into lower rates of atherosclerotic cardiovascular disease [14]. Supporting this, in two young patients, treatment with evinacumab for 5–6 months was associated with a > 75% reduction in total coronary plaque burden, as assessed by computed tomography angiography [15].

While novel LDLR-independent therapies represent a major breakthrough, LA remains an important therapeutic tool. In the most severe cases, LA can provide additional LDL-C lowering when available. However, access to LA is limited in many regions, and a cross-national French survey is currently underway to better quantify this treatment gap.

For general cardiologists, awareness of HoFH remains limited. Yet, they are often the first to encounter these patients. Several practical points should be emphasized (Central Illustration).

Cardiologists should suspect HoFH in young patients presenting with markedly elevated LDL-C levels (> 400 mg/dL or 10 mmol/L), premature atherosclerotic cardiovascular disease, or a strong family history of hypercholesterolaemia or early cardiovascular death. In such cases, prompt referral to a lipid specialist is essential for genetic confirmation, initiation of appropriate therapies and multidisciplinary management. Equally important, cascade screening of relatives should be systematically undertaken, as it allows early identification and treatment of affected family members (particularly children) before irreversible vascular damage occurs.

Management of HoFH is entering a new era. Novel LDLR-independent therapies offer powerful cholesterol reduction and, for the first time, realistic alternatives to LA. To change the natural history of this devastating disease, early recognition and aggressive treatment must begin in childhood. Ensuring timely access to these therapies across healthcare systems should now be a priority.



Central Illustration. Homozygous familial hypercholesterolaemia (HoFH) in daily cardiology practice: when to suspect, refer, and screen. LDL-C: low-density lipoprotein-cholesterol.

Sources of funding

None.

Disclosure of interest

Dr. Gallo has received grants and personal fees from Amgen, Sanofi and Regeneron, Mylan Viatris, MSD, Akcea Therapeutics, Amryt, Novartis and Ultragenyx.

Pr. Boccara has received research grants from Amgen; and lecture fees from Gilead, ViiV Healthcare, Amgen, Sanofi, Merck Sharp & Dohme, NovoNordisk, Novartis, and Servier outside the submitted work.

Pr. Beliard has received honoraria for board, conferences, clinical trial or congress from Aegerion, Amarin, Amgen, Amryt, Akcea, Novartis, Sanofi or Ultragenyx.

References

[1] Tromp TR, Hartgers ML, Hovingh GK, Vallejo-Vaz AJ, Ray KK, Soran H, et al. Worldwide experience of homozygous familial hypercholesterolaemia: retrospective cohort study. Lancet Lond Engl 2022;399(10326):719–28.
[2] D'Erasmo L, Minicocci I, Nicolucci A, Pintus P, Roeters Van Lennep JE, Masana L, et al. Autosomal recessive hypercholesterolemia: long-term cardiovascular outcomes. J Am Coll Cardiol 2018;71(3):279–88.
[3] Raal Frederick J, Pilcher Gillian J, Panz Vanessa R, van Deventer Hendrick E, Brice Brigitte C, Blom Dirk J, et al. Reduction in mortality in subjects with homozygous familial hypercholesterolemia associated with advances in lipid-lowering therapy. Circulation 2011;124(20):2202–7.
[4] Stefanutti C, Thompson GR. Lipoprotein apheresis in the management of familial hypercholesterolaemia: historical perspective and recent advances. Curr Atheroscler Rep 2015;17(1):465.
[5] Beliard S, Gallo A, Duchêne E, Carrié A, Bittar R, Chapman MJ, et al. Lipoprotein-apheresis in familial hypercholesterolemia: long-term patient compliance in a French cohort. Atherosclerosis 2018;277:66–71.
[6] Al Dubayee M, Kayikcioglu M, van Lennep JR, Hergli N, Mata P. Is liver transplant curative in homozygous familial hypercholesterolemia? A review of nine global cases. Adv Ther 2022;39(6):3042–57.
[7] Thompson GR. PCSK9 inhibitors for homozygous familial hypercholesterolemia: useful but seldom sufficient. J Am Coll Cardiol 2020;76(2):143–5.
[8] Blom DJ, Harada-Shiba M, Rubba P, Gaudet D, Kastelein JJP, Charng MJ, et al. Efficacy and safety of alirocumab in adults with homozygous familial hypercholesterolemia: the ODYSSEY HoFH Trial. J Am Coll Cardiol 2020;76(2):131–42.
[9] Cuchel M, Raal FJ, Hegele RA, Al-Rasadi K, Arca M, Averna M, et al. 2023 Update on European Atherosclerosis Society Consensus statement on homozygous familial hypercholesterolaemia: new treatments and clinical guidance. Eur Heart J 2023.
[10] Cuchel M, Meagher E, du Toit TH, Blom D, Marais A, Hegele R, et al. Efficacy and safety of a microsomal triglyceride transfer protein inhibitor in homozygous familial hypercholesterolemia. Lancet Lond Engl 2013;381(9860):40–6.
[11] D'Erasmo L, Steward K, Cefalù AB, Di Costanzo A, Boersma E, Bini S, et al. Efficacy and safety of lomitapide in homozygous familial hypercholesterolaemia: the pan-European retrospective observational study. Eur J Prev Cardiol 2022;29(5):832–41.
[12] Raal FJ, Rosenson RS, Reeskamp LF, Hovingh GK, Kastelein JJP, Rubba P, et al. Evinacumab for homozygous familial hypercholesterolemia. N Engl J Med 2020;383(8):711–20.
[13] Stefanutti C, Chan DC, Di Giacomo S, Morozzi C, Watts GF. Long-term efficacy and safety of evinacumab in patients with homozygous familial hypercholesterolemia: real-world clinical experience. Pharm Basel Switz 2022;15(11):1389.
[14] Leipold R, Raal F, Ishak J, Hovingh K, Phillips H. The effect of lomitapide on cardiovascular outcome measures in homozygous familial hypercholesterolemia: a modelling analysis. Eur J Prev Cardiol 2017;24(17):1843–50.
[15] Reeskamp LF, Nurmohamed NS, Bom MJ, Planken RN, Driessen RS, van Diemen PA, et al. Marked plaque regression in homozygous familial hypercholesterolemia. Atherosclerosis 2021;327:13–7.