Commentary | **Open Access**

Rare Disease and Orphan Drugs Journal

Rosenson. *Rare Dis Orphan Drugs J.* 2026;5:35 **DOI:**10.20517/rdodj.2026.27

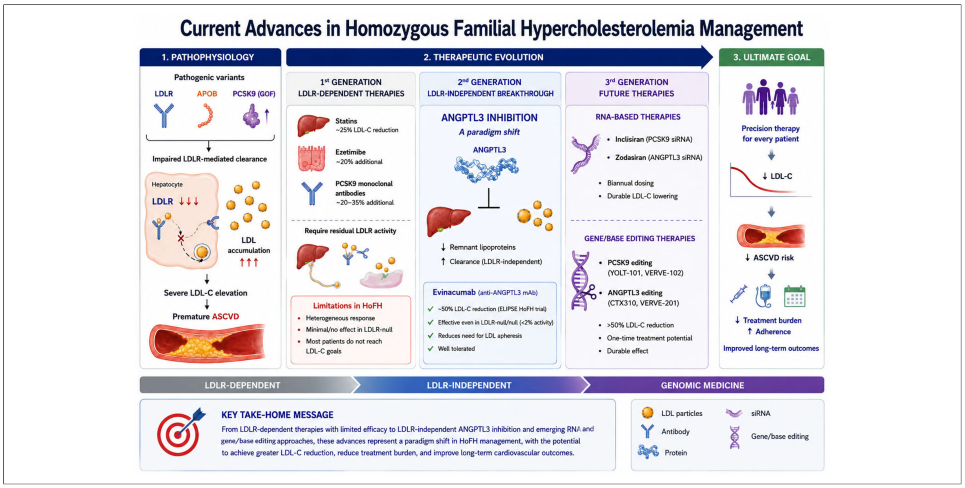
Current advances in homozygous familial hypercholesterolemia management

Robert S. Rosenson[1,2]

Citation: Rosenson RS. Current advances in homozygous familial hypercholesterolemia management. *Rare Dis Orphan Drugs J.* 2026;5:35. https://dx.doi.org/10.20517/rdodj.2026.27

Received: 8 May 2026 **First Decision:** 8 Sep 2026 **Revised:** 16 Oct 2026 **Accepted:** 20 Oct 2026 **Published:** 19 Nov 2026

Academic Editor: Daniel Scherman **Copy Editor:** Fangling Lan **Production Editor:** Fangling Lan



Familial hypercholesterolemia (FH) is among the most common autosomal dominant monogenic disorders, affecting approximately 1 in 250 to 1 in 313 individuals, whereas homozygous familial hypercholesterolemia has an estimated prevalence of approximately 1 in 250,000 to 1 in 360,000 individuals globally. The clinical phenotype is characterized by markedly elevated plasma concentrations of low-density lipoprotein cholesterol (LDL-C) and a substantially increased risk of premature atherosclerotic cardiovascular disease (ASCVD). Disease severity and age at onset are strongly influenced by zygosity; individuals with homozygous FH (HoFH) typically present in childhood with markedly elevated LDL-C levels and accelerated ASCVD compared with those with heterozygous FH (HeFH)[1-4].

FH most commonly arises from pathogenic variants in genes governing LDL receptor–mediated clearance of circulating LDL particles, including the low-density lipoprotein receptor (*LDLR*), apolipoprotein B (*APOB*; most frequently p.Arg3527Gln), and proprotein convertase subtilisin/kexin type 9 (*PCSK9*)[1-4]. These variants impair hepatic uptake and catabolism of LDL, resulting in persistently elevated LDL-C levels. Approximately 85%-90% of pathogenic variants affect *LDLR*

[1]Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA.
[2]Metabolism and Lipids Program, Mount Sinai Fuster Heart Hospital, New York, NY 10029, USA.

Correspondence to: Dr. Robert S. Rosenson, Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA; Metabolism and Lipids Program, Mount Sinai Fuster Heart Hospital, New York, NY 10029, USA. E-mail: robert.rosenson@mssm.edu

(loss-of-function; receptor-defective or null alleles), 5%-10% involve *APOB* variants that disrupt receptor binding, and 1%-3% are gain-of-function variants in *PCSK9*. Individuals with HoFH carry two pathogenic variants (including true homozygotes, compound heterozygotes, or double heterozygotes), whereas individuals with HeFH carry a single variant and generally exhibit a less severe phenotype. A subset of patients who fulfill clinical criteria for HoFH do not carry these pathogenic variants.

Conventional lipid-lowering therapies, including statins and ezetimibe, are most often inadequate to effectively lower LDL-C in most patients with HoFH. PCSK9 monoclonal antibodies provide an additional 20%-35% reduction in LDL-C in HoFH patients receiving maximally tolerated background therapy. However, treatment responses are highly heterogeneous, with some individuals demonstrating minimal or no LDL-C reduction. Notably, sequence variants that impair LDLR recycling render patients resistant to PCSK9 inhibition, thereby attenuating LDL-C lowering efficacy.

Given the limited effectiveness of conventional therapies, many HoFH patients require combination regimens that lower LDL-C independent of LDLR activity[1-4]. These categories of approved therapies include LDL apheresis, lomitapide and more recently evinacumab. LDL apheresis lowers LDL-C by 50%-75%. Lomitapide, a microsomal transfer protein inhibitor, lowers LDL-C by about 50%. A phase 3 open-label trial with lomitapide (5 to 60 mg daily) conducted in 29 patients with HoFH reported reductions in LDL-C by -44% at Week 56 and -38% at week 78[5]. However, gastrointestinal side effects of lomitapide are a limiting aspect with improved tolerability in patients on a strict low-fat diet.

Angiopoietin-like 3 (ANGPTL3) inhibition represents a major therapeutic advance, functioning via an LDLR-independent mechanism to enhance clearance of remnant lipoproteins. In the ELIPSE HoFH trial, evinacumab (15 mg/kg intravenously every 4 weeks) achieved a 49% placebo-corrected reduction in LDL-C in 65 patients with HoFH, despite intensive background therapy that included statins in 92.2% (including 79.3% on high intensity statins), ezetimibe in 80.2%, PCSK9 inhibitors in 62.1%, lomitapide in 19.0%, and LDL apheresis in 38.8%[6]. Importantly, substantial LDL-C reductions were observed even among patients with minimal or absent LDLR activity[7]. These results were confirmed in pooled analyses of patients with severe LDLR dysfunction. Furthermore, evinacumab therapy reduced the need for LDL apheresis in a subset of patients, highlighting its clinical utility in reducing treatment burden. In patients who are refractory to maximally tolerated statins and PCSK9 inhibition, treatment with evinacumab has demonstrated LDL-C reductions of approximately 50%, supporting the expansion of ANGPTL3-targeted therapies to broader FH populations[8].

Therapies requiring infrequent administration, such as small interfering RNA (siRNA)-based approaches administered biannually, may improve adherence, persistence, and overall effectiveness compared with more frequent dosing regimens such as biweekly administration of PCSK9 monoclonal antibody inhibitor[9,10]. In parallel, gene-editing strategies are emerging as potential transformative therapies. An early phase 1 trial using base-editing approaches targeting *PCSK9* was conducted in six HeFH patients who received escalating doses of YOLT-101 (0.2, 0.4 or 0.6 mg/kg), an investigational *in vivo* gene therapy that uses an adenine base editor and delivered via GalNAc-modified lipid nanoparticles, in PCSK9 and LDL-C. The highest cohort (0.6 mg/kg) reduced PCSK9 by 74.4% and LDL-C by 52.3% at 24 weeks[11]. A phase 1 trial conducted in 35 adults with HeFH or premature atherosclerosis, a single infusion of the adenine base editor VERVE-102 (0.3-1.0 mg/kg) reduced mean PCSK9 levels by 51%-88% and LDL-C by 9% to 62% (absolute LDL-C reduction up to 78 mg/dL) with durable effects through 1 year or more in 15 participants[12].

Next-generation approaches targeting ANGPTL3 include RNA interference and gene-editing strategies. Zodasiran, a siRNA targeting *ANGPTL3*, demonstrated dose-dependent LDL-C reductions of -35.7% and -39.9% in 6 months (200 and 300 mg, respectively) in the phase 2 HoFH-specific GATEWAY trial[13]. Based

on favorable efficacy and safety, zodasiran has advanced to the phase 3 YOSEMITE trial (NCT07037771). In 15 non-HoFH patients enrolled in a phase 1 trial with CTX 310, an *ANGPTL3* CRISPR-Cas9-base editor, there were dose-dependent (0.1, 0.3, 0.6, 0.7 or 0.8 mg/kg of body weight) reductions in ANGPTL3 levels. The highest dose of CTX 310 (0.8 mg/kg) reduced ANGPTL3 by -73.2% and LDL-C by -48.9%[14]. Ongoing studies are evaluating additional gene-editing approaches directed at ANGPTL3, including base editing with VERVE-201 (NCT06451770), in patients with HoFH and refractory dyslipidemias.

Despite these advances, most patients with HoFH—and a substantial proportion with HeFH—do not achieve guideline-directed LDL-C targets. The advent of ANGPTL3 inhibition, particularly with evinacumab[7], has enabled attainment of LDL-C levels previously achievable primarily with LDL apheresis, while reducing treatment burden and improving accessibility. The continued evolution of RNA-based and gene-editing therapies[14] holds promise for more durable, less burdensome interventions[15]. Together, these advances represent a paradigm shift in FH management, with the potential to substantially reduce ASCVD risk and improve long-term clinical outcomes.

DECLARATIONS

Authors' contributions

The author contributed solely to the article.

Availability of data and materials

Not applicable.

AI and AI-assisted tools statement

During the preparation of this manuscript, the AI tool Microsoft Copilot (version 1.2608.0301.01) was used solely for revising Graphical Abstract. The tool did not influence the study design, data collection, analysis, interpretation, or the scientific content of the work. The author takes full responsibility for the accuracy, integrity, and final content of the manuscript.

Financial support and sponsorship

None.

Conflicts of interest

Research funding to his institution from 89Bio, Amgen, Argo Biopharma, Arrowhead, AstraZeneca, Kalexo Bio, Lilly, Mammoth Biosciences, Merck Sharp and Dohme, NIH, Novartis, Novo Nordisk, and Verve Therapeutics; consulting fees from General Medicines, GSK, Lipigon, Novo Nordisk, Amgen, Novartis, and Rona Therapeutics; royalties from Wolters Kluwer (UptoDate); stock holdings from MediMergent, LLC.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Copyright

© The Author(s) 2026.

REFERENCES

1. Rosenson RS. Existing and emerging therapies for the treatment of familial hypercholesterolemia. *J Lipid Res.* 2021;62:100060. DOI PubMed PMC
2. Cuchel M, Raal FJ, Hegele RA, et al. 2023 update on European atherosclerosis society consensus statement on homozygous familial hypercholesterolaemia: new treatments and clinical guidance. *Eur Heart J.* 2023;44:2277-91. DOI PubMed PMC
3. Wiegman A, Bourbon M, Freiberger T, et al. Familial hypercholesterolaemia in children and adolescents: a European Atherosclerosis Society consensus statement. *Eur Heart J.* 2026;47:3324-46. DOI PubMed PMC

4. Ahmad Z, Agarwala A, Cuchel M, et al. Update on familial hypercholesterolemia: an expert clinical consensus from the National Lipid Association. *J Clin Lipidol.* 2026;20:708-37. DOI
5. Cuchel M, Bloedon LT, Szapary PO, et al. Inhibition of microsomal triglyceride transfer protein in familial hypercholesterolemia. *N Engl J Med.* 2007;356:148-56. DOI
6. Raal FJ, Greber-platzer S, Reeskamp LF, et al. Efficacy of evinacumab by genotype and low-density lipoprotein receptor function in patients with homozygous familial hypercholesterolaemia: a subanalysis from the ELIPSE open-label extension study. *Atherosclerosis.* 2026;414:120657. DOI
7. Raal FJ, Rosenson RS, Reeskamp LF, et al. Evinacumab for homozygous familial hypercholesterolemia. *N Engl J Med.* 2020;383:711-20. DOI
8. Rosenson RS, Burgess LJ, Ebenbichler CF, et al. Evinacumab in patients with refractory hypercholesterolemia. *N Engl J Med.* 2020;383:2307-19. DOI PubMed
9. Rosenson RS, Niu X, Popadic L, et al. Real-world treatment adherence and persistence among patients initiating inclisiran or PCSK9 mAbs. *Am J Prev Cardiol.* 2026;30:101739. DOI PubMed PMC
10. Marnell CS, Koenig W, Bittner V, et al. Barriers and emerging strategies to bridge gaps in implementation of evidence-based lipid-lowering therapies. *Circ Popul Health Outcomes.* 2026;19:e012330. DOI
11. Wan P, Tang S, Lin D, et al. In vivo base editing gene therapy for heterozygous familial hypercholesterolemia: a phase 1 trial. *Nat Med.* 2026;32:1045-51. DOI PubMed
12. Vafai SB, Täubel J, Ashdown T, et al. In vivo base editing of *PCSK9* with VERVE-102 for hypercholesterolemia. *N Engl J Med.* 2026;395:648-59. DOI
13. Raal FJ, Bergeron J, Gaudet D, et al. Zodasiran, an RNAi therapeutic targeting ANGPTL3, for treating patients with homozygous familial hypercholesterolaemia (GATEWAY): an open-label, randomised, phase 2 trial. *Lancet Diabetes Endocrinol.* 2026;14:123-36. DOI PubMed
14. Laffin LJ, Nicholls SJ, Scott RS, et al. Phase 1 trial of CRISPR-Cas9 gene editing targeting *ANGPTL3*. *N Engl J Med.* 2025;393:2119-30. DOI
15. Rosenson RS, Goonewardena SN. Base editing milestone for familial hypercholesterolemia. *Nat Med.* 2026;32:812-3. DOI PubMed

Disclaimer/Publisher's Note: All statements, opinions, and data contained in this publication are solely those of the individual author(s) and contributor(s) and do not necessarily reflect those of OAE and/or the editor(s). OAE and/or the editor(s) disclaim any responsibility for harm to persons or property resulting from the use of any ideas, methods, instructions, or products mentioned in the content.

© The Author(s) 2026. Open Access This article is licensed under a Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, sharing, adaptation, distribution and reproduction in any medium or format, for any purpose, even commercially, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.