Homozygous familial hypercholesterolemia (HoFH) is an inherited genetic disorder and represents a rare and severe subtype of familial hypercholesterolemia.

**Characteristics**
- Extremely high levels of low-density lipoprotein cholesterol (LDL-C) in blood since birth
- Development of atherosclerotic cardiovascular disease (ASCVD) during childhood

**Genetic causes (mutation)**
- Both alleles of LDL receptor (LDLR)
- Apolipoprotein B (ApoB)
- Proprotein convertase subtilisin/kexin type 9 (PCSK9)
- LDLR adapter protein 1 (LDLRAP1)

**Criteria for diagnosis**
- Untreated LDL-C > 400 mg/dL
- Cutaneous or tendon xanthomas before 10 years
- Identification of bi-allelic mutations in LDLR, APOB, PCSK9, or LDLRAP1 genes

**Treatment pathway and updated LDL-C goals**

<table>
<thead>
<tr>
<th>Goals</th>
<th>Pathway</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults (&gt;18 years): Target LDL-C levels of &lt;70 mg/dL</td>
<td>Lifestyle changes</td>
</tr>
<tr>
<td>Children and adolescents: Target LDL-C levels of &lt;115 mg/dL</td>
<td>Statins and ezetimibe</td>
</tr>
</tbody>
</table>

Visit https://ascvd-lipidology.knowledgehub.wiley.com/ for additional resources
Current treatment strategies for HoFH\textsuperscript{1,2}

- Effective lipid-lowering therapy (LLT) is the most widely used
- LDL-C is an effective predictor of disease progression
- Residual LDLR activity is the main determinant for achieving treatment goals
- Patients with HoFH exhibit variable responses due to diverse phenotypes and genotypes

Conventional LLT\textsuperscript{1}

**Statins and ezetimibe**
- First-line therapy
- Mechanism of action is LDLR dependent
- ↓ ASCVD mortality in adults and children with HoFH

PCSK9 inhibitors

- ↑ Expression of LDLR \(\Leftrightarrow\) ↑ LDL-C clearance

**Alirocumab and evolocumab**
- Humanised monoclonal antibodies (mAb)

**Inclisiran**
- Small interfering ribonucleic acid (siRNA)

**Lerodalcibep**
- Still in the research phase
- Small recombinant fusion protein of a PCSK9 binding domain and albumin

Pharmacological agents acting independently of LDLR\textsuperscript{1,2}

**Anti-ApoB therapies**
- Lomitapide: Inhibits microsomal triglyceride-transfer protein
- Mipomersen: Antisense oligonucleotide inhibitor

**Angiopoietin-like 3 (ANGPTL3) inhibitors**
- Evinacumab
- RNA-based treatments targeting ANGPTL3 (vulpanorsen)

Interventions to lower LDL independent of LDLR\textsuperscript{1}

**LA**
- Selectively remove the circulating ApoB-containing lipoproteins

**Liver transplantation**
- Curative treatment
- Severe complications

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Potential of ANGPTL3 inhibitors in HoFH treatment\textsuperscript{3,4,5}

ANGPTL3 is a circulating inhibitor of lipoprotein lipase (LPL) and endothelial lipase (EL)\textsuperscript{3}.

Produced only by the liver at low and constant rates\textsuperscript{3}.

Acts in coordination with ANGPTL4 and ANGPTL8 to control triglyceride breakdown\textsuperscript{3}.

ANGPTL3 inhibition leads to enhanced lipoprotein clearance\textsuperscript{4}.

Promising target to reduce ASCVD risk\textsuperscript{3}.

**Evinacumab\textsuperscript{5}**

- Fully humanised mAbs inhibiting circulating ANGPTL3
- ↓LPL and EL activities = ↑Plasma LDL-C levels
- **Recommended dose**
  - 15 mg/kg via intravenous fusion for >1 hour
  - Once monthly
- Approved by the US Food and Drug Administration and the European Medicines Agency
- 46.3% reduction in LDL-C\textsubscript{4}

**Advantages**

- Long-term efficacy
- Safe
- Well-tolerated
- Independent of residual LDLR activity

**Vupanorsen\textsuperscript{3}**

- Gal-Nac-conjugated antisense oligonucleotide targeting ANGPTL3 mRNA
- Specifically targets asialoglycoprotein receptor in hepatocytes
- Promising efficacy
- Associated with increasing liver steatosis
- Further studies needed

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**Future of HoFH treatment**

**CRISPR-based genome editing**
- Modification of ANGPTL3 and PCSK9 genes
  ▸ ↓ LDL-C levels

**Gene transfer**
- Adenovirus-mediated gene transfer > Successful expression of LDLR in the liver
  ▸ ↓ LDL-C levels
- No adverse effects

**siRNA ARO-ANG3**
- Undergoing clinical trials, ARO-ANG3 is an siRNA that targets ANGPTL3

**Vaccine targeting ANGPTL3**
- Investigating a protein-based vaccine (E1-E2-E3) targeting ANGPTL3 for novel HoFH treatment

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**Key message**

Advancements in the management of HoFH offer highly effective and diverse treatment options, from conventional therapies to cutting-edge innovations, which aim to improve LDL-C control, reduce ASCVD risk, and enhance the quality of life for patients with HoFH

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**References**


