Effective Management of Homozygous Familial Hypercholesterolemia: Therapeutic Strategies for a Complex Dyslipidemia

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Activity Chair
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Topics for Discussion

- Diagnosis of homozygous familial hypercholesterolemia (HoFH)
- Currently approved therapies for the treatment of HoFH
- Emerging therapies for the treatment of HoFH

Diagnosis of HoFH

- Multiple definitions
- Genetic basis of initial description no longer fits current paradigm of phenotypic presentation
- Varying standards in different countries based on technology and insurance/cost
**Criteria for the Clinical Diagnosis of Familial Hypercholesterolemia**

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>USA: MEDPED Criteria Total Cholesterol (and LDL-C) Levels, mg/dL</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;18</td>
<td>220 (155)</td>
<td>First-degree Relative</td>
</tr>
<tr>
<td>18-&lt;20</td>
<td>260 (165)</td>
<td>Second-degree Relative</td>
</tr>
<tr>
<td>20-&lt;21</td>
<td>290 (175)</td>
<td>Third-degree Relative</td>
</tr>
<tr>
<td>21-&lt;25</td>
<td>310 (195)</td>
<td>General Population</td>
</tr>
<tr>
<td>25-</td>
<td>330 (220)</td>
<td>96% specificity, 47% sensitivity</td>
</tr>
</tbody>
</table>

**Risk Criteria for the Clinical Diagnosis of Familial Hypercholesterolemia**

- **Severe LDL-C elevations, premature aortic stenosis, and premature atherosclerotic cardiovascular disease (ASCVD)**
- **Family history of premature peripheral or cerebrovascular disease**
- **Homozygous or compound heterozygous mutations in LDLR genes**
- **Presence of tendon xanthomas**
- **Presence of corneal arcus in patients <45 yrs old**
- **Personal history of CAD**
- **First-degree relative child (<1 yrs) with LDL-C >95th percentile, or LDL-C >330 mg/dL, or LDL-C >270 mg/dL while receiving lipid-lowering therapy at the highest tolerated dose (<15% response)**

**Diagnosis of HoFH**

- **Autosomal dominant inherited disorder (other than rare form of autosomal recessive LDLRAP1)**
- **Loss of function mutations in the LDLR (FH1), apoB (FH2) genes, and gain of function mutations in PCSK9 (FH3) gene**
- **Severe LDL-C elevations, premature aortic stenosis and premature atherosclerotic cardiovascular disease (ASCVD)**
- **Physical signs of cholesterol deposition – planar/ tendon xanthoma, xanthelasmata, corneal arcus**

**Diagnostic Criteria for HoFH from the Literature**

- **Family History**: First- or second-degree relative with premature cardiovascular disease or LDL-C >300 mg/dL.
- **Clinical Criteria**: Presence of tendon xanthomas and/or manifestations of premature coronary heart disease or corneal arcus.
- **Genetic Criteria**: Documented elevated LDL and both parents consistent with HeFH (LDL >200 mg/dL). If parent unavailable, history of CAD in first-degree relative.
- **Laboratory Criteria**: Tendinous and/or tuberous xanthomas prior to age 10.
- **Genetic Testing**: Identification of 2 LDLR gene mutations.
- **Confirmation by DNA analysis for LDLR mutations**: Fasting LDL >500 mg/dL, TG <600 mg/dL.
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? Accepted Diagnosis

- Untreated LDL-C >500 mg/dL (13 mmol/L) or treated LDL-C ≥330 mg/dL (7.76 mmol/L) or treated non-HDL-C ≥330 mg/dL (8.5 mmol/L) + either
  - Cutaneous or tendinous xanthoma before age 10 years
  - Elevated LDL-C levels before lipid-lowering therapy consistent with HeFH in both parents (except in the case of ARH)
  - OR
- Genetic confirmation of 2 mutant alleles at the LDLR, apoB, PCSK9, or ARH adaptor protein gene locus

- Genetic mutation alleles in same gene – true homozygotes
  - Same mutation in same gene – simple homozygotes
  - Different mutations in same gene – compound heterozygotes (cis or trans)
- Mutations in 2 different genes (1 usually LDLR) – double heterozygotes (cis or trans)


Estimated Frequency of HoFH

<table>
<thead>
<tr>
<th>Region</th>
<th>Estimated Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entire world</td>
<td>6,860 vs 42,880</td>
</tr>
<tr>
<td>African region</td>
<td>830 vs 5,190</td>
</tr>
<tr>
<td>Region of the Americas</td>
<td>930 vs 5,810</td>
</tr>
<tr>
<td>South-East Asia region</td>
<td>1,810 vs 11,310</td>
</tr>
<tr>
<td>European region</td>
<td>900 vs 5,630</td>
</tr>
<tr>
<td>Eastern Mediterranean region</td>
<td>590 vs 3,990</td>
</tr>
<tr>
<td>Western Pacific region</td>
<td>1,800 vs 11,250</td>
</tr>
</tbody>
</table>


LDL-C Levels in HoFH Patients

<table>
<thead>
<tr>
<th>LDL-C (mmol/L)</th>
<th>Clinical Diagnosis</th>
<th>Mutation Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>Homozygous FH</td>
<td>Homozygous LDLR negative</td>
</tr>
<tr>
<td>15</td>
<td>Homozygous LDLR defective or homozygous LDLRAP, ARH</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Heterozygous FH</td>
<td>Homozygous apoB defect/PCSK9 gain of function</td>
</tr>
<tr>
<td>10</td>
<td>Common Hypercholesterolemia</td>
<td>Compound heterozygous LDLR apoB, PCSK9</td>
</tr>
</tbody>
</table>

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**LDL-C Levels in HoFH Patients**


**Overlap of Clinical and Mutation Diagnosis of HeFH**


**FH Diagnosis Rates Worldwide**

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Discussion

Currently Approved Therapies for HoFH and HeFH

<table>
<thead>
<tr>
<th>Class</th>
<th>Major Effect</th>
<th>LDL-lowering Response</th>
<th>HoFH</th>
<th>HeFH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-cholesterol diet</td>
<td>LDLR activity</td>
<td>&lt;10%</td>
<td>10%-25%</td>
<td></td>
</tr>
<tr>
<td>Statins</td>
<td>LDLR activity</td>
<td>&lt;10%</td>
<td>&gt;25%</td>
<td></td>
</tr>
<tr>
<td>Resins</td>
<td>LDLR activity</td>
<td>&lt;10%</td>
<td>10%-25%</td>
<td></td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>Cholesterol absorption + LDLR activity</td>
<td>&lt;10%</td>
<td>10%-25%</td>
<td></td>
</tr>
<tr>
<td>Stanol esters</td>
<td>Cholesterol absorption + LDLR activity</td>
<td>&lt;10%</td>
<td>10%-25%</td>
<td></td>
</tr>
<tr>
<td>Nicotinic acid</td>
<td>VLDL synthesis</td>
<td>&lt;10%</td>
<td>&gt;25%</td>
<td></td>
</tr>
<tr>
<td>LDL apheresis</td>
<td>Removes LDL</td>
<td>&gt;25%</td>
<td>&gt;25%</td>
<td></td>
</tr>
</tbody>
</table>


Recently Approved Therapies for HoFH

<table>
<thead>
<tr>
<th>Class</th>
<th>Approval Date</th>
<th>Major Effect</th>
<th>LDL-lowering Response</th>
<th>HoFH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lomitapide</td>
<td>Dec. 2012</td>
<td>MTP activity</td>
<td>40%-50%</td>
<td>HoFH</td>
</tr>
<tr>
<td>Mipomersen</td>
<td>Jan. 2013</td>
<td>Antisense ApoB</td>
<td>25%</td>
<td></td>
</tr>
</tbody>
</table>

Lomitapide and mipomersen are not approved for HeFH.


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**Lomitapide in HoFH**

- Mean Percent Changes in LDL-C, TC, and ApoB from Baseline to Week 26 (n=23)
- ALT and AST Levels
- Percentage of Hepatic Fat in the Liver

**Mipomersen in HoFH**

- LDL-C
- ApoB
- Lp(a)

**Effects of Lomitapide and Mipomersen on Atherogenic Lipoprotein Parameters in HoFH (Phase 3 Studies)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Lomitapide* (n=29)</th>
<th>Mipomersen† (n=34)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C</td>
<td>Baseline, mg/dL</td>
<td>Endpoint, mg/dL</td>
</tr>
<tr>
<td></td>
<td>Mean change, %</td>
<td>Mean change, %</td>
</tr>
<tr>
<td>Non-HDL-C</td>
<td>Baseline, mg/dL</td>
<td>Mean change, %</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>Baseline, mg/dL</td>
<td>Mean change, %</td>
</tr>
<tr>
<td>ApoB</td>
<td>Baseline, mg/dL</td>
<td>Mean change, %</td>
</tr>
<tr>
<td>Lp(a)</td>
<td>Baseline, mg/dL</td>
<td>Mean change, %</td>
</tr>
</tbody>
</table>

*Based on values at 26 weeks in all 29 subjects in an ITT analysis, with the last observation carried forward. Change from baseline was statistically significant for all parameters.
†Based on values obtained at the visit closest to 14 days after the last dose of study treatment. Change from baseline was significant for all parameters.

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**Algorithms for Management**

- **Suspicion of FH in the Adult**
  - Use Simon Broome and/or Dutch Lipid Clinic Network

- **Probable or definite FH?**
  - Yes
  - Treatment to target LDL-C <70 mg/dL
  - Treatment as per guidelines and address comorbidities such as DM, HTN, and obesity

- **Yes**
  - LDL apheresis

- **Yes**
  - Continue to treat to sustain LDL-C <70 mg/dL

- **Yes**
  - Consider patient “very high risk FH”

- **Lp(a) >50 mg/dL?**
  - Yes
  - Monitor and review. Consider lomitapide if LDL-C >70 mg/dL
  - No

- **Clinically significant burden of disease?**
  - Yes
  - Consider patient “very high risk FH”
  - Check Lp(a) level

- **Lp(a) >50 mg/dL?**
  - Yes
  - Consider patient “very high risk FH”
  - Monitor Lp(a) level

**Discussion**

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Emerging Therapies for the Treatment of HoFH

- PCSK9 inhibition
  - Evolocumab
  - Alirocumab
- CETP inhibition
  - Anacetrapib
  - Evacetrapib
  - JTT-705
  - DEZ-001
- Gene therapy

Case Studies

Diagnosing Homozygous Familial Hypercholesterolemia

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CMO, MB Clinical Research
President Elect, ASPC
Boca Raton, FL
38-Year-Old Jewish Man with Premature Atherosclerotic Cardiovascular Disease

- 38-year-old Jewish South African man with premature atherosclerotic cardiovascular disease (ASCVD)
- Family history
  - Father’s family: hypercholesterolemia, died at young age from ASCVD
  - Mother’s family: hypercholesterolemia, no ASCVD
  - 2 brothers: hypercholesterolemia; 1 of them experienced a MI at age 38
  - Teenage son: LDL-C >300 mg/dL

Cardiovascular History

- Age 17: chest tightness and shortness of breath while playing basketball; rested for 30 min until symptoms resolved – did not seek medical attention
- Age 23: IMI
- Since then has required multiple coronary stents and a 5-vessel CABG
- Highest untreated LDL-C >400 mg/dL
- Highest total cholesterol >600 mg/dL

Lipid-Lowering Therapy

- Aggressively treated for hypercholesterolemia and ASCVD for the past 15 years
- Current lipid-lowering therapy
  - Rosuvastatin 20 mg QD
  - Ezetimibe 10 mg QD
  - Colesevelam 625 mg 6 tabs QD
  - Niacin-ER 500 mg QD
  - Lipoprotein apheresis
In considering therapeutic options for this patient, a diagnosis must first be made.

Does he have HoFH? What other data would help us make the diagnosis?

1) Genetic testing
2) Presence or absence of aortic stenosis
3) Presence or absence of xanthelasma
4) Presence or absence of eruptive xanthomas
Does he have HoFH? What other data would help us make the diagnosis?

**Audience Response**

<table>
<thead>
<tr>
<th>Data</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic Testing</td>
<td>60%</td>
</tr>
<tr>
<td>Presence/Absence of Aortic Stenosis</td>
<td>8.2%</td>
</tr>
<tr>
<td>Presence/Absence of Xanthelasma</td>
<td>15.3%</td>
</tr>
<tr>
<td>Presence/Absence of Eruptive Xanthomas</td>
<td>16.5%</td>
</tr>
</tbody>
</table>

Are we certain of the diagnosis of HoFH?

1) Yes
2) No

**Audience Response**

<table>
<thead>
<tr>
<th>Choice</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>65.9%</td>
</tr>
<tr>
<td>No</td>
<td>34.1%</td>
</tr>
</tbody>
</table>
Could genetic testing rule out the diagnosis of HoFH?

1) Yes
2) No

Audience Response

Could genetic testing rule in the diagnosis of HoFH?

1) Yes
2) No
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Could genetic testing rule in the diagnosis of HoFH?

Audience Response

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>93.5%</td>
<td>6.5%</td>
</tr>
</tbody>
</table>

Treatment Decisions in the Management of Homozygous Familial Hypercholesterolemia

Sergio Fazio, MD, PhD
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Professor of Medicine, Physiology and Pharmacology
Director, Center for Preventive Cardiology
Knight Cardiovascular Institute
Oregon Health and Science University
Portland, OR

Young Man with History of Severe Hypercholesterolemia

- 32-year-old Caucasian male, body builder
- Follows vegan meal plan
- Uses supplements, extracts, and anabolic agents
- History of severe hypercholesterolemia diagnosed at age 7
- No symptomatic CAD
- High CAC score
- No comorbidities or additional risk factors
### Young Man with History of Severe Hypercholesterolemia

**Family History**
- Mother (55 years old): hypercholesterolemia; on statin therapy; no CAD
- Maternal uncle: hypercholesterolemia; CABG x3 at age 42; former smoker
- Maternal grandfather: hypercholesterolemia; died of cardiac causes at age 65; former smoker
- Older sister: milder hypercholesterolemia (untreated LDL-C: 180 mg/dL)
- Father’s family history: unknown

---

**Young Man with History of Severe Hypercholesterolemia**

- Normal TG/HDL-C
- Untreated LDL-C: 275 mg/dL-310 mg/dL
- BMI: 27.8 kg/m²
- Recently, the patient was convinced by PCP to try atorvastatin 20 mg/day
  - LDL-C adjusted to 205 mg/dL
  - Discontinued after 3 months (fear of side effects)
  - Requested specialist referral – referred for genetic counseling

---

**Young Man with History of Severe Hypercholesterolemia**

**Fasting lipids at time of visit**
- Total cholesterol: 383 mg/dL
- LDL-C: 298 mg/dL
- HDL-C: 65 mg/dL
- Triglycerides: 100 mg/dL
- Lp(a): 49 mg/dL
- Glucose: 88 mg/dL
- CAC score: 325 (99th percentile), with deposits in LM, LAD and LCX
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What is this patient’s likely diagnosis?

1) Familial combined dyslipidemia
2) Familial hypercholesterolemia
3) Iatrogenic hypercholesterolemia (caused by diet and supplements)
4) Beta-sitosterolemia

Audience Response

Considering the patient’s history, current guideline recommendations, and available therapeutic options, you would recommend to:

1) Initiate high-dose statin therapy
2) Request genetic testing before determining therapeutic approach
3) Initiate lomitapide therapy
4) Initiate mipomersen therapy
5) Initiate LDL apheresis
Considering the patient's history, current guideline recommendations, and available therapeutic options, you would recommend to:

**Audience Response**

- Initiate High-Dose Statin Therapy: 54.2%
- Request Genetic Testing: 30.5%
- Initiate Lomitapide Therapy: 11.9%
- Initiate Mipomersen Therapy: 3.4%
- Initiate LDL Apheresis: 0.0%

### Young Man with History of Severe Hypercholesterolemia

- Genetic testing performed
  - Compound heterozygote for mutations partially inactivating LDLR
- Patient agrees to start rosuvastatin 20 mg/day and ezetimibe 10 mg/day
  - LDL-C adjusted to the 190 mg/dL range
- LDL apheresis denied by insurance

### Young Man with History of Severe Hypercholesterolemia

- Lomitapide and mipomersen entry criteria: clinical/biochemical presentation compatible with diagnosis of HoFH
  - Patient elects to add lomitapide to rosuvastatin and ezetimibe regimen