Treatment of severe Familial Hypercholesterolemia
Combination of Statin and Ezetimibe

2nd Severe FH Course: Recognize, Diagnose and Treat Severe Familial Hypercholesterolemia
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Muscat, Oman
Hani Sabbour MD FACC FHRS FASE
Clinical Assistant Professor of Cardiology
Brown University
Warren Alpert School Of Medicine, Rhode Island, USA
Consultant Cardiology
Cleveland Clinic Abu Dhabi, UAE
Outline

- Why combination therapy is needed
- Comparative FH guidelines
- Rationale for treatment
- Possible combinations
- Summary
PREMATURE ASCVD + AORTOPATHY OF FH

Figure 1: Coronary Artery Calcifications (Red Arrows) in a 37-year-old Man with Familial Hypercholesterolaemia

Cardiac CT allows us to establish the presence of coronary atherosclerotic plaques in asymptomatic subjects with familial hypercholesterolaemia.
Prevalence of clinical FH among patients with ACS (n=4778)

Patients with acute coronary syndrome (n = 4778)
- Probable/definite FH
- Possible FH

- Dutch Lipid Clinic: 17.8%, 5.4%
- Simon Broome: 17.8%, 5.4%
- Combined definition: 18.8%, 5.4%

Patients with premature acute coronary syndrome * (n = 1451)
- Probable/definite FH
- Possible FH

- Dutch Lipid Clinic: 4.8%
- Simon Broome: 4.8%
- Combined definition: 49.3%

* Premature defined as ACS < 55 y (men), < 60 y (women)
Elevated LDL-C is the cause of cardiovascular disease in HoFH

- LDL-C is a causal factor in the development of CVD
- Patients with HoFH typically develop cardiovascular disease before the age of 20 years\(^1\)
- **Even with currently existing therapies, the mean age of death is 33 years\(^2\)**

\(3.\) Adapted from Horton et al. J Lipid Res. 2009;50:S172-S177
Patients with HoFH typically develop cardiovascular disease before the age of 20 years\(^1\)

- Coronary artery disease
- Myocardial infarction
- Severe aortic stenosis
- Heart failure
- Stroke
- Sudden death
- **Statin treatment, mean age of death delayed from 18 to 32 years\(^2\)**

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Consequences of markedly elevated LDL-C in HoFH patients

![Table 1. Cardiovascular Morbidity and Mortality Characteristics of Patients With Homozygous Familial Hypercholesterolemia Pre-1990 and Post-1990](image)

<table>
<thead>
<tr>
<th>Table 1. Cardiovascular Morbidity and Mortality Characteristics of Patients With Homozygous Familial Hypercholesterolemia Pre-1990 and Post-1990</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females/males, n</td>
</tr>
<tr>
<td>Age at death, y, mean±SD</td>
</tr>
<tr>
<td>All causes</td>
</tr>
<tr>
<td>Cardiovascular cause</td>
</tr>
<tr>
<td>Age at first nonfatal MACE, y, mean±SD</td>
</tr>
<tr>
<td>Nonfatal cardiovascular events, No. of patients</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
</tr>
<tr>
<td>Coronary procedures (CABG, AVR, PTCA, stent)</td>
</tr>
<tr>
<td>Other vascular procedures (endarterectomy, aortofemoral bypass surgery)</td>
</tr>
<tr>
<td>Cerebrovascular events (TIA, stroke)</td>
</tr>
</tbody>
</table>

MACE indicates major adverse cardiac event; Mls, myocardial infarctions; CABG, coronary artery bypass surgery; AVR, aortic valve replacement; PTCA, percutaneous coronary angioplasty; and TIA, transient ischemic attack.

\(^*\)P < 0.0001.
\(^†\)P < 0.001.
\(^‡\)P < 0.01.

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### Table 2: Dietary Recommendations in the Treatment of Hyperlipidaemia

**Dietary Recommendations**

- Total fat intake <25–35 % of total caloric intake
- Saturated fat <7 % of total caloric intake
- Cholesterol <200 mg/day
- Increase intake of monounsaturated and polyunsaturated fats and fibre
- Plant sterols and stanols (2 grams of plant sterols daily) may be considered
CHD events from lowering LDL-C well below 100 mg/dL (2.6 mmol/L) with statins VS FH patients with LDL starting >190 (4.9 mmol/l)

Event rates vs LDL-C levels in secondary* prevention studies

CONVENTIONAL LIT TRIALS IN SECONDARY PREVENTION LDL ACHIEVED

STARTING LDL 190 IN FH PATIENT EVENT RATES > 25%

Patients with CHD events (%)

LDL-C, mg/dL (mmol/L)

(1.6) (2.1) (2.6) (3.1) (3.6) (4.1) (4.7) (5.2)

A = atorvastatin-treated
S = other statin-treated
P = placebo-treated

*Secondary to MI/ACS, except for SPARCL (secondary to stroke or TIA)
LDL cholesterol burden in individuals with or without FH as a function of the age of initiation of statin therapy.
Why Combination Therapy is needed in Familial Hypercholesterolemia

- Patients with FH are at risk of premature atherosclerotic disease
- Many patients with heterozygous FH do not get adequate LDL cholesterol reduction on high dose statins = STATIN HYPORESPONDERS
- Addition of other risk factors put patients at even higher risk making much greater LDL cholesterol reduction desirable
- Even in homozygous FH aggressive medication therapy can help
- Some patients do not tolerate high dose statin therapy
Advantages/disadvantages of combination therapy

- Statins, ezetimibe, niacin, and bile acid sequestrants reduce LDL cholesterol through different mechanisms and sites of action.
- Thus they can be more effective in combination than when used alone.
- Advantages of using combinations: greater efficacy, lower doses of individual drugs, possible amelioration of tolerance problems experienced with high doses of single agents.
- Disadvantages: increased drug interactions, large number of pills, increased costs, additive side effect.
- Lack of outcomes data.

Familial Hypercholesterolemia: guidelines and recommendations

- Australasia Model of Care 2011
- National Lipid Association Expert Panel on Familial Hypercholesterolemia 2011
- Consensus Statement of the European Atherosclerosis Society 2013
- International FH Foundation 2014

Treatment of familial hypercholesterolemia

NLA Statement on Familial Hypercholesterolemia

- Drug therapy required for children and adults if (after lifestyle changes)
  - LDL-C > 190 mg/dL OR
  - Non-HDL-C > 220 mg/dL (FCH)
- For adult FH patients (>20 years of age), drug treatment to lower LDL-C > 50%
- Statins should be the initial treatment for all adults with FH.

Highest Risk FH Patients = Intensify Drug Treatment

- Consider more aggressive treatment goals for highest risk FH patients
  - LDL cholesterol <100 mg/dL
  - Non-HDL cholesterol <130 mg/dL
- FH patients at highest risk
  - (very high risk compared to patients without FH)
  - Clinically evident CHD or other atherosclerotic CVD
  - Diabetes
  - Family history of very early CHD
    - Men <45 years of age or women <55 years of age
  - Current smoking
  - ≥2 CVD risk factors
VARIATION IN SEVERITY = INTENSIFICATION OF THERAPY

From the most extreme case...

- 2 years of age
- Baseline total cholesterol 1700 mg/dL (44mmol/L)
- Significant stenosis on angiogram

...to a severe case

- First clinical manifestation after 20 years despite no apheresis
- Total cholesterol 700 mg/dL (18 mmol/L)
Treatment of FH: adults

- **Lifestyle changes**
  - Decrease saturated fatty acids to ≤7% of total energy intake; limit dietary cholesterol <200 mg/day; add plant stanol/sterols (2 g daily); soluble fiber (10-20 g daily)
  - Physical activity and weight control
  - *Smoking cessation*

- **Medications:** High doses of high-potency statins (atorvastatin, rosuvastatin)
  - Increase statin dose to maximum available or tolerable dose to achieve a LDL-C reduction ≥50% from baseline
  - If not achieved, consider adding ezetimibe, bile acid sequestrant, and/or niacin

- **LDL apheresis**

- **Homozygous patients:** medications, apheresis
Treatment of FH: Children and Adolescents

- LDL ≥ 190 mg/dl or ≥ 160 mg/dl with multiple risk factors, after diet
- Clinical trials with medium term follow up suggest safety and efficacy of statins
- Goal: 50% reduction or LDL-C < 130 mg/dl; need for balance between increased dosing and potential for side effects vs achieving goals
- Consider more aggressive LDL targets for those with additional CVD risk factors
- Ideally, prevent the development of atherosclerosis

EAS/ESC Guidelines

DRUGS FOR TREATMENT OF HYPERCHOLESTEROLAEMIA

- If drug treatment is indicated to decrease LDL-C, a statin is recommended, up to the highest tolerable dose, to reach the target level.
- If the target level is not reached, statin combination with a cholesterol absorption inhibitor or bile acid sequestrant or nicotinic acid may be considered.
- A cholesterol absorption inhibitor, alone or in combination with bile acid sequestrants or nicotinic acid may also be considered in case of statin intolerance.

MANAGEMENT OF FAMILIAL HYPERCHOLESTEROLAEMIA

- In FH patients the treatment is aiming at reaching the LDL-C goals for high risk subjects <2.5 mmol/L (<~100mg/dL) or in the presence of CVD for very high risk subjects <1.8 mmol/L (<~70 mg/dL). If targets cannot be reached, maximal reduction of LDL-C should be considered using appropriate drug combinations in tolerated doses.
ACC/AHA Cholesterol Guideline

Primary prevention--LDL–C ≥190 mg/dL

Secondary causes should be ruled out

• Evidence supports high-intensity statin therapy
• LDL–C levels may still remain very high, even after the intensity of statin therapy (reduction >50%) has been achieved
• Addition of a non-statin drug may be considered to further lower LDL–C (or of LDL-C reduction is less than 50% on maximally tolerated statin)

• Do not need ASCVD risk calculation
Integrated guidance on the care of familial hypercholesterolemia from the International FH Foundation

- All adult patients with FH must receive advice on lifestyle modifications and advice to correct all non-cholesterol risk factors should be provided according to expert recommendations. [2A]
- Therapy should ideally aim for at least a 50% reduction in plasma LDL-cholesterol, followed by an LDL-cholesterol < 2.5 mmol/L (absence of CHD or other major risk factors) and < 1.8 mmol/L (presence of CHD or other major risk factors). [2C]
- Achieving these targets will require a fat-modified, heart-healthy diet and statin therapy with or without ezetimibe. [1A]
- Drug combinations including bile acid sequestrants, niacin, probucol or fibrates, may be required with more intensive strategies to further reduce LDL-cholesterol. [1B]

JAPANESE ALGORITHM HOFH

doi: [10.5551jat.CR003]

START TREATMENT AT DIAGNOSIS

Diagnosis of homozygous FH
(Necessary to consult a specialist)

Commence guidance on lifestyle modification as well as keeping appropriate body weight, and initiate lipid-lowering therapy at the same time
LDL-C management targets
- Primary prevention: <100 mg/dL
- Secondary prevention: <70 mg/dL

First-line drug: Statin; increase dosage up to the maximum tolerated dose promptly

Ezetimibe, PCSK9 inhibitor, MTP inhibitor, Resin, Probucol

Initiate LDL apheresis as early as possible
JAPANESE ALGORITHM HEFH

START TREATMENT AT DIAGNOSIS

Diagnosis of heterozygous FH

Commence guidance on lifestyle modification as well as keeping appropriate body weight, and initiate lipid-lowering therapy at the same time

LDL-C management targets
- Primary prevention: <100 mg/dL or <50% of untreated level
- Secondary prevention: <70 mg/dL

Maximum tolerated dose of statin* and/or ezetimibe in combination

Insufficient effect

Add PCSK9 inhibitor** and/or resin and/or probucol

Insufficient effect

LDL apheresis***

* In case of patient with statin intolerance, consider prescription of another statin or changing dosing interval and increase dose as much as possible
** Advisable to consult a specialist when initiating PCSK9 inhibitor
*** As PCSK9 inhibitor will be removed by LDL apheresis, injection should be administered after LDL apheresis
Rationale for treatment of FH in adults

• No outcomes trials specifically in FH patients
• West of Scotland (mostly primary prevention) and 4S (secondary prevention) enriched with FH patients
• Very high lifetime risk of CHD
• Very high risk of premature onset CHD.
• Early treatment is highly beneficial.
  • **EARLY** Long-term statin treatment ameliorates excess CVD risk due to FH
  • Risk of long-term statin-treated FH patients = Risk of general population
• FH requires lifelong treatment and regular follow-up.

Robinson JG, Goldberg AC. *J Clinical Lipidol* 2011 5:S18-29
Kaplan–Meier curve estimates of cumulative CHD-free survival among individuals with FH according to **statin treatment** (P < 0.001 for difference).

ALMOST 60% INCREASE IN 10 YEAR EVENT FREE SURVIVAL WITH STATIN THERAPY

Nordestgaard B G et al. Eur Heart J 2013;eurheartj.eht273
How-ever they are still par-tial sta-tin hy-porespon-ders

Table 4
Percentage change in low-density lipoprotein cholesterol levels with high doses of rosvu-sta-tin and atorvasta-tin in pa-tients with heterozygous familial hypercholesterolaemia [12] and homozygous familial hypercholesterolaemia [10].

<table>
<thead>
<tr>
<th>Heterozygous familial hypercholesterolaemia</th>
<th>Weeksa</th>
<th>Rosu-vastatin 20/40/80 mg (n = 435)</th>
<th>Ato rvastatin 20/40/80 mg (n = 187)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6 weeks</td>
<td>−47%</td>
<td>−38%</td>
</tr>
<tr>
<td></td>
<td>12 weeks</td>
<td>−54%</td>
<td>−46%</td>
</tr>
<tr>
<td></td>
<td>18 weeks</td>
<td>−58%</td>
<td>−50%</td>
</tr>
<tr>
<td>Homozygous familial hypercholesterolaemia</td>
<td>Weeks</td>
<td>Rosu-vastatin 80 mg (n = 21)</td>
<td>Ato rvastatin 80 mg (n = 21)</td>
</tr>
<tr>
<td></td>
<td>6 weeks (crossover treatment)b</td>
<td>−19%</td>
<td>−18%</td>
</tr>
</tbody>
</table>

a Comparative study with forced titration at 6 and 12 weeks; all differences p < 0.001 [12].
b Following 18 weeks of open-label, forced titration with rosvu-sta-tin (20/40/80 mg for 6 weeks each) in patients with homozygous familial hypercholesterolaemia [10].
Lipid concentrations of patients with homozygous familial hypercholesterolaemia according to receipt of modern lipid-lowering therapy [9].

<table>
<thead>
<tr>
<th></th>
<th>Untreated</th>
<th>Receiving modern lipid-lowering therapy</th>
<th>Change, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>17.3 ± 3.8</td>
<td>13.1 ± 3.3(^a)</td>
<td>−24.3</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.28 ± 0.81</td>
<td>1.18 ± 0.63</td>
<td>−7.8</td>
</tr>
<tr>
<td>HDL-C, mmol/L</td>
<td>0.89 ± 0.33</td>
<td>0.91 ± 0.25</td>
<td>2.2</td>
</tr>
<tr>
<td>LDL-C, mmol/L</td>
<td>15.9 ± 3.9</td>
<td>11.7 ± 3.4(^a)</td>
<td>−26.4%</td>
</tr>
<tr>
<td>LDL/HDL ratio</td>
<td>21.4 ± 10.9</td>
<td>13.5 ± 5.9(^a)</td>
<td>−36.9</td>
</tr>
</tbody>
</table>

HDL-C, high-density lipoprotein cholesterol.
LDL-C, low-density lipoprotein cholesterol.
\(^a\) \(p < 0.0001\); values of lipid parameters are expressed as mean ± standard deviation.
Goal attainment in FH patients

Results from a large cross-sectional study in The Netherlands (1249 patients)

- 96% on statin treatment
- only 21% at LDL-C goal < 100 mg/dL (2.5 mmol/L)
- among patients not at LDL-C goal, 27% were on combination therapy of maximum statin dose and ezetimibe

Pijlman et al. Atherosclerosis 2010; 209: 189-194
Goal attainment in FH patients = STATIN HYPORESPONDERS

- 15% LDL-C > 160 mg/dl
- 4.15 mmol/l (160 mg/dl)
- ≈ 85% attainment
- 21% attainment at 2.5 mmol/l

Pijlman et al. Atherosclerosis 2010; 209: 189-194
Combination therapy to lower LDL-cholesterol

- No randomized outcomes trials of a statin alone compared with statin plus second drug to lower LDL cholesterol
  - SHARP: simvastatin/ezetimibe vs placebo in patients with renal failure
  - SANDS: carotid IMT benefit
- No randomized outcomes trials of non-statin combination therapy to lower LDL cholesterol
  - Single drug outcomes trials with bile acid sequestrant and niacin
- No outcomes trials with titration to LDL cholesterol goal
Combination therapy and coronary atherosclerosis in FH

- SCOR study, Kane et al. 1990
- Randomized controlled trial 72 FH patients
- Baseline LDL cholesterol 283 mg/dL
- Treated group (n=40) initially on colestipol up to 30 grams/ per day and niacin up to 7.5 grams/day; lovastatin added when available
  - 36 on niacin, 25 >1.5 g/day
  - 28 colestipol 30 g/day; 4 on 15 g/day
  - 16 on 40 to 60 mg lovastatin in 2 or 3 drug combination

SCOR

- Control group diet alone but some on colestipol 15 g/day
- On-trial LDL C
  - Decreased 10.6% in control group
  - Decreased 38.1% in treated group (283 to 172)
- Computer-based coronary angiography
- Progression in control group
- Regression in treated group, also seen when women analyzed separately

Patients with homozygous FH can benefit from therapy

- Homozygotes often have untreated LDL-C >500 mg/dL
  - CAD onset in childhood and adolescence
  - Insufficient response to usual lipid lowering medication, even in combination
  - South African population with few patients treated with LDL apheresis
  - Pre 1990: average age at death 18.4 years, age at first cardiac event 12.8
  - Post 1990: average age at death 32.9 years, age first event 28.3 years
  - Mean LDL cholesterol reduction 26.4%

Components of Cholesterol Homeostasis

- **Synthesis**
- **Absorption**
- **Excretion**
- **Biliary Secretion**

- **Dietary Cholesterol**
  - 31%
  - 50%

- **Intestine**
  - 19%
  - 50%
Ezetimibe

- Cholesterol absorption inhibitor
- Works at the enterocyte brush border
- Inhibits cholesterol absorption through a mechanism dependent on NPC 1L1 protein
- Does not work via the LDLr so can function in FH
- Glucuronidated in the intestine and cleared by liver, extensive enterohepatic recirculation
- Minimal levels in systemic circulation
- Half-life about 22 hours
- FDA approval 2002
Ezetimibe

- Lowers LDL-C by 15% to 18%
- Additive with statins
- Side effects – muscle, GI
- Dosing: 10 mg per day (can be taken any time)
- Transaminases may increase when used in combination with statins – usually return to normal on medication
Combination therapy to lower LDL-cholesterol

- Statin plus ezetimibe
  - About 20% further decrease in LDL cholesterol
  - Tolerance usually good
  - Lack of outcomes data in FH patients
  - Cost low
  - SHARP trial as combination therapy

- Effect of ezetimibe plus statin in patients with FH
  - Wide inter-individual variability -39.2% to -4.7% further decrease in LDL cholesterol (Pisciotta et al, Atherosclerosis 2007 194 e116-e122)
Addition of Ezetimibe to Simva – incremental benefit Gaugne Et Al

The NEW ENGLAND JOURNAL OF MEDICINE

Figure 2. Effects of Simvastatin and Combined Therapy with Simvastatin plus Ezetimibe on Levels of Cholesterol and Triglycerides.
All measures of cholesterol — low-density lipoprotein (LDL) cholesterol (Panel A), high-density lipoprotein (HDL) cholesterol (Panel B), and total cholesterol (Panel C) — were calculated with the use of analysis for variance for each time point. The I bars represent standard errors. An analysis for covariance on rank-transformed data for each time point was used for the triglyceride curve (Panel D).
ADD ON EFFECT OF EZETIMIBE

Fig. 3. Reduction in low-density lipoprotein cholesterol in patients with homozygous familial hypercholesterolaemia receiving statin therapy alone or in combination with ezetimibe (EZE) [11]. †All patients were receiving statin 40 mg at baseline and prior to switch; *p = 0.02 versus statin only 80 mg; **p < 0.01 versus statin only 80 mg.
Ezetimibe Added to Statin Therapy: Effect on LDL

Statin + Placebo (n=390)  
Mean % Change in LDL-C From Treated Baseline

0%  
-10%  
-20%  
-30%  

-4%  

Statin + Ezetimibe (n=379)  

Mean LDL-C

139 mg/dL  
138 mg/dL  
133 mg/dL  
102 mg/dL

*P<0.001 for ezetimibe + statin vs placebo + statin.

WHAT ABOUT NIACIN? COMPELL: Niacin ER/Statin Combination


N = 292; 12 weeks
*P<.05 versus atorva + niacin ER
Three or four drug combinations are often needed in FH

- Statin/resin/niacin
- Statin/ezetimibe/niacin
- Statin/ezetimibe/BAS/niacin
- Statin/EZE/PCSk9i

Benefits: substantial LDL cholesterol reduction

Disadvantages: number of pills, side effects, cost
Further additive therapies for Familial Hypercholesterolemia

- Lomitapide and mipomersen for homozygous FH
  - Studied on background of combination therapy
- LDL apheresis also in addition to combination therapy
- PCSK9 inhibitors on background statin or combination therapy
- Combinations of therapies for patients with severe heterozygous FH, homozygous FH or statin intolerance offer possibility of substantial LDL cholesterol reduction and decreased risk of atherosclerotic cardiovascular disease
POOR RESPONSE RATES WITH STATIN AND EZETIMIBIE

Currently Approved Therapies for HoFH and HeFH

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

Response in LDL-c in Patients With Severe Heterozygous Familial Hypercholesterolemia*

Adding Colestipol

* Ten patients

Current cholesterol-lowering drugs are insufficient in HoFH

<table>
<thead>
<tr>
<th>Class</th>
<th>Major Effect</th>
<th>Typical LDL-C-Lowering Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statins (e.g. atorvastatin, rosvastatin)</td>
<td>↑ LDLR activity</td>
<td>&lt;10 to 25%</td>
</tr>
<tr>
<td>Bile acid sequestrants (e.g. cholestyamine, colestipol)</td>
<td>↑ LDLR activity</td>
<td>&lt;10%</td>
</tr>
<tr>
<td>Cholesterol absorption inhibitors (e.g. ezetimibe)</td>
<td>↑ LDLR activity</td>
<td>&lt;10%</td>
</tr>
<tr>
<td>Nicotinic acid (ie, niacin)</td>
<td>Unknown</td>
<td>&lt;10%</td>
</tr>
</tbody>
</table>

## ADDITIONAL THERAPY IN HOFH

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

Lomitapide and mipomersen are not approved for HeFH.
LDL apheresis is current standard of care for HoFH
LDL-C Levels acutely decrease and then rebound following apheresis

Lomitapide in HoFH

Mean Percent Changes in LDL-C, TC, and ApoB from Baseline to Week 26 (n=23)

Single-arm, open-label, phase 3 study
- LDL-C: 50%
- ApoB: 49%
- Lp(a): 15%
- TG: 45%
- Mean hepatic fat measure by NMRS (n=20) from 1% at baseline to 8.6% at week 26, 5.8% at week 56, and 8.3% at week 78

Figure 3. Cost-Effectiveness Analysis for PCSK9 Inhibitors

Conceptual relationship between the clinical effectiveness of PCSK9 inhibitor therapy, measured in QALYs added compared with statin therapy, on the horizontal axis, and their clinical value, measured in dollars per QALY added, on the vertical axis. The top curve indicates the relationship at full U.S. list price of PCSK9 inhibitor therapy ($14,000/y), the middle curve indicates the relationship if the price were reduced by 50% (i.e., to $7,000/y), and the bottom curve indicates the relationship if the price were reduced by 75% (i.e., to $3,500/y).

Reproduced from Hlatky et al. (S7.1-3).
CV indicates cardiovascular; and QALY, quality-adjusted life-years.
Take Home Messages

- Combination therapy is often needed in patients with FH
- Therapies using different mechanisms of action are additive
- There is evidence of benefit
- Ezetimibe preferred second drug in a number of international guidelines
- Pheresis and new therapies build on current combinations
Bile Acid Binding Resins: Colesevelam

- Polymer with greater binding activity than cholestyramine and colestipol
- 625 mg tablets or suspension
- 6 to 7 tablets per day with one or two meals
- 18% reduction of LDL-C at maximum dose (also additive with statins)
- Fewer drug interactions than older resins (thyroxine)
- Usually less constipating (but not always)
- BAS may lower blood sugar: decrease HgbA1c by 0.5% (Zieve et al Clinic Ther 29:74, 2007)
**Bile Acid Sequestrants: Colesevelam and Statins**

<table>
<thead>
<tr>
<th>Colesevelam</th>
<th>Statin</th>
<th>TC (%)</th>
<th>LDL-C (%)</th>
<th>HDL-C (%)</th>
<th>TG (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 mg (no tablets)</td>
<td>Atorvastatin 80 mg</td>
<td>−43</td>
<td>−56</td>
<td>+2</td>
<td>−43</td>
</tr>
<tr>
<td>3750 mg (6 tablets)</td>
<td>Atorvastatin 10 mg</td>
<td>−35</td>
<td>−51</td>
<td>+7</td>
<td>−11</td>
</tr>
</tbody>
</table>

Backup slides
Fig. 4. Estimation of low-density lipoprotein cholesterol (LDL-C) levels achieved upon treatment with current therapies in patients with homozygous familial hypercholesterolaemia, according to the severity of the disease.
# SIMON BROOME DIAGNOSTIC CRITERIA FOR FAMILIAL HYPERCHOLESTEROLEMIA

<table>
<thead>
<tr>
<th>Point</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Total cholesterol levels &gt; 290mg/dL (7.5 mmol/L) or LDL-C &gt; 190 mg/dL (4.9 mmol/L) in adults. Total cholesterol levels &gt; 260 mg/dL (6.7 mmol/L) or LDL-C &gt; 155 mg/dL (4.0 mmol/L)</td>
</tr>
<tr>
<td>2</td>
<td>Tendon xanthomas in the patient or tendon xanthomas in a first or second degree relative.</td>
</tr>
<tr>
<td>3</td>
<td>DNA-based evidence of an LDL-receptor mutation, familial defective apo B-100, or a PCSK9 mutation.</td>
</tr>
<tr>
<td>4</td>
<td>Family history of myocardial infarction before age 50 years in a second degree relative or before age 60 years in a first degree relative.</td>
</tr>
<tr>
<td>5</td>
<td>Family history of elevated total cholesterol &gt; 290 mg/dL (7.5 mmol/L) in an adult first or second-degree relative. Family history of elevated total cholesterol &gt; 260 mg/dL (6.7 mmol/L) in a child, brother, or sister 16 years or younger.</td>
</tr>
</tbody>
</table>

**DIAGNOSIS**

Definite familial hypercholesterolemia = 1+2 or 3
Possible familial hypercholesterolemia = 1+4 or 5

**MEDPED**

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>First degree relative with FH</th>
<th>Second degree relative with FH</th>
<th>Third degree relative with FH</th>
<th>General population</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20</td>
<td>220 (5.7)</td>
<td>230 (5.9)</td>
<td>240 (6.2)</td>
<td>270 (7.0)</td>
</tr>
<tr>
<td>20 – 29</td>
<td>240 (6.2)</td>
<td>250 (6.5)</td>
<td>260 (6.7)</td>
<td>290 (7.5)</td>
</tr>
<tr>
<td>30 – 39</td>
<td>270 (7.0)</td>
<td>280 (7.2)</td>
<td>290 (7.5)</td>
<td>340 (8.8)</td>
</tr>
<tr>
<td>&gt;=40</td>
<td>290 (7.5)</td>
<td>300 (7.8)</td>
<td>310 (8.0)</td>
<td>360 (9.3)</td>
</tr>
</tbody>
</table>

*The total cholesterol cutpoints for FH is dependent upon the confirmed cases of FH in the family. If FH is not diagnosed in the family, then the cutpoint for diagnosis is as per “general population.”*


New Imaging Biomarker of Coronary Inflammation Shows Prognostic Value Exceeding All Current Noninvasive Measures

Perivascular fat attenuation index could transform primary and secondary prevention

A novel imaging biomarker that quantifies perivascular fat has been found to predict all-cause and cardiac mortality above and beyond clinical risk factors and current coronary CT interpretation methods. So finds a new study published in *The Lancet* by UK researchers at the University of Oxford working with colleagues in Germany and at Cleveland Clinic.

High values of the biomarker — known as the perivascular fat attenuation index (FAI) — around the right coronary artery effectively identified individuals at risk of death in two large, independent and substantially different patient cohorts: a derivation cohort in Erlangen, Germany, and a validation cohort at Cleveland Clinic.
# VARIATION IN HOFH DX CRITERIA

## Diagnostic Criteria for HoFH from the Literature

<table>
<thead>
<tr>
<th>Publication</th>
<th>Diagnostic Criteria for HoFH</th>
</tr>
</thead>
</table>
| Seftel, et al. | - Serum cholesterol concentration >550 mg/dL  
- Appearance of xanthomas during the first decade of life  
- Hypercholesterolemia or clinical signs of hypercholesterolemia in both parents |
| Moorjani, et al. | - Plasma cholesterol levels >550 mg/dL  
- Appearance of xanthomas at an early age  
- Detection of hypercholesterolemia in both parents |
| Hahtas, et al. | - Hypercholesterolemia in both parents (when available)  
- Total serum cholesterol >500 mg/dL + presence of xanthomas in first decade of life |
| Raal, et al. | - Untreated serum LDL consistently >12 mmol/L  
- Appearance of xanthomas in first decade of life  
- Hypercholesterolemia, or its clinical features, documented in both parents  
- Confirmation by DNA analysis for LDLR mutations |
| Goldstein, et al. | - Unique yellow-orange cutaneous xanthomas (frequently present at birth)  
- Tendon xanthomas, corneal arcus, generalized atherosclerosis during childhood  
- Plasma cholesterol >650 mg/dL in non-jaundiced child |
| Cagne, et al. | - 2 mutant alleles at LDLR confirmed by genetic testing or  
- LDL-C ≥220 mg/dL while receiving lipid-lowering therapy at the highest tolerated dose (<15% response)  
- LDL-C >90th percentile in ≥2 first-degree relatives  
- Presence of tendon xanthomas and/or manifestations of premature coronary heart disease or corneal arcus |
| Marais, et al. | - Childhood cutaneous or tendinous xanthomata  
- Total cholesterol >600 mg/dL  
- Both parents should have severe hypercholesterolemia (>300 mg/dL) or tendinous xanthomas  
- Family history of premature ischemic heart disease |
| Kolansky, et al. | - Total cholesterol >500 mg/dL  
- Xanthomas at an early age  
- Presence of hypercholesterolemia in proband’s parents or other first-degree relative |
| Marais, et al. | - Clinical criteria  
- Fasting LDL >500 mg/dL, TG <600 mg/dL  
- Either xanthomata before age 10 or FH in both parents  
- Genetic criteria  
- Identification of 2 LDLR gene mutations  
- Functional criteria  
- <30% uptake compared with normal of LDL and upregulated fibroblasts |
| Santos, et al. | - Untreated LDL >500 mg/dL + at least 1 of the following:  
- Genetic testing confirmation of 2 mutated LDLR alleles  
- Tendinous and/or tuberous xanthoma prior to age 10  
- Documented elevated LDL and both parents consistent with HeFH (LDL >200 mg/dL). If parent unavailable, history of CAD in first-degree relative |
| Raal, et al. | - Untreated LDL-C >13 mmol/L and either appearance of xanthomas before age 10 or FH in both parents |
| Mabuchi, et al. | - Childhood cutaneous or tendinous xanthomata  
- Total cholesterol >600 mg/dL  
- Both parents should have severe hypercholesterolemia (>300 mg/dL) or tendinous xanthomas  
- Family history of premature ischemic heart disease |

### Combined Criteria for FH DX

#### Criteria for the Clinical Diagnosis of Familial Hypercholesterolemia

<table>
<thead>
<tr>
<th>US: MEDPED Criteria</th>
<th>Total Cholesterol (and LDL-C) Levels, mg/dL</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;18</td>
<td>First-degree Relative</td>
<td>98% specificity</td>
</tr>
<tr>
<td>20</td>
<td>240 (170)</td>
<td>87% sensitivity</td>
</tr>
<tr>
<td>30</td>
<td>270 (190)</td>
<td></td>
</tr>
<tr>
<td>40 +</td>
<td>290 (205)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>UK Simon Broome Criteria</strong></th>
<th>Plus</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol (and LDL-C) levels:</td>
<td>DNA mutation</td>
<td>Definite FH</td>
</tr>
<tr>
<td>Adults: 290 (190) mg/dL</td>
<td>Tendon xanthomas in the patient or in first- or second-degree relative</td>
<td>Definite FH</td>
</tr>
<tr>
<td>Children: 260 (155) mg/dL</td>
<td>Family history of MI at age &lt;50 in second-degree relative, or at age &lt;60 in first-degree relative or family history of TC &gt;290 mg/dL in adult first-/second-degree relative, or 260 (155) mg/dL in a child/sibling aged &lt;16 yrs</td>
<td>Possible FH</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>The Netherlands Dutch Lipid Clinic Criteria</strong></th>
<th>Feature</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rating</strong> 1 point</td>
<td>First-degree relative with premature CVD or LDL-C &gt;95th percentile, or Personal history of premature peripheral or cerebrovascular disease, or LDL-C between 155 mg/dL and 189 mg/dL</td>
<td></td>
</tr>
<tr>
<td>2 points</td>
<td>First-degree relative with tendinous xanthoma or corneal arcus, or First-degree relative child (&lt;1 yrs) with LDL-C &gt;95th percentile, or Personal history of CAD</td>
<td></td>
</tr>
<tr>
<td>3 points</td>
<td>LDL-C between 190 mg/dL and 249 mg/dL</td>
<td>Possible FH (3-5 points)</td>
</tr>
<tr>
<td>4 points</td>
<td>Presence of corneal arcus in patients &lt;45 yrs old</td>
<td></td>
</tr>
<tr>
<td>5 points</td>
<td>LDL-C between 250 mg/dL and 329 mg/dL</td>
<td></td>
</tr>
<tr>
<td>6 points</td>
<td>Presence of a tendon xanthoma</td>
<td>Probable FH (6-7 points)</td>
</tr>
<tr>
<td>8 points</td>
<td>LDL-C &gt;330 mg/dL, or Functional mutation in LDLR gene</td>
<td>Definite FH (≥8 points)</td>
</tr>
</tbody>
</table>
Mipomersen in HoFH

Randomized, double-blind, placebo-controlled, phase 2 study
<table>
<thead>
<tr>
<th>Guidelines</th>
<th>Recommendation</th>
<th>Therapy</th>
<th>Additional Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NLA</strong>††</td>
<td><strong>Adults</strong>: pharmacologic therapy to reduce baseline LDL-C by &gt; 50% with maximum statin dose tolerated. <strong>Children/Young Adults</strong>: Consider initiation of medical therapy in FH pts &gt; 8 years old.</td>
<td>Lifestyle modification. Statin therapy should be initial drug of choice. If unable to tolerate initial statin, consider alternate statin or alternate day dosing. If statin contraindicated or poorly tolerated, consider addition of ezetimibe, bile acid sequestrants or niacin. Additional options: LDL apheresis.</td>
<td><strong>Adults</strong>: Reduce LDL-C by &gt; 50%. Higher risk patients may require more aggressive therapeutic goals (LDL-C &lt; 100 mg/dl). <strong>Children</strong>: Treatment goal is &gt; 50% reduction in LDL-C or LDL-C &lt; 130 mg/dl.</td>
</tr>
<tr>
<td><strong>NICE</strong>††</td>
<td><strong>Children/Young Adults</strong>: Cholesterol lowering drugs should be considered in FH patients by age 10. Lipid lowering drugs may be considered before the age of 10 when there is a family history of CHD in early adulthood.</td>
<td>Lifestyle modification. Treatment with high-intensity statin to reduce LDL-C by 50% should be first line medical therapy. Ezetimibe is recommended as monotherapy for patients intolerant of statins. Ezetimibe can be used as adjunctive therapy in heterozygous FH patients on statins with suboptimal TC or LDL-C or when the statin dose cannot be further titrated due to side effects. Additional options: LDL apheresis.</td>
<td><strong>Adult FH patients at very high risk of coronary heart disease, or with intolerance or contraindication to statins or ezetimibe, should be referred to a FH specialist. Children and adolescents diagnosed with, or undergoing evaluation for, FH should be referred to a specialist in FH. No published studies to establish target LDL-C target levels in children with FH on lipid lowering therapy.</strong></td>
</tr>
<tr>
<td><strong>EAS</strong>‡‡</td>
<td><strong>Target LDL-C</strong>: <strong>Children</strong>: &lt; 135 mg/dl <strong>Adults</strong>: &lt; 100 mg/dl <strong>Adults with CHD or Diabetes</strong>: &lt; 70 mg/dl</td>
<td>Lifestyle modification. Lipid lowering therapy should be started between ages 8 and 10. - no safety data on the use of statins before age 8–10. Ezetimibe should be added as a second line agent if LDL is still above target. Bile acid resins are third-line agents.</td>
<td><strong>Children</strong>: statins, ezetimibe, bile acid resins and LDL apheresis in homozygous FH. <strong>Adults</strong>: maximal potency statins, ezetimibe, bile acid resins, fibrates (specifically fenofibrate), LDL apheresis in homozygous FH and treatment resistant heterozygous FH.</td>
</tr>
<tr>
<td><strong>ACC/AHA</strong>‡‡</td>
<td><strong>Recommendation to treat to a target LDL-C level was abandoned due to lack of randomised controlled trials demonstrating that treatment to a specific LDL level improved CVD outcomes. No specific recommendations for FH patients, but recent guidelines address patients with LDL-C &gt; 190</strong></td>
<td>Lifestyle modification. High Intensity statin is recommended Addition of nonstatin drugs may be considered.</td>
<td>A reasonable approach would be to reduce LDL-C by &gt; 50 percent. High potency statins include atorvastatin 40 to 80 mg and rosvuavastatin 20 to 40 mg.</td>
</tr>
</tbody>
</table>

*NLA – National Lipid Association; NICE – National Institute for Health and Care Excellence; EAS – European Atherosclerosis Society; ACC/AHA – American College of Cardiology/American Heart Association; TC – Total cholesterol.*
Cardiologist Desire To Expand Knowledge of FH

- Yes: 68%
- No: 20%
- Not Sure: 13%

Q: Is Familial Hypercholesterolemia an area where you would like to expand your knowledge? (n=152)
Q: How familiar are you with familial hypercholesterolemia? (n=571)
idents. (A) Achilles tendon in a 40-year-old man (maximum thickness: 22 mm), (B) Achilles tendon in a 29-
Thank you!