Homozygous Familial hypercholesterolaemia: From a lethal disorder to a manageable dyslipidaemia

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Director, Carbohydrate and Lipid Metabolism Research Unit
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Homozygous FH (HoFH)

Rare, but serious disorder characterized by:

• Severe hypercholesterolaemia
• Xanthomata before age 10 years
• Premature, accelerated atherosclerosis
• High mortality at an early age
  - survival beyond age 30 years uncommon

Raal FJ, Santos RD. Atherosclerosis 2012;223:262-268
# Cases of early death (<10 years) from CVD in HoFH reported in the literature

<table>
<thead>
<tr>
<th>Reference</th>
<th>Receptor function</th>
<th>LDL-R gene mutation</th>
<th>Gender</th>
<th>Age-at-death (years)</th>
<th>Tot Chol (mmol/L)</th>
<th>Country/ethnic origin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Watanabe et al (1968)</td>
<td>n.d.</td>
<td>n.d.</td>
<td>M</td>
<td>4</td>
<td>22.8</td>
<td>Japan</td>
</tr>
</tbody>
</table>
Genetics and genetic heterogeneity of FH

A

Normal subject
FH heterozygote
FH homozygote

Normal allele
FH mutation-bearing allele

LDLRAP1=Low-density lipoprotein receptor adapter protein 1
PCSK9=Proprotein convertase subtilisin/kexin type 9
APOB=Apolipoprotein B
LDLR=Low-density lipoprotein receptor

B

Chr 1
Chr 2
Chr 19
Diagnostic definition of homozygous familial hypercholesterolemia

- Genetic confirmation of 2 mutant alleles at the LDL receptor, APOB, PCSK9, or ARH adaptor protein gene locus

  OR

- An untreated LDL cholesterol of 13 mmol/L (>500 mg/dL) or treated LDL cholesterol 8 mmol/L (≥300 mg/dL) or treated non-HDL cholesterol 8.5 mmol/L (≥330 mg/dL) together with either:

  - Cutaneous or tendonous xanthoma before age 10 years

    OR

  - Elevated LDL cholesterol levels before lipid-lowering therapy consistent with heterozygous FH in both parents*

* Except in the case of ARH
Phenotypic variability in HoFH

<table>
<thead>
<tr>
<th>LDL cholesterol</th>
<th>Clinical diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>mmol/L</td>
<td>mg/dL</td>
</tr>
<tr>
<td>0–20</td>
<td>0–770</td>
</tr>
<tr>
<td>5–15</td>
<td>190–580</td>
</tr>
<tr>
<td>10–13</td>
<td>390–500</td>
</tr>
<tr>
<td>0–5</td>
<td>0–190</td>
</tr>
<tr>
<td>0–5</td>
<td>0–190</td>
</tr>
</tbody>
</table>

- **Homozygous FH**
- **Heterozygous FH**
- **Common hypercholesterolemia**

- **Mutation diagnosis**
  - Homozygous LDL-receptor negative
  - Homozygous LDL-receptor defective or homozygous LDLRAP1/ARH
  - Homozygous APOB defect/PCSK9 gain of function
  - Compound heterozygous LDL-receptor APOB/PCSK9

Cuchel M, *Eur Heart J* 2014;35:2146-57
Relationship between plasma LDL-cholesterol level and residual LDL receptor activity in cultured skin fibroblasts in patients with the clinical phenotype of HoFH

![Graph showing the relationship between plasma LDL-cholesterol level and residual LDL receptor activity. The graph includes a scatter plot with a line of best fit. The Pearson correlation coefficient (r) is 0.655 and the p-value (P) is 0.0003.](image)

- **LDL-C (mg/dL)**: 1200, 1000, 800, 600, 400, 200, 100, 50
- **Residual LDL-receptor activity (%)**: 30, 20, 15, 10, 5

Bertolini S. ATVB 1999;19:408-418
FH exposes people to very high cholesterol from birth, thus reaching a threshold for CHD earlier in life.

Cumulative exposure (cholesterol yrs) by age:
FH vs unaffected (healthy) individuals

CHD = Coronary heart disease

Adapted from Horton et al. J Lipid Res. 2009;50:S172-S177
Therapy for HoFH

- Pharmacotherapy
  - lipid modifying drugs

- Extracorporeal removal of LDL
  - plasma exchange
  - LDL apheresis

- Surgical therapy
  - portacaval shunt
  - partial ileal bypass

- Methods to restore LDL receptor activity
  - liver transplantation
  - gene therapy
Statins act mainly by increasing the synthesis of hepatic LDL receptors.

LDL in plasma

 LDL uptake

Synthesis

HMG-CoA

Cholesterol

HMG-CoA

Cholesterol

Blocked By statins

# High Dose Simvastatin and Atorvastatin in HoFH

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>% LDL-C Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simvastatin</td>
<td>80 mg/d</td>
<td>- 25%</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>160 mg/d</td>
<td>- 31%</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>40 mg/d</td>
<td>- 20%</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>80 mg/d</td>
<td>- 33%</td>
</tr>
</tbody>
</table>

Mechanisms of action of high dose statins in HoFH

- Receptor defective HoFH
  - Upregulation of LDL receptors

- Receptor negative HoFH
  - Reduction in hepatic apo-B lipoprotein synthesis

Mean percentage reduction in LDL-C for patients with HoFH receiving ezetimibe plus statin

**Entire Study Cohort (n=48)**

- **Statin-80**: -7.0%
- **Ezetimibe + Statin 80**: -27.5%

**Genotype Confirmed HoFH (n=35)**

- **Statin-80**: -5.6%
- **Ezetimibe + Statin 80**: -26.6%

Gagne *Circulation* 2002;105:2469-2475
Cardiovascular mortality characteristics of patients with HoFH pre- statin (1990) and post-statin (n = 149)

<table>
<thead>
<tr>
<th></th>
<th>pre-1990 (n=36)</th>
<th>post-1990 (n=113)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Females/Males</strong></td>
<td>24/12</td>
<td>58/55</td>
</tr>
<tr>
<td><strong>Age at death – all causes (years)</strong></td>
<td>18.4 ± 10.1</td>
<td>32.9 ± 15.5</td>
</tr>
<tr>
<td>(n=27)</td>
<td></td>
<td>(n=38) *</td>
</tr>
<tr>
<td><strong>Age at death – CV (years)</strong></td>
<td>17.7 ± 10.1</td>
<td>31.7 ± 13.3</td>
</tr>
<tr>
<td>(n=22)</td>
<td></td>
<td>(n=28) #</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± SD

* P<0.0001   #P<0.001

Raal FJ  *Circulation* 2011;124:2202-2207
Kaplan-Meier probability estimates of survival among HoFH patients before and after the introduction of modern lipid lowering therapy.

Benefit from modern lipid therapy (Endpoint: Death)

Hazard ratio 0.34
(95% CI 0.14-0.86); p=0.02

Kaplan-Meier probability estimates of survival among HoFH patients before and after the introduction of modern lipid lowering therapy.
Kaplan-Meier probability estimates of time to first major adverse cardiovascular event (MACE) among HoFH patients before and after the introduction of modern lipid lowering therapy.

Benefit from modern lipid therapy (Endpoint: MACE)

Hazard ratio 0.49
(95% CI 0.22-1.07); p=0.07

Raal FJ Circulation 2011;124:2202-2207
Plasma cholesterol (mmol/L) vs. CHD risk ratio.

Additional drug therapies for HoFH

- ACAT inhibitors
- Squalene synthase inhibitors
- Thyromimetics
- Antisense apo B (Mipomersen)
- MTP inhibitors (Lomitapide)
- PCSK9 inhibitors
- CETP inhibitors

ACAT=Acetyl-Coenzyme A Acetyl transferase
MTE=microsomal triglyceride transfer protein
CETP=Cholesteryl ester transfer protein
Apo B antisense (Mipomersen): Inhibition of Apo B-100 production

- Apo B-100 is an important structural and functional component of lipoproteins
- Blocking Apo B-100 production blocks VLDL, LDL and Lp(a) production

Brautbar A et al. Nat Rev Cardiol 2011;8:253-65
Mipomersen Significantly reduced LDL-C in HoFH Patients (ITT Analysis)

Reduction in LDL-C over 28 weeks

PET 2 weeks after final dose.

Assembly and secretion of hepatic and intestinal apolipoprotein-B containing lipoproteins requires microsomal triglyceride transfer protein (MTP)
Efficacy and safety of a microsomal triglyceride transfer protein inhibitor in patients with homozygous familial hypercholesterolaemia: a single-arm, open-label, phase 3 study

Mean percent changes in TC, LDL-C, and Apo B from Baseline to end of efficacy Phase (ITT, LOCF)

Study Week

Lomitapide in HoFH

n = 29, age 18 yrs or older

<table>
<thead>
<tr>
<th>Lomitapide dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 (n=3)</td>
</tr>
<tr>
<td>10 (n=2)</td>
</tr>
<tr>
<td>20 (n=6)</td>
</tr>
<tr>
<td>40 (n=7)</td>
</tr>
<tr>
<td>60 (n=11)</td>
</tr>
</tbody>
</table>

- # Patient was a responder at later time points during the study
- ‡ Patients discontinued from the study

## Mipomersen vs. Lomitapide for HoFH

<table>
<thead>
<tr>
<th></th>
<th><strong>Mipomersen</strong> <em>(Kynamro, Genzyme)</em></th>
<th><strong>Lomitapide</strong> <em>(Juxtapid/Lojuxta, Aegerion)</em></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug class</strong></td>
<td>Antisense oligonucleotide</td>
<td>Microsomal triglyceride transfer protein inhibitor</td>
</tr>
<tr>
<td><strong>Formulation</strong></td>
<td>200 mg/mL, vials or syringes</td>
<td>5, 10, 20 mg capsules</td>
</tr>
<tr>
<td><strong>Route</strong></td>
<td>Subcutaneous</td>
<td>Oral</td>
</tr>
<tr>
<td><strong>Dosage</strong></td>
<td>200 mg once/week</td>
<td>5-60 mg once/day</td>
</tr>
<tr>
<td><strong>Daily dietary supplement</strong></td>
<td>None</td>
<td>Vitamin E and essential fatty acids</td>
</tr>
<tr>
<td><strong>Adverse effects</strong></td>
<td>Injection-site reactions, transaminase elevations, hepatic steatosis</td>
<td>Gastro intestinal, transaminase elevations, hepatic steatosis</td>
</tr>
<tr>
<td><strong>Drug interactions</strong></td>
<td>None</td>
<td>Multiple, incl. simvastatin, lovastatin, warfarin and grapefruit juice</td>
</tr>
<tr>
<td><strong>Pregnancy category</strong></td>
<td>B (no evidence if risk in animals; no human studies)</td>
<td>X (teratogenic in animals)</td>
</tr>
<tr>
<td><strong>Annual cost</strong></td>
<td>$200,000</td>
<td>$280,000 – $360,000</td>
</tr>
</tbody>
</table>


INHIBITION OF PCSK9 in HoFH

In patients with HoFH with either no (<2%) or little (2-25%) LDL-receptor activity will PCSK9 inhibition be effective?
<table>
<thead>
<tr>
<th></th>
<th>HoFH untreated (n=20)</th>
<th>HoFH treated (n=20)</th>
<th>HeFH untreated (n=20)</th>
<th>HeFH treated (n=20)</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>25.7 ± 7.2*</td>
<td>-</td>
<td>41.4 ± 13.6*</td>
<td>-</td>
<td>42.4 ± 10.4</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>13/7</td>
<td>-</td>
<td>10/10</td>
<td>-</td>
<td>7/13</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>24.0 ± 4.6</td>
<td>-</td>
<td>25.0 ± 4.6</td>
<td>-</td>
<td>23.1 ± 2.9</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>15.0 ± 3.2*</td>
<td>12.9 ± 3.5†</td>
<td>9.2 ± 1.1*</td>
<td>5.7 ± 0.9†</td>
<td>4.8 ± 0.6</td>
</tr>
<tr>
<td>Triglyceride (mmol/L)</td>
<td>1.5 ± 1.2</td>
<td>1.5 ± 0.8</td>
<td>1.7 ± 1.0</td>
<td>1.4 ± 0.8</td>
<td>1.2 ± 0.5</td>
</tr>
<tr>
<td>HDL-cholesterol (mmol/L)</td>
<td>0.9 ± 0.3*</td>
<td>1.1 ± 0.3</td>
<td>1.4 ± 0.5</td>
<td>1.5 ± 0.5</td>
<td>1.6 ± 0.3</td>
</tr>
<tr>
<td>LDL-cholesterol (mmol/L)</td>
<td>13.4 ± 3.1*</td>
<td>11.1 ± 3.3†</td>
<td>7.0 ± 1.0*</td>
<td>3.6 ± 0.8†</td>
<td>2.6 ± 0.5</td>
</tr>
<tr>
<td>PCSK9 (ng/mL)</td>
<td>279 ± 122*</td>
<td>338 ± 226</td>
<td>202 ± 63*</td>
<td>278 ± 90†</td>
<td>132 ± 48</td>
</tr>
<tr>
<td>CIMT (mm)</td>
<td>1.4 ± 0.5*</td>
<td>-</td>
<td>0.7 ± 0.2*</td>
<td>-</td>
<td>0.5 ± 0.1</td>
</tr>
</tbody>
</table>

ANOVA *p<0.01 compared to controls; †p<0.01 treated vs. untreated

Raal FJ. *J Am Heart Assoc* 2013;2:e000028
The TESLA Part B Study in HoFH

- **Trial** Evaluating PCSK9 Antibody in Subjects with LDL Receptor Abnormalities Part B

- **Design**
  A 12-week randomized, double-blind, placebo-controlled multicenter phase 3 study

- **Objective**
  To evaluate the efficacy and safety of evolocumab in patients with HoFH

Study design

Primary endpoint: Percent change from baseline in Ultracentrifugation LDL-C at week 12

- **Screening period**: Fasting LDL-C 5–10 days before randomization

- **Randomization**: 2:1

- **Evolocumab 420 mg SC QM (N = 33)**

- **Placebo SC QM (N = 17)**

**Visits:**
- Day 1
- Week 2†
- Week 4
- Week 6
- Week 8
- Week 10†
- Week 12

**Dosing QM:**

†Week 2 and week 10 study visits were optional.

*R Randomization stratified by screening LDL-C (< 11 mmol/L (420 mg/dL) or ≥ 11 mmol/L (420 mg/dL).

Percent change in UC LDL-C from baseline to week 12

Study drug administration

Vertical lines represent the standard error around the mean. Plot is based on observed data with no imputation for missing values.

Baseline  Week 4  Week 6  Week 8  Week 12

Placebo (N = 16)
Evolocumab 420 mg QM (N = 33)

## LDL-C lowering by type of mutation

### Percent Change from Baseline in UC LDL-C at Week 12, Mean (SE)

<table>
<thead>
<tr>
<th>Mutation status</th>
<th>N</th>
<th>Placebo</th>
<th>Evolocumab 420 mg QM</th>
<th>Treatment difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>49</td>
<td>7.9 (5.3)</td>
<td>-23.1</td>
<td>-30.9 (6.4)*</td>
</tr>
<tr>
<td>LDLR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Defective/any†</td>
<td>28</td>
<td>11.2 (5.1)</td>
<td>-29.6 (3.4)</td>
<td>-40.8 (6.1)‡</td>
</tr>
<tr>
<td><strong>Defective/defective</strong></td>
<td>13</td>
<td>15.1 (7.3)</td>
<td>-31.8 (5.8)</td>
<td><strong>-46.9 (9.4)‡</strong></td>
</tr>
<tr>
<td>Negative/Defective</td>
<td>9</td>
<td>3.5 (5.8)</td>
<td>-21.0 (4.0)</td>
<td>-24.5 (7.0)#</td>
</tr>
<tr>
<td>Unclassified</td>
<td>22</td>
<td>3.8 (11.7)</td>
<td>-17.9 (8.8)</td>
<td>21.7 (13.9)</td>
</tr>
<tr>
<td>Median (Q1, Q3)</td>
<td></td>
<td>7.2 (0.0, 9.9)</td>
<td>-39.2 (48.8, 14.6)</td>
<td>-</td>
</tr>
<tr>
<td>Negative/negative</td>
<td>1</td>
<td>-</td>
<td>10.3</td>
<td>-</td>
</tr>
<tr>
<td>LDLR heterozygous</td>
<td>1</td>
<td>-</td>
<td>-55.7</td>
<td>-</td>
</tr>
<tr>
<td>Apolipoprotein B</td>
<td>2</td>
<td>10.8, 13.1</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>ARH</td>
<td>1</td>
<td>-</td>
<td>3.5</td>
<td>-</td>
</tr>
</tbody>
</table>

Data are least squares (LS) mean for groups with sufficient data; otherwise actual value at week 12. LS mean is from the repeated measures model, which includes treatment group, screening LDL, scheduled visit and the interaction of treatment with scheduled visit as covariates. *Adjusted P-value < 0.001; †Receptor defective in at least one of two affected alleles. ‡Nominal P-value < 0.001; #Nominal P-value = 0.013; †Function of one or both LDLR mutations is unknown (includes 6 patients from the defective/any group).

Lipoprotein apheresis

- Although expensive and time consuming, is an important adjunctive treatment for HoFH

- A single treatment can decrease plasma LDL-C levels (and Lpa) by 55-70%

- Long-term treatment has been shown to cause regression of cutaneous xanthomas

- Despite the lack of randomised trials, there is clinical evidence that long-term apheresis can contribute to plaque stability and/or regression, and improve prognosis

- Should be started by age 5-8 years, if not earlier

Thompson GR. Atherosclerosis 2010;208:317-21
(A) Double filtration plasmapheresis. (B) Immunoabsorption or dextran sulfate absorption. (C) Heparin extracorporeal LDL precipitation. (D) Dextran sulfate direct perfusion or polyacrylate whole blood absorption.
Mean percentage reductions in plasma lipoproteins and fibrinogen with different methods of LDL apheresis

<table>
<thead>
<tr>
<th></th>
<th>DFPP (%)</th>
<th>TF (%)</th>
<th>HELP (%)</th>
<th>DALI (%)</th>
<th>DSA (%)</th>
<th>IA (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C</td>
<td>56-62</td>
<td>61</td>
<td>55-61</td>
<td>53-76</td>
<td>49-75</td>
<td>62-69</td>
</tr>
<tr>
<td>HDL-C</td>
<td>25-42</td>
<td>6</td>
<td>5-17</td>
<td>5-29</td>
<td>4-17</td>
<td>9-27</td>
</tr>
<tr>
<td>Lp(a)</td>
<td>53-59</td>
<td>61</td>
<td>55-68</td>
<td>28-74</td>
<td>19-70</td>
<td>51-71</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>37-49</td>
<td>56</td>
<td>20-53</td>
<td>29-40</td>
<td>26-60</td>
<td>34-49</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>52-59</td>
<td>42</td>
<td>51-58</td>
<td>13-16</td>
<td>17-40</td>
<td>15-21</td>
</tr>
</tbody>
</table>
Proportion of patients without coronary events receiving LDL-apheresis in combination with lipid-lowering medications or medications alone.

Mabuchi H. Am J Cardiol 1998;82:1489-95
Disadvantages of Extracorporeal Removal of LDL

- Cost
- Frequency of procedure
- Access – shunt often required
- Must be continued indefinitely as does not restore LDL receptor actively
Methods to Restore LDL Receptor Activity

- Liver transplantation
- Gene therapy
Liver transplantation and other surgical approaches

Liver transplantation corrects the molecular deficit in the organ most active in the clearance of LDL, resulting in a marked lowering of LDL-C levels.

BUT

- Costly
- High risk of post transplantation surgical complication
- Need for livelong immunosuppressive therapy
GENE THERAPY FOR HoFH
Sweet dreams and flying machines?

HFH subject → harvest cells
harvest cells → infect with non-replicative recombinant retroviruses carrying the LDLR
infect with non-replicative recombinant retroviruses carrying the LDLR → establish hepatocyte cultures
establish hepatocyte cultures → remove hepatic lobe
remove hepatic lobe → Ex vivo gene replacement therapy
Ex vivo gene replacement therapy → infuse via portal vein
infuse via portal vein → HFH subject
Adeno-associated virus serotype 8 gene therapy for Homozygous FH – humanised mouse model

A

Cholesterol mg/dL

<table>
<thead>
<tr>
<th>Time (day)</th>
<th>0</th>
<th>7</th>
<th>21</th>
<th>35</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>700</td>
<td>600</td>
<td>500</td>
<td>400</td>
</tr>
<tr>
<td>1</td>
<td>300</td>
<td>200</td>
<td>100</td>
<td>0</td>
</tr>
</tbody>
</table>

B

Non-HDL (mg/dL)

<table>
<thead>
<tr>
<th>Time (day)</th>
<th>0</th>
<th>7</th>
<th>21</th>
<th>35</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>500</td>
<td>400</td>
<td>300</td>
<td>200</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

C

Triglycerides mg/dL

<table>
<thead>
<tr>
<th>Time (day)</th>
<th>0</th>
<th>7</th>
<th>21</th>
<th>35</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>5x10^{12} GC/kg AAV8.TBG.nLacZ</td>
<td>1.5x10^{10} GC/kg AAV8.TBG.hLDLR</td>
<td>5x10^{11} GC/kg AAV8.TBG.hLDR</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>5x10^{12} GC/kg AAV8.TBG.hLDLR</td>
<td>1.5x10^{10} GC/kg AAV8.TBG.hLDLR</td>
<td>5x10^{11} GC/kg AAV8.TBG.hLDR</td>
<td></td>
</tr>
</tbody>
</table>

Algorithm for management of HoFH

Homozygous familial hypercholesterolemia
LDL-C targets
<2.5 mmol/L (adults)
<3.5 mmol/L (children)
<1.8 mmol/L if clinical CVD

At diagnosis lifestyle and diet + statin
(most efficacious at highest dose depending on tolerability)
Ezetimibe 10 mg and/or resins or other drugs
Fibrate, nicotinic acid (use of these may be limited by tolerability and drug availability)
New therapeutic options

LDL-apheresis
As early as possible if available (by 5 years, no later than 8 years) every 1 or 2 weeks

In selected patients
Liver transplant
Lomitapide
Approved by FDA, EMA
Mipomersen
Approved by FDA

Future therapeutic options
PCSK9 inhibitors
CETP inhibitors
Gene therapy

Cuchel M et al. Eur Heart J 2014;35:2146-57
Cumulative LDL cholesterol lowering effects of statin, ezetimibe, adjunctive evolocumab and mipomersen, lomitapide or lipoprotein apheresis in HoFH

Baseline: 13.0
Statin: ~10.0 (↓10-25%)
Plus ezetimibe: ~8.0 (↓10-15%)
Plus PCSK9-I: ~4.0 (↓25-50%)
Plus mipomersen, lomitapide or lipoprotein apheresis: ~2-3 (↓25-50%)

Adapted from Cuchel M et al. Eur Heart J 2014;35:2146-57