PCSK9 inhibitors and familial hypercholesterolemia

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Austin Health
Introduction

- Familial hypercholesterolemia
- Conventional therapy: statins and atherosclerosis
- PCSK9 and its effects on LDL metabolism
- The effects of PCSK9 inhibitors on lipids and CVD
- Safety of very low LDL
Familial hypercholesterolemia

- Most common serious genetic disease
- Dominantly inherited disorder
- Incidence 1/200-1/300 (heterozygote)
- Defect in cell surface LDL receptor, binding domain of Apo B, or gain of function in PCSK9
- The receptor regulates LDL degradation and cholesterol synthesis.

Typically
- TC >8 mmol/l
- LDL > 6.5 mmol/l

High LDL cholesterol (since birth)

Leads to premature cholesterol accumulation in arteries (atherosclerosis), skin and tendons (xanthomas)

Typically
- TC >8 mmol/l
- LDL > 6.5 mmol/l
Heterozygous Familial Hypercholesterolemia:

Typical signs

Achilles tendon xanthomas

Plantar xanthomas

DAVIGNON 2006
Heterozygous Familial Hypercholesterolemia:
Non-Specific Signs

Corneal arcus

Xanthelasma
Homozygous Familial Hypercholesterolemia:

5-year old 17-year old 21-year old
Homozygous Familial Hypercholesterolemia:

12-year old girl

21-year old woman
In FH high cholesterol from birth causes very premature vascular disease

Dutch Lipid Clinic Network Score is recommended as the most sensitive clinical diagnosis tool

<table>
<thead>
<tr>
<th>Dutch Lipid Clinic criteria</th>
<th>8 points</th>
<th>DNA mutation, or LDL-C &gt; 8.5 mmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 points</td>
<td>Tendon xanthomas</td>
<td></td>
</tr>
<tr>
<td>5 points</td>
<td>LDL-C 6.5 – 8.4 mmol/L</td>
<td></td>
</tr>
<tr>
<td>4 points</td>
<td>Arcus senilis &lt; 45 years</td>
<td></td>
</tr>
<tr>
<td>3 points</td>
<td>LDL-C 5.0 - 6.4 mmol/L</td>
<td></td>
</tr>
<tr>
<td>2 points</td>
<td>Xanthomas or premature arcus in 1st degree relative, childhood LDL-C &gt; 95th percentile, or premature CHD</td>
<td></td>
</tr>
<tr>
<td>1 point</td>
<td>1st degree relative with premature CVD or LDL 95th percentile, personal history of LDL-C 4.0 – 4.9 or premature CVD</td>
<td></td>
</tr>
</tbody>
</table>

Definite FH: > 8 points  
Probable FH: 6-8 points  
Possible FH: 3-5 points

Presence of identified mutation according to Dutch Lipid Score

(A) Dutch Lipid Clinic Network Phenotype

Phenotypic Assessment of Patients referred to Clinic
n=385

Definite FH
n=276
M+ n=174 (63%)
M- n=102 (37%)
High risk of mutation
Diagnose as FH
Genetic testing optional

Probable FH
n=318
M+ n=71 (22%)
M- n=247 (78%)
Intermediate risk of mutation
Defor FH diagnosis
Genetic testing recommended

Possible FH
n=291
M+ n=22 (6%)
M- n=269 (92%)
Low risk of mutation
Diagnose as non-FH
Genetic testing not recommended
LDL-C and typical mutations in homozygous FH

Genetic screening is not required for clinical diagnosis
Management of familial hypercholesterolaemia

Initially: Diet + Statin ± Ezetimibe

LDL target:
- Children < 3.5 mmol/L
- Adults < 2.5 mmol/L
- CVD present: < 1.8 mmol/L

<table>
<thead>
<tr>
<th>Statin</th>
<th>Dose</th>
<th>Average LDL-C reduction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>10mg</td>
<td>30%</td>
</tr>
<tr>
<td></td>
<td>20mg</td>
<td>35%</td>
</tr>
<tr>
<td></td>
<td>40mg</td>
<td>38%</td>
</tr>
<tr>
<td></td>
<td>80mg</td>
<td>46%</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>10mg</td>
<td>46%</td>
</tr>
<tr>
<td></td>
<td>20mg</td>
<td>52%</td>
</tr>
<tr>
<td></td>
<td>40mg</td>
<td>55%</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>40mg</td>
<td>40%</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>40mg</td>
<td>34%</td>
</tr>
<tr>
<td>Pitavastatin #</td>
<td>2mg</td>
<td>39%</td>
</tr>
<tr>
<td></td>
<td>4mg</td>
<td>44%</td>
</tr>
<tr>
<td>Fluvastatin XL</td>
<td>80mg</td>
<td>36%</td>
</tr>
</tbody>
</table>
Response to statin therapy is variable

LDL response to rosuvastatin 20mg

P-trend < 0.00001

Management of familial hypercholesterolaemia

If not at target and existing vascular disease:

PCSK9 inhibitor or LDL apheresis

Homozygote:

LDL apheresis, Liver transplantation
PCSK9

A new target for lipid management
What is PCSK9?

- Pro-protein convertase subtilisin-like kexin type 9
- A secreted protease which is a 692 amino acid protein
- Primarily expressed in liver, intestine and kidney
- Rapid turnover in plasma (<10 mins); plasma removal principally via the LDL-R
Recycling of LDLR enables efficient clearance of LDL particles

PCSK9 regulates the recycling of LDLR by targeting the LDLR for degradation

Genetic Variants of PCSK9 Demonstrate Its Importance in Regulating LDL Levels

PCSK9 Gain of Function (GOF) = **Less** LDL-R’s

PCSK9 Loss of Function (LOF) = **More** LDL-Rs

Mutations in the human PCSK9 gene that lead to a loss of PCSK9 function are found in 1% to 3% of the population. 


Slide courtesy of Amgen
# Mutations in PCSK9 associated with altered LDL-C and coronary heart disease risk

<table>
<thead>
<tr>
<th>PCSK9 Variant</th>
<th>Population</th>
<th>LDL-C</th>
<th>CHD Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GOF mutations</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADH multiplex pedigrees$^1,2$</td>
<td>$&gt;7.5$ mmol/L</td>
<td>Premature CAD$^1,2$</td>
<td></td>
</tr>
<tr>
<td><strong>LOF mutations</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>R46L</strong></td>
<td>ARIC, DHS</td>
<td>↓ 15$^3$</td>
<td>↓ 47$^5$</td>
</tr>
<tr>
<td><strong>Y142X or C679X</strong></td>
<td>ARIC, DHS</td>
<td>↓ 28-40$^3,4$</td>
<td>↓ 88$^3$</td>
</tr>
<tr>
<td><strong>R46L</strong></td>
<td>CGPS</td>
<td>↓ 11$^5$</td>
<td>↓ 46$^5$</td>
</tr>
</tbody>
</table>

- PCSK9 LOF mutations found in 1% to 4% of population
- Associated with
  - Lower serum LDL-C
  - Lower incidence of coronary heart disease

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Therapeutic agents targeting PCSK9

- Inhibition of the binding of PCSK9 to the LDL-R e.g. monoclonal antibodies
- Inhibition of PCSK9 synthesis e.g. anti-sense oilgonucleotides
- Inhibition of the intracellular processing of PCSK9 to the mature protein (small molecules)
Evolocumab and alirocumab are fully human monoclonal antibody against PCSK9 and block PCSK9/LDL-R Interaction

Alirocumab Administered 2 weekly (Q2W) SC: Change in Calculated LDL-C from Baseline to Week 12

Mean percentage change in calculated LDL-C from baseline to weeks 2, 4, 6, 8, 10, and 12 in the modified intent-to-treat (mITT) population, by treatment group. Week 12 estimation using LOCF method.

McKenney et al JACC 2012;59:2344-53
Effects of Evolocumab (AMG-145), a monoclonal antibody to PCSK9 in combination with a statin (± exetimibe)

Patients with hypercholesterolaemia
LDL-C Lowering Effects of Evolocumab in patients With Heterozygous Familial Hypercholesterolemia

LDL-C Percentage Change from Baseline (SE)

-43%  
P<0.001

-55%

**Evolocumab in FH: adverse events**

<table>
<thead>
<tr>
<th>Incidence, n (%)</th>
<th>Placebo n = 56</th>
<th>350 mg Evolocumab n = 55</th>
<th>420 mg Evolocumab n = 56</th>
<th>All Patients Evolocumab n = 111</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients With treatment-emergent AEs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any AE</td>
<td>33 (58.9)</td>
<td>32 (58.2)</td>
<td>37 (66.1)</td>
<td>69 (62.2)</td>
</tr>
<tr>
<td>Serious AE*</td>
<td>0</td>
<td>0</td>
<td>2 (3.6)</td>
<td>2 (1.8)</td>
</tr>
<tr>
<td>AE leading to discontinuation</td>
<td>1 (1.8)</td>
<td>1 (1.8)</td>
<td>1 (1.8)</td>
<td>2 (1.8)</td>
</tr>
<tr>
<td>Treatment-related AE†</td>
<td>6 (10.7)</td>
<td>13 (23.6)</td>
<td>8 (14.3)</td>
<td>21 (18.9)</td>
</tr>
<tr>
<td>Serious treatment-related AE‡†</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Patients with common AEs (≥ 5% in any Evolocumab group)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>6 (10.7)</td>
<td>7 (12.7)</td>
<td>7 (12.5)</td>
<td>14 (12.6)</td>
</tr>
<tr>
<td>Headache</td>
<td>5 (8.9)</td>
<td>3 (5.5)</td>
<td>3 (5.4)</td>
<td>6 (5.4)</td>
</tr>
<tr>
<td>Injection site pain</td>
<td>1 (1.8)</td>
<td>5 (9.1)</td>
<td>2 (3.6)</td>
<td>7 (6.3)</td>
</tr>
<tr>
<td>Mortality</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Fatal, life-threatening, required or extended hospitalisation, or resulted in significant disability or incapacity or birth defect
†Possibly related to investigational product per investigator

Mr. AG  54 yo male

- Heterozygous familial hypercholesterolaemia (FH)
- LDL pre-treatment was 8.1 mmol/L
- Hypertension
- Investigated for chest pain age 52. No reversible ischaemia but angiogram showed: 40% Left main, 20% RCA

Family Hx

Father (AMI age 42yo), Brother (FH and CAD age 40yo), Son (Age 32 with F.H)

Medications:

Atorvastatin 80mg, Ezetemibe 10mg, Fenofibrate 145mg
Mr AG: Examination:

BP 130/70, Bilateral Achilles tendon xanthoma, corneal arcus, bilateral carotid bruits

Investigations: (on drug therapy)

<table>
<thead>
<tr>
<th>Lipid profile</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Cholesterol</td>
<td>7.1 mmol/L</td>
</tr>
<tr>
<td>TG</td>
<td>1.3 mmol/L</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>1.1 mmol/L</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>5.4 mmol/L</td>
</tr>
<tr>
<td>Lipoprotein(a)</td>
<td>0.42 g/L (RR&lt;0.24)</td>
</tr>
</tbody>
</table>

Decision made to commence LDL apheresis
Mr AG: Progress

- Apheresis since early 2010
Mr AG: Progress

• Coronary / carotid artery disease – remains asymptomatic

Current treatment

Evolocumab injection 140mg / 2 weeks commenced in June 2016 and LDL apheresis ceased.
Evolocumab commenced in June 2016

No myositis, myalgia or abnormal LFT’s with the evolocumab therapy

<table>
<thead>
<tr>
<th></th>
<th>Pre – evolocumab (May 2016)</th>
<th>On evolocumab (Nov 2016)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Cholesterol (mmol/L)</td>
<td>5.5</td>
<td>3.3</td>
</tr>
<tr>
<td>TG (mmol/L)</td>
<td>1.3</td>
<td>1.1</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>1.01</td>
<td>0.99</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/L)</td>
<td>3.9</td>
<td>1.8</td>
</tr>
<tr>
<td>Lipoprotein(a) (g/L)</td>
<td>0.52</td>
<td>0.35</td>
</tr>
</tbody>
</table>
Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease

Marc S. Sabatine, M.D., M.P.H., Robert P. Giugliano, M.D., Anthony C. Keech, M.D., Narimon Honarpour, M.D., Ph.D., Stephen D. Wiviott, M.D., Sabina A. Murphy, M.P.H., Julia F. Kuder, M.A., Huei Wang, Ph.D., Thomas Liu, Ph.D., Scott M. Wasserman, M.D., Peter S. Sever, Ph.D., F.R.C.P., and Terje R. Pedersen, M.D., for the FOURIER Steering Committee and Investigators*

March 17, 2017 at NEJM.org
Fourier: Study design

• Amgen involved in designing the trial, collecting data
• Analysis by TIMI Study group (independent of sponsor)

• Eligibility criteria
  – Existing CVD (MI, non-haemorrhagic stroke, PVD)
  – LDL $\geq$ 1.8 mmol/L, or non-HDL $\geq$ 2.6 mmol/L, while taking lipid-lowering therapy (at least equivalent to 20mg atorvastatin)

• Randomisation (double blind placebo controlled)
  – Evolocumab 140mg s/c every 2 weeks
  – 420mg s/c monthly
  – Placebo
FOURIER: Cumulative incidence of CVD events *Primary End Point* (composite of CV death, MI, stroke, hospitalization for unstable angina, or coronary revascularization)

**Graph:**
- Hazard ratio: 0.85 (95% CI, 0.79–0.92)
- P < 0.001

**Table:**

<table>
<thead>
<tr>
<th>Months</th>
<th>No. at Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
</tr>
<tr>
<td>0</td>
<td>13,780</td>
</tr>
<tr>
<td>6</td>
<td>13,278</td>
</tr>
<tr>
<td>12</td>
<td>12,825</td>
</tr>
<tr>
<td>18</td>
<td>11,871</td>
</tr>
<tr>
<td>24</td>
<td>7610</td>
</tr>
<tr>
<td>30</td>
<td>3690</td>
</tr>
<tr>
<td>36</td>
<td>686</td>
</tr>
</tbody>
</table>

P values calculated using log-rank tests

Landmark Analysis

Evolocumab vs. Placebo

CV Death, MI, Stroke

Months from Randomization

16% RRR
HR 0.84 (95%CI 0.74-0.96)
P=0.008

25% RRR
HR 0.75 (95%CI 0.66-0.85)
P<0.00001
FOURIER: Secondary Endpoints by quartile of baseline LDL-C and treatment arms

Lower LDL-C Is Better

P<0.0001

Cardiovascular Death, MI or Stroke

Achieved LDL Cholesterol (mmol/L)

Placebo

Evolocumab

Therapeutic agents targeting PCSK9

- Inhibition of the binding of PCSK9 to the LDL-R e.g. monoclonal antibodies

- Inhibition of PCSK9 synthesis e.g. anti-sense oligonucleotides

- Inhibition of the intracellular processing of PCSK9 to the mature protein (small molecules)
PCSK9 RNA silencing with inclisiran

Levin AA
Effect of one or two doses of inclisiran on PCSK9 and LDL Levels.

A Changes in PCSK9 Levels with the Single-Dose Regimen

B Changes in LDL Cholesterol Levels with the Single-Dose Regimen

C Changes in PCSK9 Levels with the Two-Dose Regimen

D Changes in LDL Cholesterol Levels with the Two-Dose Regimen

Absolute effect of statin therapy on MAJOR CARDIOVASCULAR EVENTS
(129,526 statin vs control; 39,612 more vs less statin)

Five year risk of a major vascular event, %

0 1 2 3 4 5
0 5 10 15 20

LDL cholesterol, mmol/L

Control
Statin
More statin
Ezetimibe
PCSK9i

21% relative risk reduction in CVD per 1.0 mmol/L less LDLc
16% relative risk reduction in CVD per 0.5 mmol/L less LDLc

Lancet 2010; 376:1670-81
Safety
New lipid lowering agents can achieve very low LDL levels:

Is very low LDL safe?
## Safety of very low LDL: PROVE IT-TIMI 22

<table>
<thead>
<tr>
<th>LDL</th>
<th>&gt;2.1-2.6</th>
<th>&gt;1.6-2.1</th>
<th>&gt;1.1-1.6</th>
<th>&lt;1.1</th>
<th>p trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myalgia</td>
<td>6.4</td>
<td>4.3</td>
<td>6.2</td>
<td>5.7</td>
<td>0.75</td>
</tr>
<tr>
<td>CK&gt;3x ULN</td>
<td>2.3</td>
<td>0.7</td>
<td>1.9</td>
<td>1.0</td>
<td>0.18</td>
</tr>
<tr>
<td>CK&gt;10x ULN</td>
<td>0</td>
<td>0</td>
<td>0.3</td>
<td>0</td>
<td>0.45</td>
</tr>
<tr>
<td>ALT&gt;3x ULN</td>
<td>3.2</td>
<td>3.0</td>
<td>3.2</td>
<td>2.6</td>
<td>0.98</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1.0</td>
<td>0.7</td>
<td>0.5</td>
<td>0.6</td>
<td>0.009</td>
</tr>
</tbody>
</table>

Wiviott J Am Coll Cardiol 2005;46:1411– 6
### Long term safety of evolocumab Osler extension study.

#### Annual adverse event frequency (%)

<table>
<thead>
<tr>
<th>Type of AE</th>
<th>Standard care (yr 1)</th>
<th>1 Year (1,255)</th>
<th>2 years (1,147)</th>
<th>3 years (1,082)</th>
<th>4 Years (963)</th>
<th>&gt;4 years (543)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any serious A.E.</td>
<td>6.8</td>
<td>6.9</td>
<td>6.8</td>
<td>7.8</td>
<td>4.8</td>
<td>3.5</td>
</tr>
<tr>
<td>New onset diabetes</td>
<td>4.3</td>
<td>4.1</td>
<td>2.1</td>
<td>2.6</td>
<td>3.2</td>
<td>1.4</td>
</tr>
<tr>
<td>Muscle related</td>
<td>9.3</td>
<td>8.1</td>
<td>5.9</td>
<td>4.3</td>
<td>3.1</td>
<td>1.3</td>
</tr>
<tr>
<td>Neurocognitive</td>
<td>0</td>
<td>0.6</td>
<td>0.3</td>
<td>0.6</td>
<td>0.2</td>
<td>0</td>
</tr>
<tr>
<td>Discontinuation</td>
<td>N/A</td>
<td>2.8</td>
<td>0.6</td>
<td>1.0</td>
<td>0.5</td>
<td>0.2</td>
</tr>
</tbody>
</table>

The annual frequency of adverse events did not increase with cumulative exposure

Koren MJ. JAMA Cardiol. 2017;2(6):598-607
### Alirocumab: adverse Experience Summary in Patients with very low LDL-C values in Global Safety Pool

**Primary system organ class, %**

<table>
<thead>
<tr>
<th>Preferred term, %</th>
<th>Overall Alirocumab (n=3140)</th>
<th>≥2 LDL-C &lt;0.66 mmol/L (n=796)</th>
<th>≥2 LDL-C &lt;0.39 mmol/L (n=288)</th>
<th>LDL-C &gt;0.66 mmol/L (n=2544)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4.3%</td>
<td>3.0%</td>
<td>1.4%</td>
<td>4.0%</td>
</tr>
<tr>
<td>Nausea</td>
<td>2.2%</td>
<td>0.9%</td>
<td>1.0%</td>
<td>2.5%</td>
</tr>
<tr>
<td><strong>General disorders and administration-site conditions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection-site reaction</td>
<td>5.7%</td>
<td>3.0%</td>
<td>3.5%</td>
<td>5.9%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2.8%</td>
<td>2.6%</td>
<td>2.4%</td>
<td>2.7%</td>
</tr>
<tr>
<td>Non-cardiac chest pain</td>
<td>1.6%</td>
<td>1.8%</td>
<td>0.3%</td>
<td>1.5%</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>3.0%</td>
<td>1.8%</td>
<td>1.4%</td>
<td>3.2%</td>
</tr>
<tr>
<td>Headache</td>
<td>4.6%</td>
<td>1.8%</td>
<td>1.4%</td>
<td>4.8%</td>
</tr>
<tr>
<td><strong>Hemorrhagic stroke</strong></td>
<td>0.1%</td>
<td>0</td>
<td>0</td>
<td>0.1%</td>
</tr>
</tbody>
</table>
Trial Design

**Randomized Double Blind**

- Placebo SC Q2W or QM
- Evolocumab SC 140 mg Q2W or 420 mg QM

2442 patients screened for EBBINGHAUS

1974 Enrolled (Full Analysis Pop)
Median F/U 19.8 months

Primary Analysis Cohort (N=1204)
Baseline cognitive testing on/before 1st dose of study drug and had f/u cognitive testing post dosing*
Additional 770 pts w/ baseline assessment before week 12 visit

**Major Exclusions**
1. Not enrolled in FOURIER
2. >12 wk FOURIER visit
3. H/O dementia, cognitive impairment or other conditions interfering with participation

*Cognitive tests performed at baseline; at 6, 12, 24 months; and end of study
Primary Endpoint
Spatial Working Memory Strategy Index

![Chart showing mean number of boxes for Placebo and Evolocumab at baseline and postbaseline, with change in raw scores and treatment difference in Z score.]
Cognitive Assessments by Nadir Achieved LDL-C and Treatment (Full Pop)

**Primary CANTAB Endpoint**: Average Change from Baseline

- Placebo
- Evolocumab

<table>
<thead>
<tr>
<th>LDL Value</th>
<th>Placebo</th>
<th>Evolocumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.7 mmol/L</td>
<td>0</td>
<td>661</td>
</tr>
<tr>
<td>0.7 - 1.0 mmol/L</td>
<td>13</td>
<td>206</td>
</tr>
<tr>
<td>&gt;1.0 mmol/L</td>
<td>969</td>
<td>115</td>
</tr>
</tbody>
</table>

P=NS across LDL values achieved and also between treatments

**Composite Global Score**: Average Change from Baseline

- Placebo
- Evolocumab

<table>
<thead>
<tr>
<th>LDL Value</th>
<th>Placebo</th>
<th>Evolocumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.7 mmol/L</td>
<td>-1</td>
<td>-1</td>
</tr>
<tr>
<td>0.7 - 1.0 mmol/L</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>&gt;1.0 mmol/L</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Negative score -> improvement
Lower scores are better
Safety of very low LDL: Two people identified with inactivating mutations in both PCSK9 alleles

<table>
<thead>
<tr>
<th>PCSK9 Genotype</th>
<th>PCSK9 Y142X/ΔR97</th>
<th>PCSK9 C679X/C679X</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Cholesterol</td>
<td>96 mg/dL (2.5 mmol/L)</td>
<td>85 mg/dL (2.2 mmol/L)</td>
</tr>
<tr>
<td>LDL</td>
<td>14 mg/dL (0.4 mmol/L)</td>
<td>15 mg/dL (0.4 mmol/L)</td>
</tr>
<tr>
<td>TG</td>
<td>119 mg/dL (1.3 mmol/L)</td>
<td>71 mg/dL (0.8 mmol/L)</td>
</tr>
<tr>
<td>HDL</td>
<td>65 mg/dL (1.7 mmol/L)</td>
<td>54 mg/dL (1.4 mmol/L)</td>
</tr>
<tr>
<td>Plasma [PCSK9]</td>
<td>Undetectable</td>
<td>N/A</td>
</tr>
</tbody>
</table>
| Clinical             | • Apparent good health  
|                      | • Normal fertility (mother)  
|                      | • No developmental abnormality  
|                      | • College graduate  
|                      | • Aerobics instructor  | • Apparent good health  
|                      | • Normal fertility (mother)  |

Humans with very low LDL-C levels from PCSK9 deficiency appear generally healthy, with normal fertility and development.

• PCSK9 knockout mice also have normal fertility and development

Conclusions

• Familial hypercholesterolemia is a common genetic disease resulting in very premature CVD and death.

• The diagnosis of FH is predominantly based on LDL levels and clinical criteria.

• LDL remains the primary treatment for reducing CV risk.

• Inhibiting PCSK9 can reduce LDL by 60% or more, even when added to maximal statin ± ezetimibe therapy.

• PCSK9 MCA are well tolerated, and there appears to be no hazard in reducing LDL-C below 1.0 mmol/L.
END