PCSK9 Inhibitors: Practical Aspects of their use in Patients with Familial Hypercholesterolemia

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Treasurer National Lipid Association
Outline

• FH Overview
• PCSK9 overview
  – Science
  – Inhibition
• FH Diagnosis
• PCSK9 Utilization in FH patients
  – Data in FH patients with currently available PCSK9i’s
  – Current Recommendations
  – Insurance Coverage
  – Lipoprotein (a) & FH
• Future Directions
**Familial Hypercholesterolemia FH: A Clinically Recognizable Genetic Disorder**

- The most common inheritable, autosomal dominant disorder associated with morbidity and mortality in man – present in 1 in 250 people\(^1,2\)
- Usually due to mutations in LDL receptor gene\(^3-5\) of which over 1600 have been described, and result in decreased clearance of LDL\(^1\)
  - Other mutations include those in the ApoB and PCSK9 genes
- Results in severe hypercholesterolemia and lifelong accumulation of LDL in tissues and arteries
- Evidence of CVD early in life

\(\text{FH} = \text{familial hypercholesterolemia; CVD = cardiovascular disease.}\)

Visible Signs of FH

- Bilateral xanthelasma (<25 yrs of age)
- Bilateral Corneal Arcus (<45 yrs of age)
- Extensor Tendon Xanthoma of Hand (Any time)
- Extensor Tendon Xanthoma of Achilles (Any Time)
Familial hypercholesterolaemia: A global call to arms

Familial Hypercholesterolaemia

Burden of Disease
- Heterozygous FH – 1:200-300 / Homozygous FH – 1:160,000-300,000 individuals based on contemporary data
- Over 30 million individuals worldwide could be affected
- Prevalence may be higher in e.g. subpopulations with founder effects or where consanguinity is common

Underdiagnosed
- <5% of affected individuals have been identified in most countries
- No data for a number of countries/regions

Undertreated
- Early initiation of therapy associated with lower risk of CV events compared with delayed statin initiation, but...
- Many FH individuals not treated, insufficiently treated or treatment introduced too late
- Lack of lipid goal attainment with current therapies

FH adverse outcomes preventable when FH identified and treated early and efficiently

Diagnosis / Screening
- Clinical criteria (Dutch Lipid Clinic criteria, MEDPED, Simon Broome, Japanese criteria)
- Genetic diagnosis
- Universal vs. cascade vs. opportunistic screening
- Cascade screening of relatives from index cases, cost-effective

Registries
- International initiatives, e.g. EAS FH Studies Collaboration, 10 Countries study, ScreenPro programme
- National registries, e.g. Dutch Lipid Clinic network; Spanish FH Foundation (SAFEHEART); Genyco Uruguay; LIPGEN (Italy); Cascade FH registry – US; Simon Broome registry (UK); Czech MedPed database; Portuguese FH Study; FH Australasia Network
- Lack of nationwide registries for FH in most countries

Research
- Basic sciences → epidemiological and clinical research → population Health
- Health service research
- Informing health policy and clinical practice (consensus, guidelines)

Public and patients (e healthcare professionals) organizations, e.g.
- FH Foundation
- Iberoamerican FH network
- Heart UK
- Spanish FH Foundation
- Hipercol Brasil
- FHCanada
- Czech MedPed
- FHichel Austria
- CholCo (Germany)
- FH Australasia Network
- Scientific Societies EAS, IAS FHSC

Awareness / Education

Policies
- General lack of specific public health policies aimed at FH
- Lack of specific WHO International Classification of Diseases code for FH

Therapy
- Statins
- Combination therapy
- LDI, apheresis
- Emerging therapies (PCSK9 inhibitors, mipomersen, lomitapide...), costs ?

Professional bodies: International (e.g. EAS, IAS, Iberoamerican FH network, International FH Foundation), National scientific societies, Others (e.g. FHSC, Heart UK, Czech MedPed, Spanish FH Foundation, US FH Foundation). In partnership with patients organizations and health authorities and institutions
Goal attainment

**UK 2008**
- Treated LDL-C<100 mg/dl: 30%
- Reduction in LDL-C≥50%: 64%

**CASCADE-FH**
- Treated LDL-C<100 mg/dl: 25%
- Reduction in LDL-C≥50%: 41%

**Netherlands 2010**
- Treated LDL-C<100 mg/dl: 21%
- Reduction in LDL-C≥50%: 60%

Monogenic Causes of FH

- Defective LDLR (chromosome 19)
  - Homozygous 1/1,000,000
  - Heterozygous 1/500

- Defective ApoB 100 (chromosome 2)
  - Homozygous 1/4,000,000
  - Heterozygous 1/1000

- PCSK9 gain-of-function mutation (chromosome 1)
- and IDOL
  - 1/2500

- Autosomal recessive FH (chromosome 1)
  - <1/1,000,000
- STAP1 (chromosome 4)
Mechanisms causing familial hypercholesterolemia linked to low-density lipoprotein (LDL) receptor (LDLR) function

Gidding, S. Circulation. 2015;132: In Press
Different domains in the low-density lipoprotein (LDL) receptor protein are encoded by specific regions in the LDL receptor gene.

Gidding, S. Circulation. 2015;132: In Press
### Classes of LDL Receptor Mutations

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Synthesis of receptor or precursor protein is absent. The so-called null allele is a prevalent class of mutations and is generally associated with very high LDL-C levels. The molecular basis of this type of mutation shows a wide variety: point mutations introducing a stop codon, mutations in the promoter region completely blocking transcription, mutations giving rise to incorrect excision of mRNA, and finally, large deletions preventing the assembly of a normal receptor.</td>
</tr>
<tr>
<td>2</td>
<td>Absent or impaired formation of receptor protein. This class comprises mutations in which the normal routing through the cell is not complete or is only very slowly completed. Usually, there is a complete blockade of transport, and LDL receptors are unable to leave the ER. The Golgi apparatus is not reached, and the increase of 40,000 Da in molecular weight does not take place. Truncated proteins, as a result of a premature stop codon, and misfolded proteins, as a result of mutations in cysteine-rich regions leading to free or unpaired cysteine residues, are retained in the ER. However, quality control by the ER is not perfect, given the observation that sometimes misfolded proteins leave the ER but are processed more slowly. Such mutations give rise to class 2B mutations, in contrast to class 2A mutations that cause complete retaining in the ER.</td>
</tr>
<tr>
<td>3</td>
<td>Normal synthesis of receptor protein, abnormal LDL binding. Receptors characterized by this class of alleles show the normal rate of synthesis, exhibit normal conversion into receptor protein, and are transported to the cell surface, but binding to LDL is impaired. It is obvious that mutations in the binding domain underlie this class of receptors.</td>
</tr>
<tr>
<td>4</td>
<td>Clustering in coated pits, internalization of the receptor complex does not take place. The receptors in this class lack the property to cluster in coated pits (class 4A). This phenomenon, which makes interaction of receptors with the fuzzy coat impossible, is caused by mutations in the carboxyterminal part of the receptor protein. These mutated receptors are synthesized normally, folding and transport are normal, but clustering in coated pits is impossible, and sometimes the receptors are secreted even after they have reached the cell surface (class 4B).</td>
</tr>
<tr>
<td>5</td>
<td>Receptors are not recycled and are rapidly degraded. All mutations in this class are localized in the EGF-precursor homologous domain of the LDL receptor protein. This domain seems to be involved in the acid-dependent dissociation of the receptor-ligand complex in endosomes, after which the receptor can be recycled. When the entire EGF-precursor homologous domain is deleted by site-directed mutagenesis or when such a deletion occurs naturally in a homozygous FH patient, the receptor is trapped in the endosomes, and rapid degradation subsequently is observed.</td>
</tr>
<tr>
<td>6</td>
<td>Receptors fail to be targeted to the basolateral membrane. The class of mutations was recently discovered and is caused by alterations in the cytoplasmic tail of the protein. Such receptors do not reach the liver cell membrane and are probably rapidly degraded.</td>
</tr>
</tbody>
</table>

Gidding, S. Circulation. 2015;132: In Press
Phenotypic Variability in HoFH

PCSK9: Rapid Progress From Discovery to Clinic

- Adenoviral \( \uparrow \) expression in mice
- PCSK9 KO mouse \( \downarrow \) LDL-C
- PCSK9 LOF mutations found with 28\% \( \downarrow \) LDL-C and 88\% \( \downarrow \) CHD risk
- Humans null for PCSK9 have LDL-C ~15 mg/dL
- First subject treated with PCSK9 mAb
- First patients with FH & nonFH treated with PCSK9 mAb
- First publication POC in patients

PCSK9 Regulates LDL-R Expression

PCSK9 mediated degradation of LDL-R

PCSK9 = protein convertase subtilisin/kexin type 9; LDL-R = low density lipoprotein receptor.
Impact of an PCSK9 mAb on LDL Receptor Expression

mAb = monoclonal antibody.
NON – PCSK9 Mediated LDL Receptor Degradation
# Pharmacokinetic Profiles of PCSK9 Inhibitors

<table>
<thead>
<tr>
<th>MOA</th>
<th>Alirocumab</th>
<th>Evolocumab</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Human monoclonal antibody that binds to PCSK9</td>
<td>Human monoclonal antibody that binds to PCSK9</td>
</tr>
<tr>
<td>Half-life</td>
<td>17 – 20 days</td>
<td>11 – 17 days</td>
</tr>
<tr>
<td>Steady State</td>
<td>After 2 – 3 doses or 4 – 6 weeks</td>
<td>After 12 weeks</td>
</tr>
<tr>
<td>Max Effect</td>
<td>~ 4 – 8 hours</td>
<td>~ 4 hours</td>
</tr>
</tbody>
</table>

MOA = mechanism of action.

# Currently Available PCSK9 Inhibitors

<table>
<thead>
<tr>
<th></th>
<th><strong>Alirocumab</strong></th>
<th><strong>Evolocumab</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FDA approval</strong></td>
<td>July 2015</td>
<td>August 2015</td>
</tr>
<tr>
<td><strong>Indication</strong></td>
<td>Adjunct to diet and max tolerated statin for adults with HeFH, or clinical ASCVD, who require additional lowering of LDL-C</td>
<td>Adjunct to diet and max tolerated statin for adults with HeFH, or clinical ASCVD, who require additional lowering of LDL-C, HoFH pts on other LTT</td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>75 – 150 mg SC Q2W</td>
<td>140 mg or 420 mg SC Q2W; 420 mg SC monthly for HoFH</td>
</tr>
<tr>
<td><strong>How supplied</strong></td>
<td>Single-dose pre-filled pens and pre-filled glass syringes that deliver – 75 mg/mL or 150 mg/mL solution</td>
<td>Single-use pre-filled syringe or SureClick® autoinjector that deliver – 1mL of 140 mg/mL solution</td>
</tr>
<tr>
<td><strong>Side effects</strong></td>
<td>Nasopharyngitis, injection site reactions; hypersensitivity reactions</td>
<td>Nasopharyngitis, injection site reactions; hypersensitivity reactions</td>
</tr>
</tbody>
</table>

**The effect of alirocumab/evoloumab on CV mortality and morbidity has not been established.**

HeFH = heterozygous familial hypercholesterolemia; HoFH = homozygous FH. LLT = lipid lowering therapy.

Phase 2 and 3 clinical trials of monoclonal antibodies against PCSK9 in FH patients

<table>
<thead>
<tr>
<th>Study</th>
<th>PCSK9 inhibitor; duration</th>
<th>N; entry criteria</th>
<th>Treatment groups</th>
<th>Changes versus placebo (LSM %)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Treatment groups</td>
<td>LDL-C</td>
</tr>
<tr>
<td>Phase 2 studies</td>
<td></td>
<td></td>
<td>Treatment groups</td>
<td>LDL-C</td>
</tr>
<tr>
<td>Stein et al.\textsuperscript{d} [35•]</td>
<td>Alirocumab; 12 weeks</td>
<td>77; LDL-C $\geq$100 mg/dL, on statin±ezetimibe</td>
<td>150 mg q2W</td>
<td>−68</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>150 mg q4W</td>
<td>−29</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>200 mg q4W</td>
<td>−32</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>300 mg q4W</td>
<td>−43</td>
</tr>
<tr>
<td>Dufour et al.\textsuperscript{f} [36]</td>
<td>Alirocumab; 64 weeks</td>
<td>54; same as above</td>
<td>150 mg q2W (no placebo)</td>
<td>−59\textsuperscript{c}</td>
</tr>
<tr>
<td>RUTHERFORD [37•]</td>
<td>Evolocumab; 12 weeks</td>
<td>168; LDL-C $\geq$100 mg/dL, on statin±ezetimibe</td>
<td>350 mg q4W</td>
<td>−44</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>420 mg q4W</td>
<td>−56</td>
</tr>
<tr>
<td>Phase 3 studies</td>
<td></td>
<td></td>
<td>Treatment groups</td>
<td>LDL-C</td>
</tr>
<tr>
<td>RUTHERFORD-2 [45••]</td>
<td>Evolocumab; 12 weeks</td>
<td>331; LDL-C $\geq$100 mg/dL, on statin±other LLT</td>
<td>140 mg q2W</td>
<td>−59</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>420 mg q4W</td>
<td>−61</td>
</tr>
<tr>
<td>ODYSSEY FH I\textsuperscript{b} [46]</td>
<td>Alirocumab; 24 weeks</td>
<td>483; LDL-C $&gt;$100 mg/dL without CVD or LDL-C $&gt;$70 mg/dL with history of CVD, on maximum tolerated statin and other LLT</td>
<td>75 mg q2W</td>
<td>−58</td>
</tr>
<tr>
<td>ODYSSEY FH II\textsuperscript{b} [46]</td>
<td>Alirocumab; 24 weeks</td>
<td>249; same as above</td>
<td>75 mg q2W</td>
<td>−51</td>
</tr>
<tr>
<td>ODYSSEY High FH\textsuperscript{b} [47]</td>
<td>Alirocumab; 24 weeks</td>
<td>107; on maximum tolerated statin and other LLT</td>
<td>150 mg q2W</td>
<td>−39</td>
</tr>
<tr>
<td>TESLA [49••]</td>
<td>Evolucumab; 12 weeks</td>
<td>50; HoFH on maximum tolerated statin and other LLT</td>
<td>420 mg q4W</td>
<td>−31</td>
</tr>
</tbody>
</table>
ODYSSEY FH I and FH II: Alirocumab in Patients with FH at Week 24

All patients on background max-tolerated statin ± other lipid-lowering therapy

Mean baseline LDL-C:
~145 mg/dL

FH I

-48.8

-57.9% (2.7); P<0.0001

N = 322

43.4% had dose increase at W12

N = 163

FH II

-48.7

-51.4% (3.4); P<0.0001

N = 166

38.6% had dose increase at W12

N = 81

LDL-C reductions maintained over 52 wks

RUTHERFORD-2: Evolocumab in Patients with FH at Week 12

*P<0.001; SE = standard error.

Primary endpoint: % change from baseline in ultracentrifugation LDL-C at week 12

Raal et al. Lancet 2014; doi.org/10.1016/S0140-6736(14)61399-4
# TESLA Part B: Patient Genotype and Receptor Function

<table>
<thead>
<tr>
<th>Genotype, n (%)</th>
<th>Placebo QM ( N = 16 )</th>
<th>Evolocumab 420 mg QM ( N = 33 )</th>
<th>Total ( N = 49 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDLR</td>
<td>14 (88)</td>
<td>31 (94)</td>
<td>45 (92)</td>
</tr>
<tr>
<td>Homozygous</td>
<td>7 (43)</td>
<td>15 (45)</td>
<td>22 (45)</td>
</tr>
<tr>
<td>Compound heterozygous</td>
<td>7 (43)</td>
<td>16 (49)</td>
<td>23 (47)</td>
</tr>
<tr>
<td>Heterozygous*</td>
<td>0</td>
<td>1 (3)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Apolipoprotein B</td>
<td>2 (13)</td>
<td>0</td>
<td>2 (4)</td>
</tr>
<tr>
<td>ARH</td>
<td>0</td>
<td>1 (3)</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>LDLR functional status, n (%)</th>
<th>Placebo QM ( N = 16 )</th>
<th>Evolocumab 420 mg QM ( N = 33 )</th>
<th>Total ( N = 49 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Defective/any†</td>
<td>8 (50)</td>
<td>20 (61)</td>
<td>28 (57)</td>
</tr>
<tr>
<td>Defective/defective</td>
<td>5 (31)</td>
<td>8 (24)</td>
<td>13 (27)</td>
</tr>
<tr>
<td>Negative/defective</td>
<td>3 (25)</td>
<td>6 (18)</td>
<td>9 (20)</td>
</tr>
<tr>
<td>Unclassified‡</td>
<td>6 (31)</td>
<td>16 (48)</td>
<td>22 (43)</td>
</tr>
<tr>
<td>Negative/negative</td>
<td>0</td>
<td>1 (3)</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

*Patient met clinical diagnostic criteria for HoFH based on history of untreated LDL-C concentration >13 mmol/L plus either xanthoma before 10 yr or evidence of heterozygous FH in both parents. †Receptor defective in at least one allele. ‡Function of one or both LDLR mutations is unknown (includes 6 patients from the defective/any group). ARH, autosomal recessive hypercholesterolemia; LDLR, LDL receptor.

Raal et al. Lancet 2014; doi.org/10.1016/S0140-6736(14)61399-4
TESLA Part B: Percent Change in UC LDL-C from Baseline to Week 12

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

-31% P<0.001

Study drug administration

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

Raal et al. Lancet 2014; doi.org/10.1016/S0140-6736(14)61399-4
## TESLA Part B: 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 (3.8)</td>
<td>-30.9 (6.4)*</td>
</tr>
<tr>
<td><strong>LDLR</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Defective/any</strong>†</td>
<td>28</td>
<td>11.2 (5.1)</td>
<td>-29.6 (3.4)</td>
<td><strong>-40.8 (6.1)</strong>†</td>
</tr>
<tr>
<td>Defective/defective</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><strong>-24.5 (7.0)</strong>§</td>
</tr>
<tr>
<td>Unclassifiedǁ</td>
<td>22</td>
<td>3.8 (11.7)</td>
<td>-17.9 (8.8)</td>
<td><strong>-21.7 (13.9)</strong></td>
</tr>
<tr>
<td><strong>Negative/negative</strong></td>
<td>1</td>
<td>-</td>
<td>10.3</td>
<td>-</td>
</tr>
<tr>
<td><strong>LDLR Heterozygous</strong></td>
<td>1</td>
<td>-</td>
<td>-55.7</td>
<td>-</td>
</tr>
<tr>
<td><strong>Apolipoprotein B</strong></td>
<td>2</td>
<td>-10.8, 13.1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>ARH</strong></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).*
Criteria for the clinical diagnosis of FH

<table>
<thead>
<tr>
<th>USA: MEDPED criteria</th>
<th>Total cholesterol (and LDL-C) levels, mg/dL</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>First-degree relative</td>
<td>Second-degree relative</td>
</tr>
<tr>
<td>&lt;18</td>
<td>220 (155)</td>
<td>230 (165)</td>
</tr>
<tr>
<td>20</td>
<td>240 (170)</td>
<td>250 (180)</td>
</tr>
<tr>
<td>30</td>
<td>270 (190)</td>
<td>280 (200)</td>
</tr>
<tr>
<td>40+</td>
<td>290 (205)</td>
<td>300 (215)</td>
</tr>
<tr>
<td>Total cholesterol (and LDL-C) levels</td>
<td>Plus</td>
<td></td>
</tr>
</tbody>
</table>

UK: Simon Broome criteria
- Adults: 290 (190) mg/dL
- Children: 260 (155) mg/dL
- DNA mutation
- Tendon xanthomas in the patient or in a first- or second-degree relative
- Family history of myocardial infarction at age <50 in a second-degree relative or at age <60 in a first-degree relative or family history of total cholesterol >290 mg/dL in an adult first- or second-degree relative or 260 (155) mg/dL in a child or sibling aged <16 years

Rating
The Netherlands: Dutch Lipid Clinic criteria
- 1 point: A first-degree relative with premature CVD or LDL-C >95th percentile, or personal history of premature peripheral or cerebrovascular disease, or LDL-C between 155 and 189 mg/dL
- 2 points: A first-degree relative with tendinous xanthoma or corneal arcus, or a first-degree relative child (<18 years) with LDL-C >95th percentile, or personal history of CAD
- 3 points: LDL-C between 190 and 249 mg/dL
- 4 points: Presence of corneal arcus in patients <45 years old
- 5 points: LDL-C between 250 and 329 mg/dL
- 6 points: Presence of a tendon xanthoma
- 8 points: LDL-C >330 mg/dL, or functional mutation in the LDLR gene

Risk
- Possible FH (3–5 points)
- Probable FH (6–7 points)
- Definite FH (≥8 points)
## FH Diagnostic Categories

### AHA Scientific Statement

**The Agenda for Familial Hypercholesterolemia**

**A Scientific Statement From the American Heart Association**

<table>
<thead>
<tr>
<th>ICD-10 Category</th>
<th>Clinical Criteria</th>
<th>With Genetic Testing Performed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heterozygous FH</td>
<td>LDL-C ≥160 mg/dL (4 mmol/L) for children and ≥190 mg/dL (5 mmol/L) for adults and with 1 first-degree relative similarly affected or with premature CAD or with positive genetic testing for an LDL-C–raising gene defect (LDL receptor, apoB, or PCSK9)</td>
<td>Presence of 1 abnormal LDL-C–raising (LDL receptor, apoB or PCSK9) gene defect</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diagnosed as heterozygous FH if gene-raising defect positive and LDL-C &lt;160 mg/dL (4 mmol/L)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Occasionally, heterozygotes will have LDL-C &gt;400 mg/dL (10 mmol/L); they should be treated similarly to homozygotes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Presence of both abnormal LDL-C–raising (LDL receptor, apoB or PCSK9) gene defect(s) and LDL-C–lowering gene variant(s) with LDL-C &lt;160 mg/dL (4 mmol/L)</td>
</tr>
<tr>
<td>Homozygous FH</td>
<td>LDL-C ≥400 mg/dL (10 mmol/L) and 1 or both parents having clinically diagnosed familial hypercholesterolemia, positive genetic testing for an LDL-C–raising (LDL receptor, apoB, or PCSK9) gene defect, or autosomal-recessive FH</td>
<td>Presence of 2 identical (true homozygous FH) or nonidentical (compound heterozygous FH) abnormal LDL-C–raising (LDL receptor, apoB or PCSK9) gene defects; includes the rare autosomal-recessive type</td>
</tr>
<tr>
<td></td>
<td>If LDL-C &gt;560 mg/dL (14 mmol/L) or LDL-C &gt;400 mg/dL (10 mmol/L) with aortic valve disease or xanthomata at &lt;20 y of age, homozygous FH highly likely</td>
<td>Occasionally, homozygotes will have LDL-C &lt;400 mg/dL (10 mmol/L)</td>
</tr>
<tr>
<td>Family history of FH</td>
<td>LDL-C level not a criterion; presence of a first-degree relative with confirmed FH</td>
<td>Genetic testing not performed</td>
</tr>
</tbody>
</table>

Gidding, S. Circulation. 2015;132: In Press
Role of Genetic Testing

Many patients with phenotype may not have mutations and many with mutations may not have typical phenotypic presentations. Availability of genetic testing varies by geographic region, and type of testing available. Insurance coverage also varies based on insurance and area of country.

Proposed Treatment Protocols

1. **Initial drug monotherapy**
   - High-intensity Statin Therapy (>50% LDL-C reduction)
     - Rosuvastatin or atorvastatin
   - If LDL-C above goal after 3 months of therapy and patient is adherent, proceed to two-drug combination
     - Rosuvastatin or Atorvastatin
     - Ezetimibe
   - If LDL-C above goal after 3 months of therapy and patient is adherent, proceed to three-drug combination
     - Rosuvastatin or Atorvastatin
     - Ezetimibe
     - PCSK9 inhibitors
     - Colesevelam or other bile acid sequestrant
     - Niacin
   - If LDL-C above goal after 3 months of therapy and patient is adherent, proceed to complex-therapy combination

2. **Two-drug Combination**

3. **Three-drug Combination**

4. **Complex-therapy Combination**

   - Consider four-drug combination† and LDL Apheresis
Until cardiovascular outcomes trials are completed with PCSK9 inhibitors, these drugs should be considered heterozygous FH patients without ASCVD who have LDL-C >130 mg/dL (non-HDL-C >160 mg/dL) while on maximally-tolerated statin (+/- ezetimibe) therapy

Strength: B     Quality: Moderate
Lipids

Per cent reduction in LDL cholesterol following high-intensity statin therapy: potential implications for guidelines and for the prescription of emerging lipid-lowering agents

Paul M Ridker*, Samia Mora, and Lynda Rose, on Behalf of the JUPITER Trial Study Group

The Center for Cardiovascular Disease Prevention, Brigham and Women’s Hospital, Harvard Medical School, 900 Commonwealth Avenue, Boston, MA 02215, USA

Received 12 November 2015; revised 4 December 2015; accepted 21 January 2016

Conclusions

As documented for low- and moderate-intensity regimens, variability in % LDL reduction following high-intensity statin therapy is wide yet the magnitude of this % reduction directly relates to efficacy. These data support guideline approaches that incorporate % reduction targets for statin therapy as well as absolute targets, and might provide a structure for the allocation of emerging adjunctive lipid-lowering therapies such as PCSK9 inhibitors should these agents prove broadly effective for cardiovascular event reduction.
Change in LDLC on Statin and Event Rates

![Graph showing the relationship between LDL cholesterol change and event rates.]

- **Placebo**
- **No reduction/increase**
- **<50% reduction**
- **≥50% reduction**

Event rate / 1000 person-years:
- 11.2
- 9.2
- 6.7
- 4.8
LDL-C response variability to high-intensity statin therapy & implications for the allocation of PCSK9 inhibitors
Until cardiovascular outcomes trials are completed with PCSK9 inhibitors, these drugs should be considered primarily in: 1) patients with ASCVD who have LDL-C ≥100 mg/dL (non-HDL-C ≥130 mg/dL) while on maximally-tolerated statin (±ezetimibe) therapy; and 2) heterozygous FH patients without ASCVD who have LDL-C ≥130 mg/dL (non-HDL-C ≥160 mg/dL) while on maximally-tolerated statin (±ezetimibe) therapy.

In addition, PCSK9 inhibitor use may be considered for selected high risk patients with ASCVD (e.g., recurrent ASCVD events) who have atherogenic cholesterol levels below the specified values, but above their treatment goals (i.e., LDL-C ≥70 mg/dL [non-HDL-C ≥100 mg/dL]). Such use would be based on clinical judgment, weighing the potential benefits relative to the ASCVD event risk and the risks and costs of therapy.

PCSK9 inhibitor use may also be considered in selected high or very high risk patients who meet the definition of statin intolerance (as previously defined by the NLA Statin Expert Panel) and who require substantial additional atherogenic cholesterol lowering, despite the use of other lipid lowering therapies. Such use would be based on clinical judgment, weighing the potential benefits relative to the ASCVD event risk and the risks and costs of therapy.
Insurance Coverage for PCSK9i in FH Patients

- Documentation, Documentation!
- Know preferred status by Rx provider not Insurer
- Understand Insurer FH criteria, but this can be negotiable
- Physical Exam KEY
- Family History
- Persistence
- Utilization of Support Provided by Pharma
## Base Case and Clinical Outcomes among Patients with FH

<table>
<thead>
<tr>
<th></th>
<th>Person-years of treatment (millions)</th>
<th>Total MACE averted</th>
<th>NNT&lt;sup&gt;+&lt;/sup&gt;</th>
<th>QALYs gained&lt;sup&gt;^&lt;/sup&gt;</th>
<th>Incremental Drug Costs&lt;sup&gt;^&lt;/sup&gt; (million $)</th>
<th>Incremental Costs, Other CV Care&lt;sup&gt;^&lt;/sup&gt; (million $)</th>
<th>ICER ($/QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statin§</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statin + Ezetimibe</td>
<td></td>
<td>,¶</td>
<td>22.3</td>
<td>115,900</td>
<td>77</td>
<td>250,600</td>
<td>40,359</td>
</tr>
<tr>
<td>Statin + PCSK9 inhibitor**,¶</td>
<td></td>
<td>23.7</td>
<td>324,200</td>
<td>28</td>
<td>665,200</td>
<td>210,516</td>
<td>-17,304</td>
</tr>
</tbody>
</table>

Institute for Clinical and Economic Review, 2015
https://mail.nyumc.org/owa/redir.aspx?C=XIMkhpTnZUiOQGNCa7lJY5YzBdSOVdMIlXiT6pUj8rvvV8x0tFi8mjDLhPMD8r2gaAgJ1naw.&URL=http%3a%2f%2fcepac.icer-review.org%2fwpccontent%2fuploads%2f2015%2f04%2fFinal-Report-for-Posting-11-24-15.pdf
What is the frequency of FH in the US?

Prevalence of Familial Hypercholesterolemia in the 1999 to 2012 United States National Health and Nutrition Examination Surveys (NHANES)

Sarah D. de Ferranti, MD, MPH; Angie Mae Rodday, PhD, MS; Michael M. Mendelson, MD, SM; John B. Wong, MD; Laurel K. Leslie, MD, MPH; R. Christopher Sheldrick, PhD

Race/Ethnicity

Overall Incidence 1:250 in US

Now lets do the math ... 

- ICER $/QALY for FH = $ 290,000 based on 1/500 HeFH
- ICER estimate 605,000 in 2015
- SO real # is 1.2 million
- FH (FAMILIAL Hypercholesterolemia) impacts families (Average US family size ?)
- The average household size for the U.S. in 2015 is 2.6 people per household. It is calculated by dividing the household population by total households
- SO perhaps real QALY should be 290,000/2/2 ?

- $ 100,000.00 QALY at minimum!

http://www.arcgis.com
Lipoprotein(a) and FH

- Lp(a) is increased in patients with FH and associated with increased ASCVD risk
- Lp(a) is associated with increased risk of Aortic Stenosis (Seen in patients with homozygous FH)
- Lp(a) is lowered by PCSK9i (But NOT an approved indication)
- Lp(a) may be an additional target when elevated in patients with FH for which PCSK9i can be utilized in the future

Thanassoulis, G JLR 2016 Lipoprotein(a) in Calcific Aortic Valve Disease: Article in Press
Lipoprotein (a) and the LDL Receptor
Reduction in Lipoprotein(a) with PCSK9 Monoclonal Antibody Evolocumab (AMG 145)
A Pooled Analysis of More than 1,300 Patients in 4 Phase II Trials

<table>
<thead>
<tr>
<th></th>
<th>Evolocumab Q2W</th>
<th></th>
<th>Evolocumab Q4W</th>
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<tbody>
<tr>
<td></td>
<td>70 mg</td>
<td>105 mg</td>
<td>140 mg</td>
</tr>
<tr>
<td>Lipoprotein (a) Percentage Change From Baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>-13.8%*</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>-25.2%*</td>
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<td></td>
<td></td>
<td>-29.5%*</td>
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<tr>
<td></td>
<td>280 mg</td>
<td>350 mg</td>
<td>420 mg</td>
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<td></td>
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<td>-18.7%*</td>
<td></td>
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<td></td>
<td></td>
<td>-21.3%*</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>-24.5%*</td>
<td></td>
</tr>
</tbody>
</table>

Error bars represent standard error. * P < 0.001

Alirocumab: Lp(a) Reductions in ODYSSEY Combo II, Long Term, FH I and FH II Studies

-29.3 -27.8 -25.2 -30.3
-3.7 -6.1 -7.5 -10

LS mean (SE) % change from baseline to Week 24

All comparisons vs. placebo are $P<0.0001$

Adjusted mean (SE) shown for Lp(a). LLT = lipid-lowering therapy.
Robinson, Farnier. Presented at the ESC; Barcelona, August 31, 2014.
Future Directions of PCSK9i in FH

- Pediatrics
- Early Combination Therapy
- Role of Genetic Testing
- Unknown impacts
Pediatric PCSK9i Trials

HAUSER-RCT Trial Assessing Efficacy, Safety and Tolerability of PCSK9 inhibition in Pediatric Subjects with Genetic LDR Receptor Disorders (Evolocumab)

Children with Genetic LDL Receptor Disorders (efficacy and safety trial)

Not Enrolling yet
Robinson, J. Emerging innovative therapeutic approaches targeting PCSK9 to lower lipids. Accepted Article, doi: 10.1002/cpt.281
LDL Cholesterol “Burden”

- Homozygous FH
  - Threshold for CHD: 12.5 years
  - Start high dose statin

- Heterozygous FH
  - 35 years
  - 48 years
  - 53 years
  - Start low dose statin

- Without FH

- Female sex
- Smoking
- Hypertension
- Diabetes
- ↑Triglycerides
- ↓HDL-C
- ↑Lipoprotein(a)
Genetic Testing in FH

• Genetic Testing not yet “Gold Standard” in US
• Regional differences in availability and cost.
• Overlap exists between phenotype and genotype
• Variability in testing technology and genes screened
• Rarely required for diagnosis, but if so, and positive still does not guarantee approval
• May be an adjunct to risk assessment in future.

Source: ClinicalTrials.gov
Targeting PCSK9 for therapeutic gains: Have we addressed all the concerns?

Yajnavalka Banerjee a, *, Raul D. Santos b, Khalid Al-Rasadi c, Manfredi Rizzo d, e

a Department of Biochemistry, College of Medicine and Health Sciences, Sultan Qaboos University, Muscat, Oman
b Lipid Clinic Heart Institute (InCor), University of Sao Paulo Medical School Hospital, Sao Paulo, Brazil
c Department of Clinical Biochemistry, Sultan Qaboos University Hospital, Muscat, Oman
d Department of Internal Medicine and Medical Specialties, University of Palermo, Italy
e Euro-Mediterranean Institute of Science and Technology, Italy
Life Cycle of PCSK9 and its important pleiotropic functions

Multiple Cell-Signaling Pathways
- Protein Ubiquitination (SQSTM1)
- Xenobiotic Metabolism
- Cell Cycle
- Response to stress

Pleiotropic Actions of PCSK9

PCSK9’s Lipid Homeostatic Activity via Regulation of LDLR Degradation
Additional lipid effects of PCSK9 such as its role in lipoprotein synthesis are not shown (Refer to text for details)

Hepatic Regeneration

Neuronal Functions
- Cortical Neuron Differentiation
- Neuronal Apoptosis Regulation
- Role in Alzheimer’s Disease

Anti-viral Activity
Antimalarial Activity
Degradation of Na+-channels in Renal Cells
Pancreatic Integrity and Glucose homeostasis
Summary

• FH is a common disorder with multiple monogenic causes, LDL-R most often seen
• PCSK9 plays an important role in regulating the LDL-R
• PCSK9 inhibition has been demonstrated to be safe and efficacious in patients with both HoFH and HeFH
• The diagnosis and documentation of such is an important part of obtaining PCSK9i approval for use in the US
• Several organizations and associations have already published guidance for PCSK9i utilization and these offer the practitioner guidance when dialoging with payors
• There may be a role for PCSK9i in patients with FH and elevated Lp(a) levels
• The role of genetic testing is evolving in the US.
• The use in of PCSK9i in pediatric patients has yet to be determined