PCSK9 for LDL Cholesterol Reduction: What have we learned from clinical trials?

Slide deck kindly supplied as an educational resource by
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Part I: The rationale for PCSK9 inhibition

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Why do we need more LDL reducing drugs?

- Growing number of statin adverse patients with limited alternatives
- Special populations (e.g. FH and severe hypercholesterolemia) do not achieve optimal LDL-C levels
- Numerous cardiovascular end point trials have confirmed more LDLc reduction results in more CVD reduction
- European, Canadian, NCEP-ATP III guidelines continue to lower LDLc goal in high risk and even lower risk CVD patients
Proprotein convertase subtilisin/kexin 9 (PCSK9)

- Background: function, genetics and role in LDL-C control
- Potential mechanisms to reduce PCSK9 activity
- Clinical trials
Hypercholesterolemia and early CAD Associated With PCSK9 GOF Mutations

**F216L mutation**

- French proband died from MI
- Age: 49 years
- TC: 441 mg/dL
- LDL-C: 356 mg/dL

**R218S mutation**

- French proband presented with tendinous xanthoma and arcus corneae
- Age: 45 years
- TC: 402 mg/dL
- LDL-C: 293 mg/dL

**Acute Myocardial Infarction**

TC = total cholesterol.


Mean LDL-C Levels in Patients with GOF PCSK9 Mutations

- Control: 105
- D35Y: 249
- L108R: 266
- S127R: 287
- F216L: 227
- R218S: 216
- D374Y: 350

PCSK9: Rapid Progress From Discovery to Clinic

- Adenoviral ↑ expression in mice
- PCSK9 KO mouse ↓ LDL-C
- PCSK9 LOF mutations found with 28% ↓ LDL-C and 88% ↓ 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 (NARC-1) discovered
PCSK9 GOF mutations associated with ADH

Plasma PCSK9 binds to LDLr

LDL-C in mice and non-human primates treated with anti-PCSK9 mAb

Low LDL-C and decreased CAD associated with PCSK9 loss of function mutations

Case Reports of Patients Double Loss-of-Function PCSK9 Mutations


- 21 year-old Zimbabwean woman had no measurable PCSK9 and a LDL-C of 15. (Atherosclerosis. 2007;193: 445-448)

- 49 year-old French male had no detectable PCSK9 levels and a LDL-C of 16. (Arterioscler Thromb Vasc Biol. 2009;29:2192-2197)
Mean LDL-C Levels in Patients with LOF PCSK9 Mutations

<table>
<thead>
<tr>
<th>Mutation</th>
<th>LDL-C Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>105</td>
</tr>
<tr>
<td>R46L</td>
<td>88</td>
</tr>
<tr>
<td>R97</td>
<td>56</td>
</tr>
<tr>
<td>G106R</td>
<td>89</td>
</tr>
<tr>
<td>Y142X</td>
<td>53</td>
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<tr>
<td>C679X</td>
<td>68</td>
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</table>

Association of PCSK9 Mis-sense/LOF Variant R46L with Early-Onset Myocardial Infarction

Table 1. Association of PCSK9 Missense Variant R46L with Early-Onset Myocardial Infarction.

<table>
<thead>
<tr>
<th>Site</th>
<th>Study</th>
<th>No. of Case Patients</th>
<th>No. of Controls</th>
<th>Frequency of Minor L Allele Case Patients</th>
<th>Frequency of Minor L Allele Controls</th>
<th>Odds Ratio for Early-Onset Myocardial Infarction (95% CI)*</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finland</td>
<td>FINRISK</td>
<td>209</td>
<td>210</td>
<td>1.3</td>
<td>4.1</td>
<td>0.30 (0.11–0.84)</td>
<td>0.02</td>
</tr>
<tr>
<td>Sweden</td>
<td>Malmö Diet and Cancer Study — cardiovascular cohort</td>
<td>150</td>
<td>149</td>
<td>0.7</td>
<td>2.0</td>
<td>0.32 (0.07–1.61)</td>
<td>0.17</td>
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<tr>
<td>Spain</td>
<td>Registre Gironi del Cor (REGICOR)</td>
<td>361</td>
<td>361</td>
<td>1.0</td>
<td>2.8</td>
<td>0.35 (0.15–0.82)</td>
<td>0.02</td>
</tr>
<tr>
<td>Seattle</td>
<td>Heart Attack Risk in Puget Sound</td>
<td>542</td>
<td>631</td>
<td>0.9</td>
<td>1.9</td>
<td>0.45 (0.21–0.98)</td>
<td>0.049</td>
</tr>
<tr>
<td>Boston</td>
<td>Massachusetts General Hospital Premature Coronary Artery Disease Study</td>
<td>192</td>
<td>266</td>
<td>1.4</td>
<td>2.3</td>
<td>0.59 (0.21–1.69)</td>
<td>0.46</td>
</tr>
<tr>
<td>Combined analysis</td>
<td></td>
<td>1454</td>
<td>1617</td>
<td>0.99</td>
<td>2.4</td>
<td>0.40 (0.26–0.61)</td>
<td>0.00002</td>
</tr>
</tbody>
</table>

* CI denotes confidence interval.
The Role of PCSK9 in the Regulation of LDL Receptor Expression
Statin Effect on PCSK9 & LDL receptor

Blood

LDL Particle

Endocytosis

Clathrin-Coated vesicle

Recycling of LDL-R

Endosome

Hepatocyte

Golgi Apparatus

HMG-CoA

SREBP-2

Endoplasmic Reticulum

Nucleus

Free Cholesterol
Secreted PCSK9 forms a complex with the EGF-A domain of the LDLR extracellular domain (ECD), leading to endocytosis of the PCSK9-LDLR complex and subsequent degradation of the LDLR.

Horton JD, Cohen JC, and Hobbs HH. J Lipid Research 2009;50:S172-177
Approaches to Reducing PCSK9 interaction with LDL receptor

- **Bind plasma PCSK9**
  - Monoclonal antibodies (Regeneron/Sanofi, Amgen, Genentech, Novartis, Pfizer)
  - Adnectins (Adnexitis/BMS)

- **Reduce PCSK9 synthesis**
  - siRNA (Alnylam)
Impact of an PCSK9 mAb on LDL Receptor Expression
Evolution of Therapeutic Monoclonal Antibodies

- **mouse mAb**
  - mAbs: rituximab, cetuximab
  - mouse variable
  - mouse constant
  - no repeated dosing

- **chimeric**
  - mAbs: trastuzumab, bevacizumab
  - all mouse variable
  - human constant
  - time-consuming to create

- **humanized**
  - mAbs: adalimumab, panitumumab
  - part mouse variable
  - human constant
  - time-consuming to create

- **human mAb**
  - human variable
  - human constant
  - repeated dosing possible

Potential immune response to therapeutic antibody