Accumulating Clinical data on PCSK9 Inhibition: Key Lessons and Challenges

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Brigham and Women’s Hospital, Boston MA
1961 Framingham Heart Study: factors of risk

1972 Bill Friedewald, Bob Levy, Don Fredrickson
Formula to estimate plasma LDL

1973 Michael Brown and Joseph Goldstein
Identification of LDLr mutations in FH

1976 Akira Endo
identification of mevastatin as an inhibitor of HMG-CoA (Sankyo)

1994 Scandinavian Simvastatin Survival Study

2003 Abifabel M et al, Gain of function mutation in PCSK9 as a cause of FH

2005 Cohen et al, loss of function PCSK9 mutation

2008 JUPITER: Event reduction and safety driving LDL from 100mg/dL to below 50 mg/dL

2013 Introduction of three new classes of therapy for aggressive LDL reduction

2015 Initial approval of first PCSK9 inhibitors
1. LDL-C is a strong, independent predictor of future CV events
2. Statins Lower LDL-C
3. The level of LDL-C achieved after starting statin therapy predicts recurrent event rates ("lower is better")

Statin Therapy and LDL Cholesterol: The Primary Pharmacologic Target for Cardiovascular Event Reduction

Recurrence of Myocardial Infarction or Coronary Death

LDL-C ≥ 70 mg/dL
(>1.8 mmol/l)

LDL-C < 70 mg/dL

"Residual Risk"

JUPITER
Outcomes bases on Achieving LDL-Cholesterol (<50 mg/dL)

Ridker et al Lancet 2009
JUPITER
Predicted vs Observed Benefit Based on Percent LDL Reduction

Relative Risk Reduction (%) vs % Reduction in LDL-C
JUPITER
Event Reduction At All Levels of Baseline LDLC

Baseline LDLC Levels  N

LDLC ≤100 mg/dL (2.6 mmol/L)  6,269
LDLC <90 mg/dL (2.3 mmol/L)  3,687
LDLC <80 mg/dL (2.0 mmol/L)  2,033
LDLC <70 mg/dL (1.8 mmol/L)  1,022
LDLC <60 mg/dL (1.5 mmol/L)  511

All Participants  17,802

On Treatment
LDL < 50 mg/dL
(<1.3 mmol/L)
25% On Treatment
LDL < 25 mg/dL
(<0.64 mmol/L)
## JUPITER

### Safety of Lowering LDL-C to Below 50 mg/dL

<table>
<thead>
<tr>
<th>Condition</th>
<th>LDL-C &gt;50mg/dL (&gt;1.3 mmol/L)</th>
<th>LDL-C &lt; 50mg/dL (&lt;1.3 mmol/L)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myalgia</td>
<td>4.0</td>
<td>3.5</td>
<td>0.49</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>14.0</td>
<td>14.4</td>
<td>0.32</td>
</tr>
<tr>
<td>Respiratory</td>
<td>8.0</td>
<td>8.9</td>
<td>0.08</td>
</tr>
<tr>
<td>CNS</td>
<td>8.3</td>
<td>8.3</td>
<td>0.60</td>
</tr>
<tr>
<td>Memory Loss</td>
<td>0.2</td>
<td>0.1</td>
<td>0.04</td>
</tr>
<tr>
<td>Renal</td>
<td>4.3</td>
<td>4.8</td>
<td>0.30</td>
</tr>
<tr>
<td>Cancer</td>
<td>1.5</td>
<td>1.4</td>
<td>0.36</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.2</td>
<td>1.6</td>
<td>0.70</td>
</tr>
<tr>
<td>ALT&gt;3x ULN</td>
<td>0.7</td>
<td>0.7</td>
<td>0.78</td>
</tr>
<tr>
<td>CK&gt;10x ULN</td>
<td>0.01</td>
<td>0.01</td>
<td>0.99</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>2.5</td>
<td>2.6</td>
<td>0.29</td>
</tr>
</tbody>
</table>

Hsia et al, JACC ;57:1666-75
Why Are Additional Agents Beyond Statins Needed?

- Residual risk is substantial
- Statin intolerance is a real issue in clinical practice
- By looking only at average response rates in our meta-analyses and guidelines, we have systematically ignored the wide variation that exists in individual lipid response to statin therapy.
- This wide variation in response impacts directly on clinical outcomes, yet has been at least partially forgotten in the US based guidelines that have moved away from cholesterol targets.
- We need to consider individual statin response, not only population statin response.
What Pharmacologic Strategies for LDL Reduction Beyond Statins are Emerging?

- **Cholesterol Absorption Inhibitor**
  - Ezetimibe

- **CETP Inhibitors**
  - Torcetrapib, Dalcetrapib, Anacetrapib, Evacetrapib

- **Microsomal Triglyceride Transfer Protein (MTP) Inhibition**
  - Lomitapide

- **Anti-Sense Oligonucleotide (ASO) binding to APO B coding RNA**
  - Mipomersen

- **PCSK9 inhibitors – monoclonal antibodies**
  - Alirocumab
  - Bococizumab
  - Evolocumab

- **PCSK9 inhibitors – other modalities**
  - Small molecule inhibitors
  - Adnectins
  - Therapeutic RNAi

- **ETC-1002** (dual modulator ATP-citrate lyase/AMP-activated protein kinase)
- **MBX-8025** (PPAR-δ agonist)
Monoclonal Antibodies to PCSK9 and Recycling of the LDL Receptor - Phase II

Effective as monotherapy
- Koren Lancet 2012;380:1995-06
- Sullivan JAMA 2012;308:2497-06

Effective as statin add-on
- Stein Lancet 2012;380:29-36
- Stein NEJM 2012;366:1108-18
- McKenney JACC 2012;59:1108-18
- Guigliano Lancet 2012;380:2007-17
- Roth NEJM 2012;367:1891-900
- Blom NEJM 2014;370:1809-19

Effective in statin intolerance
- Stroes JACC 2014;63:2541-8

Effective in heterozygous FH (reduced LDLr activity)
- Raal Circulation 2012;126:2408-17

Effective in homozygous FH (LDLr defective)
- Stein Circulation 2013;128:2113-20
Monoclonal Antibodies to PCSK9 and Recycling of the LDL Receptor – Phase III

Evolocumab (Amgen)
Fourier
NCT 01764633

Alirocumab (Sanofi/Regeneron)
ODYSSEY
NCT 01663402

Bococizumab (Pfizer)
SPIRE I, SPIRE II
NCT 01975376
NCT 01975389

> 70,000 + patients worldwide
Sabatine et al for the OSLER Investigators NEJM March 15, 2015 (evolocumab)
Robinson et al for the ODYSSEY Investigators NEJM March 15, 2015 (alirocumab)
**FIGURE 1** Cardiovascular Events in Long-Term PCSK9 Trials

<table>
<thead>
<tr>
<th></th>
<th>Event Rate (%)</th>
<th>Events</th>
<th>Total Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>3.3</td>
<td>26/788</td>
<td>788</td>
</tr>
<tr>
<td>Alirocumubab</td>
<td>1.7</td>
<td>27/1,550</td>
<td>1,550</td>
</tr>
<tr>
<td><strong>ODYSSEY LONG TERM</strong></td>
<td></td>
<td><strong>63/2,338</strong></td>
<td><strong>2,338</strong></td>
</tr>
<tr>
<td>SOC</td>
<td>2.2</td>
<td>31/1,489</td>
<td>1,489</td>
</tr>
<tr>
<td>Evolocumubab</td>
<td>1.0</td>
<td>29/2,976</td>
<td>2,976</td>
</tr>
<tr>
<td><strong>OSLER-1 and OSLER-2</strong></td>
<td></td>
<td><strong>60/4,465</strong></td>
<td><strong>4,465</strong></td>
</tr>
</tbody>
</table>

HR 0.52 [0.31, 0.90] for Placebo vs. Alirocumubab.

HR 0.47 [0.28, 0.78] for SOC vs. Evolocumubab.

Gugliano, RP, Sabatine, MS. JACC 2015;24:2638-51
**FIGURE 1** Cardiovascular Events in Long-Term PCSK9 Trials

<table>
<thead>
<tr>
<th>Group</th>
<th>Event Rate (%)</th>
<th>Total Events (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ODYSSEY</td>
<td>3.3</td>
<td>53</td>
</tr>
<tr>
<td>LONG TERM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alirocumub</td>
<td>1.7</td>
<td></td>
</tr>
<tr>
<td>SOC OSLER-1</td>
<td></td>
<td>60</td>
</tr>
<tr>
<td>Evolocumub</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OSLER-2</td>
<td>1.0</td>
<td></td>
</tr>
</tbody>
</table>

Event Rate: HR 0.52 [0.31, 0.90], HR 0.47 [0.28, 0.78]

Gugliano, RP, Sabatine, MS. JACC 2015;24:2638-51
FIGURE 1 Cardiovascular Events in Long-Term PCSK9 Trials

High Dose Statins (%)

- ODYSSEY LONG TERM:
  - Placebo: 26/788 (3.3%)
  - Alirocumab: 27/1,550 (1.7%)

- OSLER-1 and OSLER-2:
  - SOC: 31/1,489 (2.2%)
  - Evolocumab: 29/2,976 (1.0%)

HR 0.52 [0.31, 0.90] (Placebo vs. Alirocumab)
HR 0.47 [0.28, 0.78] (SOC vs. Evolocumab)

Gugliano, RP, Sabatine, MS. JACC 2015;24:2638-51
## Are There Early Side Effect Signals?

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Agent</th>
<th>Drug</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection Site Reaction</td>
<td>Evolocumab</td>
<td>4.3</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>Alirocumab</td>
<td>5.9</td>
<td>4.2</td>
</tr>
<tr>
<td>Arthralgia or Myalgia</td>
<td>Evolocumab</td>
<td>4.6</td>
<td>3.2</td>
</tr>
<tr>
<td></td>
<td>Alirocumab</td>
<td>5.4</td>
<td>2.9</td>
</tr>
<tr>
<td>Neurocognitive Events</td>
<td>Evolocumab</td>
<td>0.9</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td>Alirocumab</td>
<td>1.2</td>
<td>0.5</td>
</tr>
<tr>
<td>Ophthalmologic Events</td>
<td>Alirocumab</td>
<td>2.9</td>
<td>1.9</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Evolocumab</td>
<td>2.8</td>
<td>1.0</td>
</tr>
<tr>
<td>Headache</td>
<td>Evolocumab</td>
<td>3.6</td>
<td>2.1</td>
</tr>
</tbody>
</table>

Sabatine et al for the OSLER Investigators NEJM March 15, 2015
Robinson et al for the ODYSSEY Investigators NEJM March 15, 2015
PCSK9 Inhibitors: From Target Discovery to Phase III in 10 Years

2003
- PCSK9 (NARC-1) discovered
- PCSK9 GOF mutations associated with ADH*

2004
- Adenoviral ↑ expression in mice
- PCSK9 KO mouse LDL-C

2005
- PCSK9 LOF Mutations found with 28% ↓ LDL-C and 88% ↓ CHD risk
  - Humans null for PCSK9 have LDL-C ~15 mg/dL
  - Plasma PCSK9 binds to LDL-R

2006
- First subject treated with PCSK9 mAb
  - ↓ LDL-C in mice and non-human primates treated with anti-PCSK9 mAb

2007
- First Patients with FH / non-FH treated with PCSK9i mAb

2008
- First publication POC in patients

2009
- 1st FDA / EMEA PCSK9i filing
# Major CV Outcome Trials of PCSK9 inhibition

<table>
<thead>
<tr>
<th></th>
<th>PROFICIO Evolocumab</th>
<th>ODYSSEY Alirocumab</th>
<th>SPIRE Bococizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lipid Lowering</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HeFH</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>HoFH</td>
<td>✓</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>CVD / CVD RE</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Statin Intolerance and/or Monotherapy</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Imaging</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>✓</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td><strong>CV Outcomes</strong></td>
<td>Fourier</td>
<td>Outcomes</td>
<td>1</td>
</tr>
<tr>
<td>Prior MI / Post ACS</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Prior Stroke</td>
<td>✓</td>
<td>—</td>
<td>✓</td>
</tr>
<tr>
<td>PVD</td>
<td>✓</td>
<td>—</td>
<td>✓</td>
</tr>
<tr>
<td>Diabetes without CHD</td>
<td>—</td>
<td>—</td>
<td>✓</td>
</tr>
<tr>
<td>CKD without CHD</td>
<td>—</td>
<td>—</td>
<td>✓</td>
</tr>
<tr>
<td>Statin Intolerance</td>
<td>—</td>
<td>?</td>
<td>✓</td>
</tr>
</tbody>
</table>
Major CV Outcome Trials of PCSK9 inhibition: timelines

- **Pfizer – Bococizumab**
  - CVOT: SPIRE-1
  - LDL-C 70–100 mg/dL
  - Lipid Lowering Studies
  - CVOT: SPIRE-2 with LDL-C ≥100 mg/dL

- **Sanofi/Regen – Alirocumab**
  - CVOT: ODYSSEY Outcomes
  - Lipid Lowering Studies

- **Amgen – Evolocumab**
  - CVOT: FOURIER
  - Lipid Lowering

Years: 2011-2018
Is aggressive LDL-C reduction with PCSK9 inhibition safe and clinically effective?

Can we lower LDL-C too far?

What is the evidence for LDL-C reduction even when LDL-C levels are low?

Is LDL lowering without inflammation inhibition effective?

Will our patients live longer and more productive lives?

Why Completing the Phase III Trials Is Crucial
We are exceptionally lucky to be in era with ongoing direct tests of both the LDL hypothesis and the inflammation hypothesis.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Event Reduction?</th>
<th>LDL-Lowering?</th>
<th>CRP-Lowering?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statins</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Ezetimibe + Statin</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Evolocumab</td>
<td>??</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Alirocumab</td>
<td>??</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Bococizumab</td>
<td>??</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Canakinumab</td>
<td>??</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Low Dose MTX</td>
<td>??</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>