LDL Reduction Therapy – What is the Place of PCSK9 Inhibitors?

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April 22, 2017
Overview of Talk

• Review of pathogenesis of atherosclerosis and residual risk
• Beyond LDL: Overview of other biomarkers in CV risk stratification
• Review mechanism of action of PCSK9 inhibitors
• Review of recent clinical trials with PCSK9 inhibitors
• Outcome Trial Results with PCSK9 Inhibitors (Finally)
• New therapies on the horizon
Pathogenesis of Atherosclerosis

• Atherosclerosis is a DIFFUSE DISEASE driven by inflammation, atherogenic lipoproteins and in the acute phase platelet aggregation.

• A multi biomarker strategy is needed for better risk factor stratification.

Libby, NEJM 2013
- Serial angiographic studies reveal culprit lesion of a future acute MI often does not cause significant stenosis.

- Plaque can cause outward expansion of the artery wall which accommodates the growth of the plaque and minimizes luminal narrowing.

- Luminal stenosis occurs late in the process of atherosclerosis.

- Angiography is an assessment of luminal narrowing.
Low Grade Stenoses Cause Most Infarctions

Coronary Stenosis Severity Prior to MI

- 50-70% Stenosis: 14%
- >70% Stenosis: 18%
- <50% Stenosis: 68%

From Nissen NLA Presentation  3/19/16
Medical Management = PCI

- Landmark clinical trials such as COURAGE show that medical treatment of chronic angiographically defined CAD has the same outcome as percutaneous coronary intervention.
- The cornerstone of medical management of CAD is treatment of dyslipidemia.
**Key Finding:**

- Intensive lipid-lowering treatment with atorvastatin for 18 months reduced progression of coronary atherosclerosis compared with pravastatin in CAD patients.

Aggressive LDL-C Lowering Therapy Does Not Eliminate CVD Risk

Significant Residual Risk Remains Untreated

IMPROVE-IT Study*

Residual risk: Due to increased triglycerides, elevated Lp(a), other untreated risk factors

Cannon et al NEJM 2015
Atherosclerosis is a Gradient Driven Process

LDL particle number (LDL-P), as opposed to size, is a key driver of atherogenic plaque formation.

A gradient driven process, LDL particles invade the arterial wall and set in motion the cascade of events that leads to atherosclerosis.

After adjustment for LDL-P concentration, particle subclass and size do not impact outcomes.

1. Fredrickson et al. NEJM 1967; 276: 148
Beyond LDL Cholesterol

- **LDL-C**: amount of cholesterol in LDL particles
- **LDL-P**: number of LDL particles
- **Apo-B**: reflection of number of atherogenic particles
- **Non-HDL**: (Total cholesterol - HDL) amount of cholesterol in atherogenic particles
- **Low HDL and high TG** are associated with higher LDL-P
  - If triglycerides are high there will be less space for cholesterol and it may take more LDL particles to carry a given amount of cholesterol
MESA: LDL-P and LDL-C Discordance

MetSyn

- LDL-P > LDL-C: 54%
- Concordant: 33%
- LDL-P < LDL-C: 16%

**LDL-C underestimates LDL-attributable risk**

**LDL-C overestimates LDL-attributable risk**

Lipoprotein A is a modified form of LDL in which apolipoprotein(a) is bound to apolipoprotein B.

Major landmark RCTs show Lp(a) is associated with less benefit of statins and associated with residual CVD risk:

- 4S
- LIPID
- HPS
- JUPITER
- AIM HIGH
PCSK9 Regulates LDLR Turnover Through Increased Intracellular Degradation
Blocking PCSK9 Activity Inhibits Intracellular Degradation of LDLR
Odyssey Trial Results

![Graph showing calculated LDL cholesterol levels over time. The graph compares Placebo + statin therapy at maximum tolerated dose ± other LLT to Alirocumab + statin therapy at maximum tolerated dose ± other LLT.](image)

**Figure 2. Calculated LDL Cholesterol Levels over Time (Intention-to-Treat Analysis).**

Calculated LDL cholesterol levels are shown in milligrams per deciliter (left axis) and millimoles per liter (right axis). Values above the data points indicate least-squares mean absolute LDL cholesterol levels, and values below the data points indicate least-squares mean percentage changes from baseline. Values below the chart indicate the number of patients with LDL cholesterol values available for the intention-to-treat analysis at each time point; these include levels measured while the study drug was being taken and, in the case of patients who discontinued the study drug but returned to the clinic for assessments, after the study drug was discontinued. Missing data were accounted for with the use of a mixed-effects model with repeated measures. For statin therapy, the maximum tolerated dose was the highest dose associated with an acceptable side-effect profile. LLT denotes lipid-lowering therapy.
Significant Reductions in Secondary Lipid Parameters at Week 24

All patients on background of maximally-tolerated statin ± other lipid-lowering therapy.

<table>
<thead>
<tr>
<th></th>
<th>Non-HDL-C</th>
<th>Apo B</th>
<th>Lp(a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alirocumab</td>
<td>-52%</td>
<td>-54%</td>
<td>-26%</td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
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</table>

LS mean difference versus placebo:
-52% \( P<0.0001 \)
-54% \( P<0.0001 \)
-26% \( P<0.0001 \)
Osler Trial Results

Figure 1. Low-Density Lipoprotein (LDL) Cholesterol Levels.

LDL cholesterol was measured in both the OSLER-1 and OSLER-2 trials at 12, 24, and 48 weeks and in the OSLER-1 trial at 4 and 36 weeks. Shown are median values with 95% confidence intervals in the two studies. Values for the baseline measurement were obtained before randomization into a parent study. The dashed lines indicate that patients were receiving either evolocumab or placebo during the period from baseline to enrollment into OSLER. In the chart below the graph, the absolute and percentage reductions in the LDL level in the evolocumab group are compared with those in the standard-therapy group and are presented as means. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586.

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Baseline</th>
<th>4</th>
<th>12</th>
<th>24</th>
<th>36</th>
<th>48</th>
</tr>
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<tbody>
<tr>
<td>Standard therapy</td>
<td>1489</td>
<td>394</td>
<td>1388</td>
<td>1376</td>
<td>402</td>
<td>1219</td>
</tr>
<tr>
<td>Evolocumab</td>
<td>2976</td>
<td>864</td>
<td>2871</td>
<td>2828</td>
<td>841</td>
<td>2508</td>
</tr>
<tr>
<td>Absolute reduction (mg/dl)</td>
<td>60.4</td>
<td>73.4</td>
<td>70.4</td>
<td>72.7</td>
<td>70.5</td>
<td></td>
</tr>
<tr>
<td>Percentage reduction</td>
<td>45.3</td>
<td>60.9</td>
<td>58.8</td>
<td>54.0</td>
<td>58.4</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>
OSLER: Effect of Evolocumab on Other Lipid Parameters at 1 Year

- **ApoB**:
  - Week 52 vs baseline: 
    - $P < 0.0001$; $\dagger P < 0.001$; $§ P < 0.01$; $‡ P < 0.05$
  - Evolocumab vs placebo: $§ P < 0.0001$; $¶ P < 0.001$

- **Lp(a)**:
  - Week 52 vs baseline: 
    - $-11%§ (-32 to 4)$
    - $-9%* (-23 to 0)$

- **HDL-C**:
  - Week 52 vs baseline: 
    - $4%‡$
  - Evolocumab vs placebo: $9%*$

- **ApoA1**:
  - Week 52 vs baseline: 
    - $4%*$
  - Evolocumab vs placebo: $5%*$

- **Triglycerides**:
  - Week 52 vs baseline: 
    - $4% (-17 to 34)$
    - $-1% (-19 to 20)$

Error bars represent standard error.
Data in parentheses represent interquartile ranges.

Week 52 vs baseline:
* $P < 0.0001$; † $P < 0.001$; § $P < 0.01$; ‡ $P < 0.05$
Evolocumab vs placebo:
§ $P < 0.0001$; ¶ $P < 0.001$
Glagov Study

970 patients with angiographic CAD with elevated LDL cholesterol ≥80 mg/dl on chronic statin therapy were randomized to monthly subcutaneous evolocumab versus monthly subcutaneous placebo and followed for 76 weeks.

Primary Outcome:
• Change in percent atheroma volume at 78 weeks, was -0.95% in the evolocumab group versus 0.05% in the placebo group (p < 0.001 for between-group comparison).

Secondary outcomes:
• Patients with plaque regression: 64.3% with evolocumab versus 47.3% with placebo (p < 0.001)
• Major adverse cardiac events: 12.2% with evolocumab versus 15.3% with placebo
**Trial design:** Patients with CAD and elevated LDL cholesterol on statin therapy were randomized to subcutaneous evolocumab (n = 484) vs. subcutaneous placebo (n = 486).

**Results**
- Nominal change in percent atheroma volume at 78 weeks: -0.95% in the evolocumab group vs. 0.05% in the placebo group (p < 0.001 for between-group comparison)
- Patients with plaque regression: 64.3% with evolocumab vs. 47.3% with placebo (p < 0.001)
- Major adverse cardiac events: 12.2% with evolocumab vs. 15.3% with placebo

**Conclusions**
- Among patients with angiographic evidence of CAD on chronic statin therapy, the PCSK9 inhibitor evolocumab resulted in a greater change in percent atheroma volume and a greater proportion of patients with plaque regression

Nicholls SJ, et al. JAMA 2016;316:2373-84
Figure 4. Post Hoc Analysis Examining the Relationship Between Achieved LDL-C Level and Change in Percent Atheroma Volume

Local regression (LOESS) curve illustrating the post hoc analysis of the association (with 95% confidence intervals) between achieved low-density lipoprotein cholesterol (LDL-C) levels and the change in percent atheroma volume in all patients undergoing serial IVUS evaluation. Curve truncated at 20 and 110 mg/dL owing to the small number of values outside that range. To convert LDL-C values to mmol/L, multiply by 0.0259.
Trial Design

27,564 high-risk, stable patients with established CV disease (prior MI, prior stroke, or symptomatic PAD)

Screening, Lipid Stabilization, and Placebo Run-in
High or moderate intensity statin therapy (± ezetimibe)

LDL-C ≥70 mg/dL or non-HDL-C ≥100 mg/dL

RANDOMIZED DOUBLE BLIND
Evolocumab SC 140 mg Q2W or 420 mg QM

Follow-up Q 12 weeks

Placebo SC Q2W or QM
Endpoints

- **Efficacy**
  - Primary: CV death, MI, stroke, hosp. for UA, or coronary revasc
  - Key secondary: CV death, MI or stroke

- **Safety**
  - AEs/SAEs
  - Events of interest incl. muscle-related, new-onset diabetes, neurocognitive
  - Development of anti-evolocumab Ab (binding and neutralizing)

- **TIMI Clinical Events Committee (CEC)**
  - Adjudicated all efficacy endpoints & new-onset diabetes
  - Members unaware of treatment assignment & lipid levels
Primary Endpoint

Hazard ratio 0.85
(95% CI, 0.79-0.92)
P<0.0001

CV Death, MI, Stroke, Hosp for UA, or Cor Revasc

Months from Randomization

Placebo

Evolocumab

14.6%
12.6%
Summary for Evolocumab

- ↓ LDL-C by 59%
  - Consistent throughout duration of trial
  - Median achieved LDL-C of 30 mg/dl (IQR 19-46 mg/dl)

- ↓ CV outcomes in patients already on statin therapy
  - 15% ↓ broad primary endpoint; 20% ↓ CV death, MI, or stroke
  - Consistent benefit, incl. in those on high-intensity statin, low LDL-C
  - 25% reduction in CV death, MI, or stroke after 1st year
  - Long-term benefits consistent w/ statins per mmol/L ↓ LDL-C

- Safe and well-tolerated
  - Similar rates of AEs, incl DM & neurocog events w/ EvoMab & pbo
  - Rates of EvoMab discontinuation low and no greater than pbo
  - No neutralizing antibodies developed
Alirocumab Outcome Trial

Giugliano RP, Sabatine MS. JACC 2015;65:2638
Cognition and PCSK9 Inhibitors

Brain synthesizes cholesterol locally

mAb (e.g., evolocumab) are too large to cross the intact blood-brain barrier

Nevertheless meta-analysis* of adverse events from 6 trials in 9581 pts suggested an increased risk with PCSK9 inhibitors: HR 2.3 [1.1, 4.9]

- Event rates low (<1%)
- Unadjudicated, diverse AE terms reported
- Not correlated with LDL-C achieved

Conclusions

In patients with known cardiovascular disease on background statin followed for 20 months

1. No differences btw evolocumab vs placebo
   A. A battery of cognitive tests
   B. Patient-reported everyday cognition
   C. Adverse cognitive events reported by MD

2. No evidence of differences in cognitive tests by achieved nadir LDL-C, even <25 mg/dL
New Therapy on the Horizon

• In contrast to PCSK9 monoclonal antibodies that bind to PCSK9 in blood, Inclisiran is a PCSK9siRNA (Small interfering RNA) is a first-in-class investigational medicine that acts by turning off PCSK9 synthesis in the liver.

• This compound turns off messenger RNA that is responsible for producing PCSK9 protein.
Orion-1 Study: Inhibition of PCSK9 Synthesis Via RNA Interference

- Phase II Randomized Controlled study of 501 patients
- 69% had ASCVD, 24% had diabetes 5%
- Inclisiran was administered either once or twice (90 days after 1st injection)
- One dose of 300mg achieved a mean 51 percent LDL-C reduction, while two doses of 300mg achieved a mean 57 percent reduction.
- Inclisiran was found to be well tolerated with no significant safety issues.
Conclusions

1. Statins are the cornerstone of therapy in patients with hyperlipidemia

2. PCSK9 inhibitors reduce LDL cholesterol and have favorable safety profile and also lower non HDL cholesterol, Lp(a) and maybe an important tool in reducing residual risk

3. Get the LDL as low as you can for secondary prevention