PCSK9 Inhibitors Reduce LDL Cholesterol and CV Events

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Disclosures

• Speaker’s bureau for Sanofi/Regeneron and Amgen
Overview of Talk

• Review of pathogenesis of atherosclerosis and residual risk
• Review mechanism of action of PCSK9 inhibitors
• Review of recent clinical trials with PCSK9 inhibitors
• Outcome Trial Results with PCSK9 Inhibitors
• 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: 68%
- <50% Stenosis: 18%

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.
REVERSAL Study: Plaque Stabilization Associated with Decrease in Biomarkers

Key Finding:

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

PCSK9 Regulates LDLR Turnover Through Increased Intracellular Degradation
Blocking PCSK9 Activity Inhibits Intracellular Degradation of LDLR
PCSK9 Inhibitors

• Currently 2 PCSK9 inhibitors on the market
  • Repatha/ Evolocumab and Praluent/Alirocumab
  • FDA indication for these agents are:
    1. Heterozygous familial hypercholesterolemia (LDL >190)
    2. Homozygous familial hypercholesterolemia (LDL>400) (Repatha only)
    3. or clinical atherosclerotic cardiovascular disease (MI, stroke, TIA, PAD) who require additional lowering of LDL cholesterol (LDL >>100)

New addition to Repatha Label in December 2017:

1. To prevent heart attacks, strokes and coronary revascularizations in adults with cardiovascular disease
2. Can be used alone.
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

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<tr>
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<th>Non-HDL-C</th>
<th>Apo B</th>
<th>Lp(a)</th>
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<tbody>
<tr>
<td>Alirocumab</td>
<td>-52%</td>
<td>-54%</td>
<td>-26%</td>
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<tr>
<td>Placebo</td>
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LS mean (SE) % change from baseline to Week 24

LS mean difference versus placebo:

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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

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.
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 $\geq 70$ mg/dL or non-HDL-C $\geq 100$ mg/dL

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

Placebo SC
Q2W or QM

Follow-up Q 12 weeks

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

Placebo = Statin

Evolocumab

- 15% relative risk reduction vs placebo for CV death, MI, Stroke, hospitalization for UA or coronary revasc (primary composite endpoint)
- 20% relative risk reduction vs placebo for CV death, MI or stroke (secondary composite endpoint).
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
Patient Disposition

Randomized 18,924 patients

Alirocumab (N=9462)  Placebo (N=9462)

Follow-up*: median 2.8 (Q1–Q3 2.3–3.4) years
8242 (44%) patients with potential follow-up ≥3 years

1955 patients experienced a primary endpoint
726 patients died

- Premature treatment discontinuation
  - 1343 (14.2%)  - 1496 (15.8%)

- Blinded switch to placebo (2 consecutive LDL-C values <15 mg/dL)
  - 730 (7.7%)  - Not applicable

- Patients lost to follow-up (vital status)
  - 14  - 9

*Ascertainment was complete for 99.1% and 99.8% of potential patient-years of follow-up for the primary endpoint and all-cause death, respectively
Primary Efficacy Endpoint: MACE

MACE: CHD death, non-fatal MI, ischemic stroke, or unstable angina requiring hospitalization

Number at Risk
- Placebo: 9462
- Alirocumab: 9462

Years Since Randomization
- 0: 8805 (Placebo), 8846 (Alirocumab)
- 1: 8201 (Placebo), 8345 (Alirocumab)
- 2: 3471 (Placebo), 3574 (Alirocumab)
- 3: 629 (Placebo), 653 (Alirocumab)

ARR* 1.6%

HR 0.85
(95% CI 0.78, 0.93)
P=0.0003

*Based on cumulative incidence
Post Hoc Analysis: All-Cause Death by Baseline LDL-C Subgroups

- <80 mg/dL
  - HR 0.89
  - (95% CI 0.69, 1.14)
- 80 to <100 mg/dL
  - HR 1.03
  - (95% CI 0.78, 1.36)
- ≥100 mg/dL
  - HR 0.71
  - (95% CI 0.56, 0.90)

ARR* 1.7%  \( P_{interaction} = 0.12 \)

*Based on cumulative incidence
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 and improving CV outcomes.

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