What’s New in Treating Hyperlipidemia: Update on PCSK9 Inhibition and Treating Hypertriglyceridemia

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Disclosures

- Speaker’s bureau and consultant for Sanofi/Regeneron, Amarin and Amgen
Overview of Talk

- Review of pathogenesis of atherosclerosis and residual risk
- Review mechanism of action of PCSK9 inhibitors
- Outcome Trial Results with PCSK9 Inhibitors
- Results of Recent Improve-It Trial
- 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: 18%
- >70% Stenosis: 14%
- <50% Stenosis: 68%

From Nissen NLA Presentation  3/19/16
**Aggressive LDL-C Lowering Therapy Does Not Eliminate CVD Risk**

*Significant Residual Risk Remains Untreated*

**IMPROVE-IT Study***

![Graph showing CV event percentages for different LDL-C levels.](image)

- **LDL-C = 70 mg/dL**
  - Simvastatin (n=9077): 34.7%
- **LDL-C = 53 mg/dL**
  - Ezetimibe + Simvastatin (n=9067): 32.7%

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

*Cannon et al NEJM 2015*
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:
  - Heterozygous familial hypercholesterolemia (LDL >190)
  - Homozygous familial hypercholesterolemia (LDL>400) (Repatha only)
    - 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:
    - To prevent heart attacks, strokes and coronary revascularizations in adults with cardiovascular disease
    - Can be used alone
Significant Reductions in Secondary Lipid Parameters at Week 24

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

- **Alirocumab**
- **Placebo**

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

- **LS mean difference versus placebo:**
  - Non-HDL-C: -52% \( P<0.0001 \)
  - Apo B: -54% \( P<0.0001 \)
  - Lp(a): -26% \( P<0.0001 \)

Adjusted mean (SE) shown for Lp(a).
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
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

Placebo SC
Q2W or QM

Follow-up Q 12 weeks
Primary Endpoint

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

Placebo = Statin

Evolocumab

Absolute Risk Reduction 2%

Evolocumab has demonstrated:
- 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).

Odyssey Outcomes Trial

Population:
- 18,000 pts 4-52 weeks post-ACS
- Age >40 years

LDL-C at Entry:
- ≥70 mg/dL (1.81 mmol/L)
- On evidence-based medical Rx

Primary Endpoint:
- Composite of
  - CHD death
  - Non-fatal MI
  - Ischemic stroke
  - High-risk UA → hospitalization

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

1343 (14.2%)  1496 (15.8%)
730 (7.7%)     Not applicable
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

• Premature treatment discontinuation
• Blinded switch to placebo (2 consecutive LDL-C values <15 mg/dL)
• Patients lost to follow-up (vital status)
Primary Efficacy Endpoint: MACE

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

Placebo

Alirocumab

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

ARR* 1.6%

Number at Risk

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Alirocumab</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td>9462</td>
<td>9462</td>
</tr>
<tr>
<td>1</td>
<td>8805</td>
<td>8846</td>
</tr>
<tr>
<td>2</td>
<td>8201</td>
<td>8345</td>
</tr>
<tr>
<td>3</td>
<td>3471</td>
<td>3574</td>
</tr>
<tr>
<td>4</td>
<td>629</td>
<td>653</td>
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</tbody>
</table>

*Based on cumulative incidence


ODYSSEY OUTCOMES
<table>
<thead>
<tr>
<th><strong>ODYSSEY</strong></th>
<th><strong>FOURIER</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient Population</strong></td>
<td>Post ACS 2-4-52 Weeks from index event (median 2.6 months)</td>
</tr>
<tr>
<td><strong>Number of Patients</strong></td>
<td>18,924</td>
</tr>
<tr>
<td><strong>Age, years</strong></td>
<td>58 (median)</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td>25%</td>
</tr>
<tr>
<td><strong>LDL-C entry criteria mg/dl (mmol/L)</strong></td>
<td>$&gt; 70$ (1.8)</td>
</tr>
<tr>
<td><strong>Baseline LDL-C mg/dl (mmol/L)</strong></td>
<td>87 (2.3)</td>
</tr>
<tr>
<td><strong>High intensity statin</strong></td>
<td>89%</td>
</tr>
<tr>
<td><strong>PCSK9 Inhibitor Dose Regimen</strong></td>
<td>Alirocumab 75 or 150mg every 2 weeks titrated to target LDL-C (25-50mg/dl)</td>
</tr>
<tr>
<td><strong>Duration of follow-up (years)</strong></td>
<td>2.8 (44% &gt; 3 years)</td>
</tr>
<tr>
<td><strong>Primary Endpoint</strong></td>
<td>4-point: CHD Death MI Ischemic stroke Unstable angina requiring hospitalization</td>
</tr>
<tr>
<td><strong>Absolute Risk Reduction In Primary Endpoint</strong></td>
<td>1.6%</td>
</tr>
<tr>
<td><strong>Number needed to Treat</strong></td>
<td>63</td>
</tr>
</tbody>
</table>
CV Death, MI or Stroke in Patients with and without Peripheral Artery Disease

- **Placebo**
  - N=3,642
  - 27% RRR
  - HR 0.73 (0.59 – 0.91)
  - P=0.0040

- **Evolocumab**
  - 13.0%
  - 3.5% ARR
  - NNT_{2.5y} 29

- No PAD
  - 7.6%
  - 1.4% ARR
  - NNT_{2.5y} 72

- **No PAD**
  - HR 0.81
  - 95% CI (0.73 – 0.90)
  - P<0.001

- **p-interaction** = 0.41

Major Adverse Limb Events

All Patients
N=27,564
42% RRR
HR 0.58
(0.38 – 0.88)
P=0.0093

Restricting to those on High Intensity Statin only HR 0.56 (0.33 – 0.93), P=0.022

Outcome	HR	95% CI
MALE	0.58	(0.38-0.88)
ALI or major amputation	0.52	(0.31-0.89)
ALI	0.55	(0.31-0.97)
Major amputation	0.57	(0.17-1.95)
Urgent revascularization	0.69	(0.38-1.26)

Alirocumab reduced first and subsequent nonfatal cardiovascular events and all-cause mortality

Less data currently available for high risk subgroups with alirocumab

(as Odyssey Outcomes results released later than Fourier)
# How Repatha’s Availability at Lower List Price Impacts Patients

## Commercially Insured Patients

| High Risk Cardiovascular Patient Split: | 35%¹ |
| Patient Out-of-Pocket: | $5 Copay Card* |
| PCSK9 Abandonment Rate: (Prescriptions Left Unfilled at Pharmacy) | 18%² |

### 2017 Challenge: 28% of Patients Approved⁴
- Complex prior authorization
- Long, complicated document
- Specific documentation needed (lab reports, etc.)

### 2018 Solution: Negotiated Rebates to Simplify Process
Increased rebates in exchange for streamlined prior authorization, and no documentation submitted

### 2018 Result: Improved Access
42% of Patients Approved and Rising⁵ vs. 28% in 2017⁴

## Medicare Patients

| Average Copay $350+* |
| Estimated 75%³ |

### 2018 Challenge: High Patient Out-of-Pocket
The patient out-of-pocket is calculated as a percent of list price (WAC). Below is an illustrative example assuming 33% co-insurance.

<table>
<thead>
<tr>
<th>Current List Price</th>
<th>Out-of-Pocket Monthly</th>
</tr>
</thead>
<tbody>
<tr>
<td>$14,523 per year</td>
<td>$1,117 per four weeks</td>
</tr>
<tr>
<td>With 33%* co-insurance</td>
<td>$370</td>
</tr>
</tbody>
</table>

### 2018 Solution: Lower List Price
Amen is making Repatha available at a lower list price

60% US List Price Reduction to $5,850 per year ($450 per RX)

### 2019+ Result: More Affordable (Illustrative)
Today

$370 → $150 to $25 Monthly Out-of-Pocket

$150 if on tier with 33% coinsurance to as low as $25 on a fixed copay tier.
Triglycerides and CV Risk

- Multiple studies have shown elevated triglyceride levels are independently associated with increased risk of CV events [1]

- The recent REDUCE-IT trial is the first study to show targeting hypertriglyceridemia with isosapent ethyl (pure EPA) improves CV outcomes

- Fibrates do not reduce CV mortality [2]

1. Thompson et al., Arch Intern med 2009;169:578
REDUCE-IT Population

Double-blind parallel group trial; median follow-up 4.9 years

8179 Patients

At High Risk for CV Events Due To:
- TG 150-499 mg/dL (median baseline 216 mg/dL), and
- Established CVD OR
- Diabetes mellitus + aged ≥50 years + ≥1 risk factor for CVD

Randomization 1:1

Stable Statin + icosapent ethyl (Vascepa) 4g/d

Stable Statin + Placebo

PRIMARY COMPOSITE (MACE) ENDPOINT
- CV Death
- Nonfatal MI
- Coronary Revascularization
- Nonfatal Stroke
- Unstable Angina requiring hospitalization
REDUCE-IT Trial: Topline Results

In patients with well controlled LDL on stable statin therapy with elevated triglycerides addition of icosapent ethyl resulted in a 4.8% absolute risk reduction and 25% relative risk reduction (P<0.001) in the composite endpoint of:

- CV death
- nonfatal MI
- nonfatal stroke
- coronary revascularization
- Unstable angina requiring hospitalization
Adding VASCEPA 4 g/d showed a 25% RRR in CV events.

**Primary Composite Endpoint**

- **Placebo**
- **VASCEPA**

![Graph showing the primary composite endpoint](image)

- **Hazard Ratio:** 0.75 (95% CI, 0.68–0.83)
- **RRR:** 24.8%
- **ARR:** 4.8%
- **NNT:** 21 (95% CI, 15–33)
- **P:** 0.00000001

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**No. at Risk**

- **Placebo:** 4090, 3743, 3327, 2807, 2347, 1358
- **VASCEPA:** 4089, 3787, 3431, 2951, 2503, 1430

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25% **RRR**

**NNT=21**
Orion-1 Study: Inhibition of PCSK9 Synthesis Via RNA Interference

- Phase II Randomized Controlled study of 501 patients
- 69% had ASCVD, 24% had diabetes
- 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

- Statins are the cornerstone of therapy in patients with hyperlipidemia
- PCSK9 inhibitors reduce LDL cholesterol and have favorable safety profile and also lower non HDL cholesterol, Lp(a) and may be an important tool in reducing residual risk
- EPA in the form of icosapent ethyl/vascepa is associated with reduction in MACE
- Get the LDL as low as you can for secondary prevention