“How Low Should You Go: Lipid Management in the PCSK9 Era”
ACCE, Meet-the-Expert
May 26, 2016

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Duality of Interests
– Consultant/Advisory Boards
  • Merck
  • Regeneron/Sanofi aventis
– Grants/Research Fellowships
  • Ionis Pharmaceuticals
  • UniQure
– Medical Education
  • CMHC
  • HealthTeamWorks
  • Medscape
  • Medical Education Resources
  • MedIntelligence
  • VOX Media
The FDA’s History of Cholesterol Lowering Drugs: The First Statin

- February 1987 – EMDAC discussed approvability of lovastatin
- Based in part on the CPPT, bile-acid resins, such as cholestyramine, were the drugs of choice for isolated hypercholesterolemia
- Clinicians were desperate for new options to reduce CVD risk
- “I think our recommendation is to approve this drug (lovastatin) and hope that it does as much as we think it might, but that it should be used carefully.”
  - Dr. Frederick Singer, EMDAC Chairman, 19 Feb 1987

The FDA’s History of Cholesterol Lowering Drugs

- 1994 – Scandinavian Simvastatin Survival Study (4S)
- Multiple cardiovascular outcomes trials (CVOTs) investigating the benefits of statins followed.
- For statins, ~40 mg/dL reduction in LDL-C reduced the risk for major CVD events by ~22%.

Surrogate Endpoints

• What is a surrogate?
  – “....a laboratory measurement or physical sign that is used in therapeutic trials as a substitute for a clinically meaningful endpoint that is a direct measure of how a patient feels, functions, or survives and is expected to predict the effect of therapy.”

• Use depends on the evidence that a drug’s effect on the surrogate predicts clinical benefit.
  – Known to predict benefit → “traditional” or “full” approval
  – Reasonably likely to predict benefit → accelerated approval

• Risk Factor ≠ Surrogate Endpoint

Controversy

• Until 2015 the last first-in-class drug to lower LDL-C in a broad population was Zetia (ezetimibe) in 2002
• ENHANCE (2008)¹: addition of ezetimibe to simvastatin was not shown to reduce progression of atherosclerosis as measured by carotid intima-media thickness among patients with heterozygous familial hypercholesterolemia
• SEAS (2008)²: ezetimibe/simvastatin vs. placebo among patients with asymptomatic aortic stenosis
  – No evidence of reducing risk of a composite endpoint of CVD events
  – Raised cancer-related safety concern

More Controversy

• Drug Safety Communications in 2009
  – **ENHANCE** did not change the FDA’s position that “an elevated LDL cholesterol is a risk factor for ASCVD and that lowering LDL-C reduces the risk for CVD”.¹
  – **SEAS**: “FDA believed it is unlikely that Vytorin [ezetimibe/simvastatin] or Zetia [ezetimibe] increased the risk of cancer or cancer-related death.”²

• Despite FDA’s conclusions, the lack of CVD outcomes data for ezetimibe remained highly controversial.

• Approval based on a surrogate endpoint always leaves uncertainty regarding true clinical benefit.
  – And this creates challenges when safety concerns arise.


Even More Controversy

• The ezetimibe **IMPROVE-IT** trial has been completed.¹

• Adding ezetimibe to simvastatin in the setting of acute coronary syndrome led to a statistically significant reduction in the risk of CVD events expected based on the degree of LDL-C lowering achieved.
  – Indications for ezetimibe failed to follow – 2016.

• Increasing emphasis on using therapies that have proven clinical benefit, not just specific biomarker targets?
  – 2013 ACC/AHA Guideline on Treatment of Blood Cholesterol to Reduce ASCVD Risk in Adults
  – Controversy acknowledged

But Surrogates Can Fail

- Off-target adverse effects that are unexpected can occur.
- Sometimes the causal relationship is wrong.
  - Example: Despite ~25% reduction in LDL-C and ~70% increase in HDL-C, torcetrapib increased risk of CVD events by 25% and increased risk of all-cause mortality by 58%.¹


Established Epidemiologic Association Between Cholesterol and CVD

MRFIT: Age-Adjusted CHD Death Rate and Serum Cholesterol in 361,662 US Men (aged 35-57 years)

4.5 mmol/l = ~175 mg/dL

CHD Event Rates in Secondary Prevention and ACS Trials

$y = 0.1629x - 4.6776$

$R^2 = 0.9029$

$p < 0.0001$

Are we still in the surrogate age?
How PCSK9 Monoclonal Antibodies Restore LDL Receptor Function
Now who are the candidates for PCSK9 inhibitor therapy?

Patient Populations with an Unmet Need for Additional LDL-C Lowering

<table>
<thead>
<tr>
<th>FH Population</th>
<th>High / Very High CV Risk Population</th>
<th>Statin-Intolerant Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Genetic disorder</td>
<td>• Previous MI/stroke / CVD or multiple CV risk factors incl. T2DM</td>
<td>• 10-15% on high-intensity statins show intolerance</td>
</tr>
<tr>
<td>• High risk of early CHD</td>
<td>• Difficult to achieve LDL-C goals, despite current therapies</td>
<td>• Many discontinue due to muscle pain and/or weakness</td>
</tr>
<tr>
<td>• HeFH prevalence 1:200 to 1:250</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Untreated LDL-C of 200-400 mg/dL</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

79% with HeFH not at goal (<100 mg/dL)

20% with CHD not at goal (<100 mg/dL)

59% at very high CV risk not at goal (<70 mg/dL)

Nearly all patients who need considerable LDL-C reductions will not reach goal

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### Expected Dose Response to the PCSK9 Inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>% LDL-C Lowering</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alirocumab</td>
<td>75 mg every 2 wks.</td>
<td>45%</td>
</tr>
<tr>
<td></td>
<td>150 mg every 2 wks.</td>
<td>60%</td>
</tr>
<tr>
<td>Evolocumab</td>
<td>140 mg every 2 wks.</td>
<td>60%</td>
</tr>
<tr>
<td></td>
<td>420 mg every 2 wks</td>
<td>60%</td>
</tr>
</tbody>
</table>

### Pharmacokinetics of Alirocumab: Effect on Free PCSK9 and LDL-C

FL is a 72 year old woman with FH, CIMT thickening and LDL-C 560 mg/dL in 2008 now taking
  – Rosuvastatin 40 mg daily
  – Colesevelam 1875 mg bid
  – Ezetimibe 10 mg daily
  – Fenofibrate 145 mg daily

Labs on 3/17/15
  – Cholesterol 195 mg/dL
  – TG 75 mg/dL
  – HDL-C 67 mg/dL
  – LDL-C 113 mg/dL
  – Lipoprotein (a) 18 mg/dL

Let’s begin by setting a LDL-C target or goal

(not precluded by the 2013 ACC/AHA Cholesterol Guideline, just not evidence-based).
• VK is a 69 year old woman S/P AMI with combined hyperlipidemia, HTN, prediabetes and intolerant to multiple statins, fibrates and bile acid sequestrants taking
  – Ezetimibe 10 mg daily
  – Omega-3 fatty acids 930 mg bid
• Labs on 5/15/15
  – Cholesterol 254 mg/dL
  – TG 192 mg/dL
  – HDL-C 58 mg/dL
  – LDL-C 158 mg/dL
  – Lipoprotein (a) 14 mg/dL
  – HbA1c – 5.8%
Alirocumab Significantly Reduced LDL-C from Baseline to Week 24 vs. Ezetimibe

% change from baseline to Week 24 in LDL-C

ITT (primary endpoint) On-treatment (key secondary endpoint)

LS mean (SE) % change from baseline to Week 24

-45.0% 49.5% of 109 patients who received at least one injection after Week 12 had dose increase.

Absolute change of -34 (4.1) mg/dL

Absolute change of -33 (4.2) mg/dL

LS mean difference (SE) vs ezetimibe:

-30.4 (3.1); P<0.0001

-35.1 (2.8); P<0.0001

n=126 n=122

n=123 n=118

Alirocumab Ezetimibe

Fewer Skeletal Muscle AEs with Alirocumab than with Atorvastatin

Kaplan-Meier estimates for time to first skeletal muscle event

Cox model analysis:

HR ALI vs ATV = 0.61 (95% CI: 0.38 to 0.99), nominal P=0.042

HR ALI vs EZE = 0.71 (95% CI: 0.47 to 1.06), nominal P=0.096

Cumulative probability of event

Week
### PCSK9 Inhibitors: Efficacy in Other Lipid Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Range of Mean Changes with PCSK9 Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apo B</td>
<td>-32% to -53%</td>
</tr>
<tr>
<td>Non-HDL-C</td>
<td>-37% to -52%</td>
</tr>
<tr>
<td>Lipoprotein(a)</td>
<td>-17% to -30%</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>-6% to -26%</td>
</tr>
<tr>
<td>HDL-C</td>
<td>+3% to +9%</td>
</tr>
<tr>
<td>Apo A-1</td>
<td>+2% to +7%</td>
</tr>
</tbody>
</table>

But do PCSK9 inhibitors reduced ASCVD events?
OSLER-1 & OSLER-2: Cumulative Incidence of CVD Events

![Graph showing cumulative incidence of CVD events over time with hazard ratio 0.47 (95% CI, 0.28-0.78), p=0.003. Standard therapy vs Evolocumab.]

Sabatine MS et al, NEJM 372:1500, 2015

Emerging Evidence from ODYSSEY Program

Continuous relationship between lower on-treatment LDL-C levels and lower CV risk

Direct relationship between greater LDL-C % reduction from baseline and lower ASCVD event rates

Adjusted MACE rate by average LDL-C (absolute or % reduction from baseline) during treatment period. Multivariate analysis adjusted on baseline characteristics; pool of Phase 3 ODYSSEY trials. HR were calculated for each 39 mg/dL difference or 50% reduction in LDL-C.

PCSK9 Phase 3 Trials for CVD Events Reduction (Statin Treated)

<table>
<thead>
<tr>
<th>Trial</th>
<th>Drug</th>
<th>LDL-C Criterion</th>
<th>Sample Size</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOURIER</td>
<td>Evolocumab</td>
<td>≥ 70 mg/dL</td>
<td>27,500</td>
<td>Jan 2018</td>
</tr>
<tr>
<td>ODYSSEY</td>
<td>Alirocumab</td>
<td>≥ 70 mg/dL</td>
<td>18,000</td>
<td>Jan 2018</td>
</tr>
<tr>
<td>OUTCOMES</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SPIRE-1</td>
<td>Bococizumab</td>
<td>≥ 70 mg/dL</td>
<td>17,000</td>
<td>June 2018</td>
</tr>
<tr>
<td>SPIRE-2</td>
<td>Bococizumab</td>
<td>≥ 100 mg/dL</td>
<td>9,000</td>
<td>Jan 2018</td>
</tr>
</tbody>
</table>

Can LDL-C be Too Low?

- Abetalipoproteinemia & homozygous hypobetalipoproteinemia
  - Autosomal recessive
    - MTP and/or apo B gene mutations
  - Absent apo B-containing lipoproteins
    - Chylomicrons, VLDL, LDL
  - Neurological and ophthalmological sequela prevented by fat-soluble vitamins
  - Malabsorption prevented by low fat diet + essential fatty acids
  - Hepatic steatosis and AST/ALT elevations
    - No fibrosis
  - No ASCVD

Baseline LDL-C and Starting Dose Predict LDL-C<25

Starting Dose: 75 mg Q2W  150 mg Q2W

Percent of Patients Achieving 2x LDL-C <25mg/dL

Baseline LDL-C (mg/dL)

TEAEs of Interest in Patients with 2 Consecutive LDL-C < 25mg/dL (0.6 mmol/L)

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

<table>
<thead>
<tr>
<th>% of patients</th>
<th>Alirocumab* (N=1550)</th>
<th>Alirocumab* with 2 consecutive LDL-C &lt;25mg/dL (&lt;0.6 mmol/L) (N=575)</th>
<th>Placebo (N=788)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event</td>
<td>1255 (81.0)</td>
<td>435 (75.7)</td>
<td>650 (82.5)</td>
</tr>
<tr>
<td>Serious adverse event</td>
<td>290 (18.7)</td>
<td>98 (17.0)</td>
<td>154 (19.5)</td>
</tr>
<tr>
<td>Adverse event leading to death</td>
<td>8 (0.5)</td>
<td>4 (0.7)</td>
<td>10 (1.3)</td>
</tr>
<tr>
<td>Adverse event leading to study drug discontinuation</td>
<td>111 (7.2)</td>
<td>26 (4.5)</td>
<td>46 (5.8)</td>
</tr>
</tbody>
</table>

Safety Analysis (at least 52 weeks for all patients continuing treatment, including 607 patients who completed W78 visit)

* Alirocumab is not licensed in EU

### TEAEs in Both Arms Patients With 2 Consecutive LDL-C < 0.65 mmol/L (25 mg/dL)

<table>
<thead>
<tr>
<th>% (n) of patients</th>
<th>All patients (n=1550)</th>
<th>Alirocumab* (n=1550)</th>
<th>Alirocumab* with 2 consecutive LDL-C &lt;25 mg/dL (0.6 mmol/L) (n=562, 37%)</th>
<th>Placebo (n=788)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections + infestations</td>
<td>48.3% (748)</td>
<td>42.3% (241)</td>
<td>48.6% (383)</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal + connective tissue disorders</td>
<td>30.1% (467)</td>
<td>26.1% (150)</td>
<td>30.7% (242)</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>20.5% (318)</td>
<td>16.7% (96)</td>
<td>20.6% (162)</td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>18.6% (289)</td>
<td>12.9% (74)</td>
<td>19.7% (155)</td>
<td></td>
</tr>
<tr>
<td>General disorders + administration site conditions</td>
<td>16.1% (250)</td>
<td>11.3% (65)</td>
<td>17.8% (140)</td>
<td></td>
</tr>
<tr>
<td>Injury, poisoning, + procedural complications</td>
<td>15.5% (241)</td>
<td>13.2% (76)</td>
<td>15.7% (124)</td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic, + mediastinal disorders</td>
<td>11.7% (182)</td>
<td>8.9% (51)</td>
<td>12.6% (99)</td>
<td></td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>11.0% (171)</td>
<td>10.6% (61)</td>
<td>12.9% (102)</td>
<td></td>
</tr>
<tr>
<td>Skin + subcutaneous tissue disorders</td>
<td>10.1% (156)</td>
<td>8.3% (48)</td>
<td>9.4% (74)</td>
<td></td>
</tr>
<tr>
<td>Metabolism + nutrition disorders</td>
<td>10.2% (158)</td>
<td>9.6% (55)</td>
<td>9.3% (73)</td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>8.6% (133)</td>
<td>5.4% (31)</td>
<td>10.0% (79)</td>
<td></td>
</tr>
<tr>
<td>Eye disorders</td>
<td>7.0% (108)</td>
<td>7.0% (40)</td>
<td>6.2% (49)</td>
<td></td>
</tr>
<tr>
<td>Laboratory investigations</td>
<td>6.4% (99)</td>
<td>4.3% (25)</td>
<td>5.5% (43)</td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>6.5% (101)</td>
<td>5.2% (30)</td>
<td>8.5% (67)</td>
<td></td>
</tr>
<tr>
<td>Renal + urinary disorders</td>
<td>5.5% (85)</td>
<td>4.7% (27)</td>
<td>6.6% (52)</td>
<td></td>
</tr>
<tr>
<td>Neoplasms, benign, malignant (incl cysts/polyps)</td>
<td>3.0% (47)</td>
<td>3.8% (22)</td>
<td>4.3% (34)</td>
<td></td>
</tr>
<tr>
<td>Reproductive system + breast disorders</td>
<td>3.2% (50)</td>
<td>2.8% (16)</td>
<td>3.4% (27)</td>
<td></td>
</tr>
<tr>
<td>Blood + lymphatic system disorders</td>
<td>3.0% (46)</td>
<td>2.4% (14)</td>
<td>3.7% (29)</td>
<td></td>
</tr>
<tr>
<td>Ear + labyrinth disorders</td>
<td>2.4% (37)</td>
<td>1.7% (10)</td>
<td>3.9% (31)</td>
<td></td>
</tr>
</tbody>
</table>

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Adapted from J. Robinson et al NEJM 372:1489, 2015, Appendix

### Some Final Thoughts About Reduced LDL-C

- **Definition ↓ LDL-C**
  - Low <40 mg/dL, 2013 ACC/AHA Cholesterol Guideline
  - Very Low <25 mg/dL
- Not uncommon when statins are used in patients with ↑TG and LDL-C is calculated.

- **CVA risk increased?**
  - SPARCL, *NEJM* 355:549,

- **Risk of T2DM**
Using FDA-Approved PCSK9 Inhibitors in Clinical Practice

- ↓ LDL-C by 45-60%
  - On top of maximum statin ± ezetimibe therapy
- Probably reduce ASCVD events
  - But is LDL-C still a surrogate for events?
- Appear safe, but risk may need decades to prove
  - Is <40 too low?
  - Is <25 mg/dL too low?
- Appear indicated when LDL-C lowering is needed
  - FH
  - High risk patients with clinical ASCVD.
  - Statin intolerant with clinical ASCVD.

Thank You!