Beyond Statins: The Current Cholesterol Controversy

Joseph Saseen, PharmD, BCPS, BCACP
Evan Sisson, PharmD, MHA, CDE
Vincent Willey, PharmD, BCACP

Supporter

• Supported by independent educational grants from AstraZeneca LP and Pfizer.

Disclosures

• Joseph Saseen: declares no conflicts of interest, real or apparent, and no financial interests in any company, product, or service mentioned in this program, including grants, employment, gifts, stock holdings, and honoraria

• Evan Sisson: declares no conflicts of interest, real or apparent, and no financial interests in any company, product, or service mentioned in this program, including grants, employment, gifts, stock holdings, and honoraria

• Vincent Willey: declares no personal conflicts of interest, real or apparent, and no financial interests in any company, product, or service mentioned in this program, including grants, employment, gifts, stock holdings, and honoraria

• His employer, HealthCore, does perform research studies that are funded by multiple pharmaceutical companies

Disclosures

• Target Audience: Pharmacists

• ACPE#: 0202-0000-16-011-L01-P

• Activity Type: Knowledge-based
Learning Objectives

1. Describe current guideline recommendations regarding the use of stains and ezetimibe to treat patients with high cholesterol.
2. Explain results from recent clinical trials investigating the risks and benefits of combination therapy with statins and ezetimibe.
3. Describe characteristics of PCSK9 inhibitors including mechanism of action and role in therapy.
4. Review data from clinical trials investigating the safety and efficacy of PCSK9 inhibitors.
5. Discuss potential issues surrounding the use of PCSK9 Inhibitors, including patient selection, cost and delivery.

According to the National Lipid Association (NLA), which of the following is the most appropriate goal of therapy for a patient with very high ASCVD risk?

A. LDL-C < 130 mg/dL
B. Non-HDL-C < 100 mg/dL
C. 30% LDL-C reduction from baseline
D. 50% reduction in hs-CRP from baseline

Which of the following is the approximate additional percent reduction in LDL-C when ezetimibe is added to a patient already treated with statin therapy?

A. 5%
B. 20%
C. 40%
D. > 50%

Which of the following is true regarding the Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors?

A. PCSK9 inhibitors work by blocking cholesterol absorption in the intestines
B. Alirocumab is dosed orally every 2 weeks
C. Evolocumab is indicated for both heterozygous and homozygous familial hypercholesterolemia
D. PCSK9 inhibitors on average lower LDL-C by the same amount as titrating a statin from the lowest dose to the highest dose (i.e., atorvastatin 10mg to 80mg)

In the IMPROVE-IT trial, which endpoint was significantly lower in patients treated with ezetimibe/simvastatin combination therapy compared to simvastatin alone?

A. All-cause mortality
B. Stroke
C. CVD/MI/Stroke
D. All of the above

Which of the following is most appropriate initial therapy for a patient at very high ASCVD risk?

A. Alirocumab
B. Rosuvastatin
C. Ezetimibe
D. Lomitapide
EZETIMIBE + STATINS
A GOOD MATCH?

2013 ACC/AHA Guidelines: Four Statin Benefit Groups

- Clinical ASCVD (MI, angina, stroke, TIA, PAD)
  - Moderate-intensity statin (Age >75)
  - High-intensity statin (Age ≤75)
- LDL-C ≥190 mg/dL
  - High-intensity statin
- 10-y risk ≥7.5% (Age 40-75)
  - Moderate-to-high intensity statin
- Diabetes (Age 40-75)
  - Moderate-intensity statin
  - High-intensity statin if 10-y risk ≥7.5%

Recommended Statin Doses

- **High-Intensity**
  - LDL-C ≥50%
  - Atorvastatin 40-80mg
  - Rosuvastatin 20-40mg

- **Moderate-Intensity**
  - LDL-C 30 - 50%
  - Atorvastatin 10-20mg
  - Rosuvastatin 5-10mg
  - Simvastatin 20-40mg
  - Pravastatin 40-80mg
  - Lovastatin 40mg
  - Fluvastatin 80mg
  - Pitavastatin 2-4mg

- **Low-Intensity**
  - LDL-C <30%
  - Simvastatin 10mg
  - Pravastatin 10-20mg
  - Lovastatin 20mg
  - Fluvastatin 20-40mg
  - Fluvastatin 80mg
  - Simvastatin 1-2mg


Statins – Residual Risk


Ezetimibe – Mechanism of Action


ENHANCE Study Results

ENHANCE Study Results

Ezetimibe & 2013 ACC/AHA Guidelines

- "Nonstatin therapies do not provide acceptable ASCVD risk reduction benefits compared to their potential for adverse effects in the routine prevention of ASCVD."

SHOULD WE RECOMMEND STATINS AND EZETIMIBE FOR TREATMENT OF PATIENTS WITH DYSLIPIDEMIA?

Let the debate begin!!!!!

Variability of Achieved LDL-C with High-Intensity Statin Therapy

- Meta-analysis of 8 RCT with statins
- 38,153 subjects
- 6,286 major CV events in 5,387 patients

NLA Steps in ASCVD Risk Assessment

1) Identify patients with very high risk conditions
   - ASCVD
   - Diabetes with 2 or other major ASCVD risk factors or end organ damage

2) Identify patients with high risk conditions
   - Diabetes with 1 or other major ASCVD risk factors
   - Chronic kidney disease Stage 3 or 4
   - LDL-C >190 mg/dL

3) Count major ASCVD risk factors
   - 0-1 and no other indicators of higher risk, assign to low risk category
   - 0-3 major ASCVD risk factors present, assign to high risk category

4) Risk scoring
   - LDL-C >100 mg/dL, assign to moderate risk category
   - LDL-C >100 mg/dL, assign to high risk category
   - Consider assigning to high or very high risk category, if appropriate, if other risk indicators are present based on additional testing.

NLA Criteria for ASCVD Risk Assessment and Treatment Goals

<table>
<thead>
<tr>
<th>Target Goals (mg/dL)</th>
<th>Non-HDL</th>
<th>LDL</th>
<th>ApoB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very High Risk</td>
<td>ASCVD</td>
<td>Diabetes mellitus (type 1 or 2)</td>
<td>&lt;100</td>
</tr>
<tr>
<td></td>
<td>Diabetes risk factor(s) OR</td>
<td>&lt;70</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Evidence of end-organ damage</td>
<td>&lt;80</td>
<td></td>
</tr>
<tr>
<td>High Risk</td>
<td>ASCVD</td>
<td>Diabetes mellitus (type 1 or 2)</td>
<td>&lt;130</td>
</tr>
<tr>
<td></td>
<td>2 or other major ASCVD risk factors OR</td>
<td>&lt;100</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Evidence of end-organ damage</td>
<td>&lt;90</td>
<td></td>
</tr>
<tr>
<td>Moderate Risk</td>
<td>ASCVD</td>
<td>Diabetes mellitus (type 1 or 2)</td>
<td>&lt;130</td>
</tr>
<tr>
<td></td>
<td>2 or other major ASCVD risk factors</td>
<td>&lt;100</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Evidence of end-organ damage</td>
<td>&lt;90</td>
<td></td>
</tr>
<tr>
<td>Low Risk</td>
<td>ASCVD</td>
<td>2 or other major ASCVD risk factors</td>
<td>&lt;130</td>
</tr>
<tr>
<td></td>
<td>Evidence of end-organ damage</td>
<td>&lt;100</td>
<td></td>
</tr>
</tbody>
</table>
Proportional effects on MAJOR VASCULAR EVENTS per mmol/L LDL-C reduction, by baseline LDL-C

<table>
<thead>
<tr>
<th>Statin/more Control/less</th>
<th>No. of events (%)</th>
<th>Relative risk (CI) per mmol/L LDL-C reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2.0 (&lt;77 mg/dL)</td>
<td>910 (14.7%)</td>
<td>0.71 (0.62 - 0.80)</td>
</tr>
<tr>
<td>2.0-2.5 (&lt;97 mg/dL)</td>
<td>1528 (14.0%)</td>
<td>0.77 (0.64 - 0.91)</td>
</tr>
<tr>
<td>2.5-3.0 (&lt;116 mg/dL)</td>
<td>1866 (12.4%)</td>
<td>0.77 (0.70 - 0.85)</td>
</tr>
<tr>
<td>3.0-3.5 (&lt;135 mg/dL)</td>
<td>2007 (12.3%)</td>
<td>0.76 (0.70 - 0.82)</td>
</tr>
<tr>
<td>&gt;3.5 (&gt;135 mg/dL)</td>
<td>4508 (13.0%)</td>
<td>0.80 (0.76 - 0.83)</td>
</tr>
<tr>
<td>Total</td>
<td>10973 (13.0%)</td>
<td>0.78 (0.76 - 0.80)</td>
</tr>
</tbody>
</table>

PROVE-IT Substudy: Primary End Point* and Achieved LDL-C Levels

<table>
<thead>
<tr>
<th>Achieved LDL (mg/dL)</th>
<th>Hazard Ratio†</th>
<th>Relative risk (CI) per mmol/L LDL-C reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;80-100</td>
<td>Referent</td>
<td></td>
</tr>
<tr>
<td>&gt;60-80</td>
<td>0.89 (0.59, 1.37)</td>
<td></td>
</tr>
<tr>
<td>&gt;40-60</td>
<td>0.67 (0.50, 0.92)</td>
<td></td>
</tr>
<tr>
<td>≤40</td>
<td>0.61 (0.40, 0.91)</td>
<td></td>
</tr>
</tbody>
</table>

Lower Better 1 Higher Better 2

*All-cause mortality, myocardial infarction, coronary revascularization, unstable angina, and stroke
†Adjusted for multiple baseline characteristics, including LDL-C level.
‡Significantly lower than the referent group.

Safety
Muscle and Rhabdomyolysis
- Myalgia
  - Muscle pain or soreness, weakness, and/or cramps without CK elevations
- Myopathy
  - Muscle symptoms plus CK >10 times the ULN
  - Occurs in 5 patients per 100,000 person-years
- Rhabdomyolysis
  - CK >10,000 U/L, or CK >10 times ULN with worsening renal function
  - Occurs in 1.6 patients per 100,000 person-years

55 yo with statin intolerance
- 55 yo AAM with HTN (166/94 mmHg) on therapy with history of CABG 2 months ago. He does not smoke, and has no significant family history. He does not like the grittiness of colestipol. He has been tried on numerous statins but had to stop them due to muscle aches. He currently feels fine off all statins.


“How low is too low?”

In vitro fibroblasts
- 2.5 mg/dL of LDL cholesterol required to meet cellular needs
  - Translates to 25 mg/dL plasma LDL cholesterol in vivo

Human newborns
- LDL cholesterol of 40-50 mg/dL

Hypobetalipoproteinemia
- LDL cholesterol of 10 mg/dL
  - Appears to be resistant to atherosclerosis with a normal life expectancy

Hypoglycemia
- LDL cholesterol of 10 mg/dL

Statins reduce major vascular events by 22% for each 1 mmol/L (~40 mg/dL) LDL reduction
- LDL <70 mg/dL yielded definite benefits (p=0.004)


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  - CK >10,000 U/L, or CK >10 times ULN with worsening renal function
  - Occurs in 1.6 patients per 100,000 person-years

Creatinine → Myoglobin
CK levels rarely change clinical decisions but are necessary for diagnosis of rhabdomyolysis

Statin Dose-Response Curves
LDL Reduction from Baseline

Average LDL cholesterol reduction in patients with primary hypercholesterolemia on nonstatin based Food and Drug Administration product labeling for each compound.
Simvastatin – Myalgia

<table>
<thead>
<tr>
<th>SEARCH Trial*</th>
<th>Simvastatin 80 mg (n=1683)</th>
<th>Simvastatin 20 mg (n=4633)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myopathy</td>
<td>52 (0.9%)</td>
<td>18 (0.02%)</td>
</tr>
<tr>
<td>Rhabdomyolysis</td>
<td>11 (0.2%)</td>
<td>0</td>
</tr>
</tbody>
</table>

*MAE in patients with previous heart attack over 6.7 years

Heart Protection Study 2 (HPS2)
- Initial HPS2 results – 40 mg simvastatin plus ≥1 g/day niacin
  - Myopathy: higher incidence in patients of Chinese descent (0.43%) compared with patients not of Chinese descent (0.03%)
  - Not known if the increased risk for myopathy applies to other patients of Asian descent
- FDA revised label in March 2010
  - Patients of Chinese descent should not receive simvastatin 80 mg with cholesterol-modifying doses of niacin-containing products.
  - Use caution… with simvastatin 40 mg or less with niacin

SHARP: Effect of Simvastatin/Ezetimibe on Lipids and Apolipoproteins at 2.5 years

<table>
<thead>
<tr>
<th>Biochemical parameter</th>
<th>Simvast/Ezet (mg/dL)</th>
<th>Placebo (mg/dL)</th>
<th>Percentage difference</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol</td>
<td>142</td>
<td>183</td>
<td>-23%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>70</td>
<td>102</td>
<td>-32%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>44</td>
<td>44</td>
<td>2%</td>
<td>0.03</td>
</tr>
<tr>
<td>Non-HDL cholesterol</td>
<td>97</td>
<td>139</td>
<td>-30%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>163</td>
<td>188</td>
<td>-13%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Apolipoprotein A1</td>
<td>70</td>
<td>93</td>
<td>-24%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Apolipoprotein A2</td>
<td>145</td>
<td>143</td>
<td>1%</td>
<td>0.003</td>
</tr>
</tbody>
</table>

SHARP: Major Vascular Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Simvast/Ezet (n=4650)</th>
<th>Placebo (n=4640)</th>
<th>Risk ratio &amp; 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major coronary event</td>
<td>213 (4.6%)</td>
<td>230 (5.0%)</td>
<td>1.16 (95% CI 0.94-1.43)</td>
</tr>
<tr>
<td>Non-fatal myocardial infarction</td>
<td>131 (2.8%)</td>
<td>175 (3.8%)</td>
<td>0.81 (95% CI 0.66-0.98)</td>
</tr>
<tr>
<td>Any myocardial infarction procedure</td>
<td>266 (5.8%)</td>
<td>352 (7.8%)</td>
<td>0.80 (95% CI 0.67-0.96)</td>
</tr>
<tr>
<td>Major Atherothrombotic Event</td>
<td>52 (1.1%)</td>
<td>62 (1.4%)</td>
<td>1.00 (95% CI 0.71-1.42)</td>
</tr>
<tr>
<td>Other causes of death</td>
<td>182 (3.9%)</td>
<td>182 (3.9%)</td>
<td>1.00 (95% CI 0.71-1.42)</td>
</tr>
<tr>
<td>Major Vascular Event</td>
<td>257 (5.7%)</td>
<td>218 (4.7%)</td>
<td>1.15 (95% CI 0.95-1.41)</td>
</tr>
</tbody>
</table>

Simvast/Ezet better Placebo better
IMPROVE-IT: Ezetimibe + Simvastatin vs. Simvastatin for Post-MI Patients

- 18,144 patients stabilized post ACS ≤10 days
- Randomized to ezetimibe + simvastatin or simvastatin alone
- Baseline LDL-C at time of ACS event was 95 mg/dL
- Primary composite endpoint: CV death, MI, hospital admission for UA, revascularization, or stroke.
  - 32.7% event rate in EZ/Simva group vs. 34.7% in Placebo/Simva group

Lipid Measurement (1 Year Mean)

<table>
<thead>
<tr>
<th></th>
<th>Ezetimibe/Simva</th>
<th>Placebo/Simva</th>
<th>Change in mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDL-C</td>
<td>48.7 mg/dL</td>
<td>48.1 mg/dL</td>
<td>+0.6</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>120.4 mg/dL</td>
<td>137.1 mg/dL</td>
<td>-16.7</td>
</tr>
<tr>
<td>LDL-C</td>
<td>53.2 mg/dL</td>
<td>69.9 mg/dL</td>
<td>-16.7</td>
</tr>
<tr>
<td>hs-CRP</td>
<td>3.3 mg/dL</td>
<td>3.8 mg/dL</td>
<td>-0.5</td>
</tr>
</tbody>
</table>

Response to LIPTRUZET in Patients with Primary Hyperlipidemia at 12 weeks

Response to LIPTRUZET in Patients with Primary Hyperlipidemia at 12 weeks

<table>
<thead>
<tr>
<th></th>
<th>Liptruzet 10/10</th>
<th>Liptruzet 10/20</th>
<th>Liptruzet 10/40</th>
<th>Liptruzet 10/80</th>
<th>Atorv 10</th>
<th>Atorv 20</th>
<th>Atorv 40</th>
<th>Atorv 80</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C</td>
<td>-35%</td>
<td>-54%</td>
<td>-61%</td>
<td>-62%</td>
<td>-24%</td>
<td>-28%</td>
<td>-30%</td>
<td>-34%</td>
</tr>
<tr>
<td>Non-HDL-C</td>
<td>-45%</td>
<td>-50%</td>
<td>-50%</td>
<td>-50%</td>
<td>-30%</td>
<td>-30%</td>
<td>-34%</td>
<td>-41%</td>
</tr>
<tr>
<td>Apo B</td>
<td>-15%</td>
<td>-15%</td>
<td>-15%</td>
<td>-15%</td>
<td>-15%</td>
<td>-15%</td>
<td>-15%</td>
<td>-15%</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>-70%</td>
<td>-60%</td>
<td>-50%</td>
<td>-40%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TC</td>
<td>-53%</td>
<td>-54%</td>
<td>-55%</td>
<td>-56%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TG</td>
<td>-50%</td>
<td>-50%</td>
<td>-50%</td>
<td>-50%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL-C</td>
<td>-40%</td>
<td>-40%</td>
<td>-40%</td>
<td>-40%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL</td>
<td>-37%</td>
<td>-42%</td>
<td>-45%</td>
<td>-54%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

55 yo with statin intolerance

- 55 yo AAM with HTN (166/94 mmHg) on therapy with history of CABG 2 months ago. He does not smoke, and has no significant family history. He does not like the grittiness of colestipol. He has been tried on numerous statins but had to stop them due to muscle aches. He currently feels fine off all statins.

Plan: Start pravastatin 20mg then consider combination therapy with niacin or ezetimibe.

PRO Ezetimibe – Summary Points

- Significant residual CVD risk remains
  - Statin response is variable
  - Residual risk is related to non-HDL-C levels above goal
  - Statin intolerance amplifies the need for effective combination therapy
  - Ezetimibe consistently lowers LDL-C and non-HDL-C in combination with statins
- Poor results of ENHANCE related to trial design
- IMPROVE-IT reinforces LDL Hypothesis and supports benefits of ezetimibe + statin

Heartwire from Medscape

FDA Advisors: Reject Secondary-Prevention Ezetimibe Indication

Deborah Brauser
December 14, 2015

SILVER SPRING, MD (UPDATED) — The Endocrinologic and Metabolic Drugs Advisory Committee of the US Food and Drug Administration (FDA) voted 10 to 5 against recommending the expanded use of ezetimibe (Zetia, Merck) by adding it to statin therapy for reduction of cardiovascular events in patients with coronary heart disease.
Schizophrenic Life of Ezetimibe

- 2002 – Approval of ezetimibe
- 2004 – Approval of ezetimibe/simvastatin combination
- 2005 – IMPROVE-IT study starts targeting 12,500 patients
- 2006 – ENHANCE published after 18 month delay
- 2008 – IMPROVE-IT changes target enrollment to 18,000; completion delayed until 2012
- 2009 – FDA investigation concludes cancer risk unlikely
- 2010 – IMPROVE-IT completion delayed until 2013
- 2015 – Release of IMPROVE-IT results

IMPROVE-IT: Study Design Changes

- Original Design:
  - Hypothesis: ezetimibe/simvastatin would reduce the incidence of the composite CV end point over at least 2.5 years of follow-up relative to simvastatin monotherapy
  - Sample Size Calculation
    - 10,000 based a 2 year event rate of 23.5% (simvastatin alone)
    - Statistical power to detect a 10% relative risk reduction
    - Endpoint driven with 5,250 primary end points needed
- Enrollment changes
  - Increased to 12,500 in the second study amendment
  - Increased to 18,000 in the third study amendment

IMPROVE-IT: Primary Endpoint Results

Primary endpoint events:
- Rate at 7-years:
  - 34.7% vs. 32.7% (p=0.016)
- Absolute Risk Reduction:
  - 2.0%; NNT = 50
- Relative Risk Reduction:
  - 5.8%

IMPROVE-IT: Other Endpoints

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>EZ/Simva*</th>
<th>Simva*</th>
<th>Risk Ratio &amp; 95% CI</th>
<th>HR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause death</td>
<td>15.4</td>
<td>15.3</td>
<td>0.99</td>
<td>0.782</td>
<td></td>
</tr>
<tr>
<td>Death from CV disease</td>
<td>6.9</td>
<td>6.8</td>
<td>1.00</td>
<td>0.997</td>
<td></td>
</tr>
<tr>
<td>Death from CHD</td>
<td>3.7</td>
<td>5.8</td>
<td>0.96</td>
<td>0.499</td>
<td></td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>13.1</td>
<td>14.8</td>
<td>0.87</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>4.2</td>
<td>4.8</td>
<td>0.86</td>
<td>0.052</td>
<td></td>
</tr>
<tr>
<td>Ischemic Stroke</td>
<td>3.4</td>
<td>4.1</td>
<td>0.79</td>
<td>0.008</td>
<td></td>
</tr>
<tr>
<td>Revascularization</td>
<td>21.8</td>
<td>23.4</td>
<td>0.95</td>
<td>0.107</td>
<td></td>
</tr>
<tr>
<td>Unstable angina</td>
<td>2.1</td>
<td>1.9</td>
<td>1.06</td>
<td>0.618</td>
<td></td>
</tr>
<tr>
<td>CVD/MI/Stroke</td>
<td>20.4</td>
<td>22.2</td>
<td>0.90</td>
<td>0.003</td>
<td></td>
</tr>
</tbody>
</table>

*7-year event rates (%) Risk ratio & 95% CI

Randomized Aldactone Evaluation Study (RALES)

- Randomized, double-blind study in 1663 patients with heart failure for 2 years
- Absolute Risk Reduction:
  - 11%; NNT = 9
- Relative Risk Reduction:
  - 24%

IMPROVE-IT: Clinically relevant?

- Composite Primary Endpoint:
  - CV death, major coronary event (nonfatal MI, unstable angina, or coronary revascularization), or nonfatal stroke
- After 7 years, among 100 patients:

Randomized Aldactone Evaluation Study (RALES)

- Randomized, double-blind study in 1663 patients with heart failure for 2 years
- Absolute Risk Reduction:
  - 11%; NNT = 9
**National Lipid Association: Familial Hypercholesterolemia**

- Familial hypercholesterolemias (FH) are genetic defects resulting in severe cholesterol elevations and increased risk of premature CHD
- Prevalence of FH is 1 in 300 to 500
  - Homozygous FH affects 1 in 1,000,000
- Aggressive lipid lowering is necessary
  - Target LDL-C reduction of at least 50%
  - Greater LDL-C reductions may be necessary for FH patients with other CHD risk factors

*Journal of Clinical Lipidology 2011;5:133–140.*

**Limited Applicability FH Patients**

- Ezetimibe failed to demonstrate benefits in the ENHANCE, patients with familial hypercholesterolemia (FH)
  - Baseline LDL-C values of 318-319 mg/dL
  - No difference in primary endpoint of cIMT
  - No difference in CV events
  - 12 with ezetimibe/simvastatin and 9 with simvastatin alone
- IMPROVE-IT eliminated FH patients based on LDL-C criteria for eligibility
- Despite IMPROVE-IT results, ezetimibe is unproven in very high CV risk patients with FH


**The LDL-C Principle**

- LDL-C lowering is the principal driver for benefit, not ezetimibe


**ACC/AHA 2013 Blood Cholesterol Guideline: ASCVD**

<table>
<thead>
<tr>
<th>Class I Recommendations</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-Intensity statin therapy should be initiated or continued as first line therapy in men and women for ≤75 years of age, unless contraindicated</td>
<td>A</td>
</tr>
<tr>
<td>If high-Intensity statin therapy is contraindicated or when characteristics predisposing to statin-associated adverse effects are present, Moderate-Intensity statin therapy should be the second option if tolerated</td>
<td>A</td>
</tr>
</tbody>
</table>

TNT Trial: Results

- Mean LDL-C Value (mg/dL)
- Atorvastatin 10 mg
- Atorvastatin 80 mg

<table>
<thead>
<tr>
<th>Months of Follow-up</th>
<th>Pravastatin 40 mg (26.3%)</th>
<th>Atorvastatin 80 mg (22.4%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
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<td>27</td>
</tr>
<tr>
<td>30</td>
<td>30</td>
<td>30</td>
</tr>
</tbody>
</table>

P<0.001

PROVE-IT: Results

- Median LDL-C values:
  - Atorvastatin 62 mg/dL
  - Pravastatin 95 mg/dL (P<0.001)

ALLHAT-Lipid Lowering Trial (LLT)

- Randomized, blinded trial of 10,355 patients from the ALLHAT trial for up to 8 years

- Mean LDL-C values:
  - Pravastatin 104 mg/dL
  - Usual Care 121 mg/dL

P=0.88

IMPROVE-IT: Results

- Median time-weighted LDL-C values achieved
  - Simvastatin 40 mg daily 69.5 mg/dL
  - Ezetimibe/Simvastatin 10/40 mg daily 53.7 mg/dL

Additional Safety Monitoring Needed

- Statin Product Labeling (revised February 28, 2012)
  - Labels revised to remove the need for routine periodic monitoring of liver enzymes in patients taking statins
- Ezetimibe Product Labeling
  - Persistent elevations in hepatic transaminase can occur when ezetimibe is added to a statin; monitor hepatic transaminase levels before and during treatment
  - Incidence of consecutive elevations (>3 X ULN) in hepatic transaminase 1.3% in patients treated with ezetimibe/statin therapy and 0.4% for patients treated with statin therapy alone

CON Ezetimibe – Summary Points

- IMPROVE-IT trial required multiple study design modifications to demonstrate a benefit
- Proven benefits, but minimal with questionable clinical significance in patients requiring robust LDL-C lowering to assure meaningful CV event reductions (i.e., FH)
- Additional safety monitoring required when ezetimibe is added to statin therapy
WHAT ARE THESE NEW CHOLESTEROL DRUGS ALL ABOUT?

PCSK9 Inhibitors

Role of LDL-C Receptors (LDLR)

- Expressed on the surface of the liver
- Function as the primary mechanism to reduce LDL-C from the bloodstream
- Pro-protein convertase subtilisin/kexin-type 9 (PCSK9)
  - Enzyme that is responsible for degrading the LDLR
  - Inhibit PCSK9  »»»  ↑LDLR  »»»  ↓LDL-C in the bloodstream


PCSK9 Inhibitor Mechanism of Action


PCSK9 INHIBITORS AVAILABLE IN THE US

Alirocumab (Praluent)
Evolocumab (Repatha)

Alirocumab

- **Indications**
  - Adjunct to diet and maximally tolerated statin dose in patients who require additional LDL-C lowering with
    - Heterozygous familial hypercholesterolemia
    - Clinical ASCVD
- **Route of administration**
  - Subcutaneous – self administered
- **Dosing**
  - Starting dose = 75mg SC every 2 weeks
  - Maximum dose = 150mg SC every 2 weeks

Evolocumab

- **Indications**
  - Adjunct to diet and maximally tolerated statin dose in patients who require additional LDL-C lowering with:
    - Heterozygous familial hypercholesterolemia (HeFH)
    - Clinical ASCVD
  - Adjunct to diet and other LDL-C lowering therapies in patients who require additional LDL-C lowering with:
    - Homozygous familial hypercholesterolemia (HoFH)

- **Route of administration**
  - Subcutaneous – self administered

Evolocumab - Dosing

- **Clinical ASCVD and HeFH indications**
  - 140mg SC every 2 weeks
  - 420 mg SC every month
  - Need to administer 3 – 140mg injections consecutively within 30 minutes

- **HoFH indication**
  - 420 mg SC every month
  - Need to administer 3 – 140mg injections consecutively within 30 minutes

Should we recommend PCSK9 inhibitors for treatment of patients with dyslipidemia?

Let the debate begin!!!!!
Very Low LDL-C Linked to Reduced CV Events

- Meta-analysis of 8 randomized controlled trials (n=38,153)
- More than 40% of patients randomized to high-dose statin therapy did not achieve an LDL-C <70 mg/dL
- Results:
  - Risk for major CV Events by achieved on-trial LDL-C (mg/dL)

<table>
<thead>
<tr>
<th>LDL-C (mg/dL)</th>
<th>n</th>
<th>Adjusted HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50</td>
<td>194</td>
<td>0.44 (0.35-0.55)</td>
</tr>
<tr>
<td>50-74</td>
<td>1,184</td>
<td>0.51 (0.42-0.62)</td>
</tr>
<tr>
<td>75-99</td>
<td>1,664</td>
<td>0.56 (0.46-0.68)</td>
</tr>
<tr>
<td>100-124</td>
<td>1,480</td>
<td>0.54 (0.43-0.69)</td>
</tr>
<tr>
<td>125-149</td>
<td>557</td>
<td>0.71 (0.51-0.99)</td>
</tr>
<tr>
<td>≥175</td>
<td>123</td>
<td>1.00 (Ref)</td>
</tr>
</tbody>
</table>

William H. Shrank, MD, MSHS
Jane F. Barlow, MD, MPH
Troyen A. Brennan, MD, JD

Drugs Affecting Lipoprotein Metabolism

- Statins
  - LDL-C: ↓18-55%
  - HDL-C: ↑7-30%
- Bile acid sequestrants
  - LDL-C: ↓15-30%
  - HDL-C: ↑3-5%
- Nicotinic acid
  - LDL-C: ↓5-72%
  - HDL-C: ↑10-20%
- Fibric Acids
  - LDL-C: ↓20-50%
- Ezetimibe
  - LDL-C: ↓13-20%
  - HDL-C: ↑5-11%
- Omega-3 fatty acids
  - LDL-C: ↓16-72%
  - HDL-C: ↑15-77%
  - TG: ↓19-44%
- PCSK9 inhibitors
  - LDL-C: ↓40-72%
  - HDL-C: ↑10-17%

For LDL-C lowering
Primarily for hypertriglyceridemia

Evolocumab (OSLER-1 and OSLER-2): LDL-C Levels Over Time

<table>
<thead>
<tr>
<th>LDL-C (mg/dL)</th>
<th>Time (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>12</td>
<td>16</td>
</tr>
<tr>
<td>24</td>
<td>36</td>
</tr>
<tr>
<td>48</td>
<td></td>
</tr>
</tbody>
</table>

* All P < 0.001


Evolocumab (ODYSSEY LONGTERM): Calculated LDL-C Levels Over Time

<table>
<thead>
<tr>
<th>Least-Square Mean Calculated LDL-C Level (mg/dL)</th>
<th>Time (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* All P < 0.001

LLT = Lipid-lowering therapy

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Alirocumab (ODYSSEY LONGTERM)
Safety Analysis

<table>
<thead>
<tr>
<th>Summary of Adverse Events</th>
<th>Alirocumab (n = 1,550)</th>
<th>Placebo (n = 788)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious Adverse Events</td>
<td>290 (18.7%)</td>
<td>154 (19.5%)</td>
<td>0.66</td>
</tr>
<tr>
<td>• AE leading to discontinuation</td>
<td>111 (7.2%)</td>
<td>46 (5.8%)</td>
<td>0.26</td>
</tr>
<tr>
<td>• AE leading to death</td>
<td>8 (0.5%)</td>
<td>10 (1.3%)</td>
<td>0.68</td>
</tr>
<tr>
<td>General allergic reaction events</td>
<td>156 (10.1%)</td>
<td>70 (9.5%)</td>
<td>0.71</td>
</tr>
<tr>
<td>Local injection site reactions</td>
<td>91 (5.9%)</td>
<td>33 (4.2%)</td>
<td>0.10</td>
</tr>
<tr>
<td>Neurological events</td>
<td>65 (4.1%)</td>
<td>35 (4.4%)</td>
<td>0.83</td>
</tr>
<tr>
<td>Neurocognitive events</td>
<td>18 (1.2%)</td>
<td>4 (0.5%)</td>
<td>0.17</td>
</tr>
</tbody>
</table>

*Among patients who received alirocumab, 575 (37.1%) had a calculated LDL-C level of < 25 mg/dL at 2 consecutive measurements. Rates of AEs were similar to those in the overall alirocumab group.


Outcomes Studies with PCSK9’s

• Several pending large-scale outcome trials

• Preliminary Findings
  – Meta-analysis of 24 clinical trials (n=10,159)
    • Reduced MI OR 0.49 (0.26-0.93)
    • Reduced all cause mortality OR 0.45 (0.23-0.86)
    • No increase in serious adverse events


Post-Hoc Analysis of Adjudicated Major CV Events* from ODYSSEY LONG TERM

Cumulative Probability of Event (%)

<table>
<thead>
<tr>
<th>Time (weeks)</th>
<th>0.00</th>
<th>0.02</th>
<th>0.04</th>
<th>0.06</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
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<td></td>
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<td>36</td>
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</tr>
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<td>52</td>
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</tr>
<tr>
<td>78</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

*Cox model analysis
HR = 0.52 (95% CI 0.31-0.89)
Nominal P value ≤ 0.01


Evolocumab and CV Events from OSLER-1 and OSLER-2

• Open-label trials: 1489 placebo, 2976 evolocumab


Targeted Populations for PCSK9 Inhibitors

- Clinical ASCVD
- Familial Hypercholesterolemia (FH)

• Residual CV risk as CV events seen despite aggressive LDL-lowering therapy in many patients, especially in FH
• Other options do not provide robust LDL-C reductions
• Some other options are inconvenient, not well tolerated and more costly than PCSK9 inhibitors

Options for FH patients after Statin Therapy

• Traditional nonstatins (ezetimibe, bile acid resins, niacin)
• Homozygous FH only drugs: Mipomersen and Lomitapide
  – REMS program required
  – Significant adverse events limit use
  – $176,000 to >250,000 annually!
• LDL Apheresis
  – $2500/treatment, repeated every 1 to 2 weeks
  – Each treatment takes 2 to 3 hours

Monoclonal Antibodies are not new...

TNF-alpha blockers
• Entered the market in the late 90’s
• Novel mechanism of action
• Highly effective
• Slowly increased in use
• Long term data demonstrated significant benefits
• Now have revolutionized treatment of rheumatoid arthritis, Crohn’s disease, psoriasis

Could this happen with PCSK9 inhibitors?

PRO PCSK9 – Summary Points
• Robust reductions in LDL-C have best potential to significantly lower CV events, on top of statin therapy
• Every 2 to 4 week dosing that is well tolerated
• Preliminary outcomes data has positive trends and early benefit, with complete data available in the future
• Best option after statin therapy for patients with FH

STEPS to Drug Selection

Safety
Tolerability
Effectiveness
Price

Quantitative Effects on Lipid Profile

<table>
<thead>
<tr>
<th>Agents</th>
<th>Lower LDL-C</th>
<th>Raise HDL-C</th>
<th>Lower VLDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>HMG-CoA Reductase Inhibitors (statins)</td>
<td>18-55%</td>
<td>5-15%</td>
<td>7-30%</td>
</tr>
<tr>
<td>PCSK9 Inhibitors</td>
<td>58%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>18%</td>
<td>1%</td>
<td>7-9%</td>
</tr>
<tr>
<td>Bile acid sequestrants</td>
<td>15-30%</td>
<td>3-5%</td>
<td>↔ or ↑</td>
</tr>
<tr>
<td>Niacin</td>
<td>5-25%</td>
<td>15-35%</td>
<td>20-50%</td>
</tr>
<tr>
<td>Mipomersen</td>
<td>25%</td>
<td>NR</td>
<td>18%</td>
</tr>
<tr>
<td>Lomitapide</td>
<td>40%</td>
<td>NR</td>
<td>45%</td>
</tr>
<tr>
<td>Bile acid derivatives</td>
<td>5-20%</td>
<td>10-20%</td>
<td>20-50%</td>
</tr>
<tr>
<td>Omega 3 Fatty Acids (fish oil)</td>
<td>↔ or ↑ 45%</td>
<td>9%</td>
<td>42%</td>
</tr>
</tbody>
</table>

Adapted from NCEP ATP-III Guidelines and product information.

PCSK9 Inhibitor Clinical Outcomes
• Randomized, double-blind, placebo-controlled
  − Alirocumab – ODYSSEY LONG-TERM
  − Evolocumab – OSLER long-term extension
• 50% reduction in major cardiovascular events
• Treatment duration of 11-18 months
• Limitations of post-hoc analyses
  − Underpowered observations

Meta-analysis of PCSK9-Inhibitor Outcomes
• Meta-analysis 24 phase II and III of 10,159 patients
• LDL-C reduction 50% vs. placebo (36% vs. ezetimibe)
• Limitations – small sample size and short duration of follow-up

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PCSK9-Inhibitor</th>
<th>Placebo</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>0.31%</td>
<td>0.53%</td>
<td>0.45 (0.23-0.86)</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>0.19%</td>
<td>0.33%</td>
<td>0.50 (0.23-1.10)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0.58%</td>
<td>1.0%</td>
<td>0.49 (0.26-0.93)</td>
</tr>
<tr>
<td>Adverse events</td>
<td>9.26%</td>
<td>7.73%</td>
<td>1.01 (0.87-1.18)</td>
</tr>
</tbody>
</table>

### Ongoing PCSK9 Outcomes Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Number of patients</th>
<th>Baseline LDL-C</th>
<th>Patient characteristics</th>
<th>Background therapy</th>
<th>Regimen</th>
<th>Regimen Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>ODYSSEY OUTCOMES</td>
<td>18,000</td>
<td>&gt;70 mg/dL</td>
<td>&lt;1 yr post ACS or ACS, or CVD</td>
<td>Max tolerated atorvastatin or rosvastatin</td>
<td>Alirocumab</td>
<td>75mg every 2 weeks (150mg for LDL-C &gt;50 mg/dL)</td>
</tr>
<tr>
<td>FOURIER</td>
<td>27,500</td>
<td>&gt;70 mg/dL</td>
<td>Prior MI, PVD, or CVD</td>
<td>Statins NR</td>
<td>Evolocumab</td>
<td>140mg every 2 weeks or 420mg every 4 weeks</td>
</tr>
<tr>
<td>SPIRE 1</td>
<td>17,000</td>
<td>70-100 mg/dL</td>
<td>High CV risk</td>
<td></td>
<td>Bococizumab</td>
<td>150mg every 2 weeks</td>
</tr>
<tr>
<td>SPIRE 2</td>
<td>9,000</td>
<td>&gt;100 mg/dL</td>
<td>High CV risk</td>
<td></td>
<td>Bococizumab</td>
<td>150mg every 2 weeks</td>
</tr>
</tbody>
</table>


### PCSK9 Cost Effectiveness

- **Annual Cost**
  - Alirocumab: $14,600
  - Evolocumab: $14,100

- **Assumptions**
  - 100% reduction in cardiovascular events
  - 3% absolute risk reduction
  - $20,000 cost savings per event
  - Annual cost savings = $600


### Effect on Insurance Premiums

- **Assumptions**
  - 25% negotiated discount for drug acquisition
  - $600 annual cost savings
  - 27% of US adults 40-64 years old with elevated LDL-C
  - 5% eligible for treatment with PCSK9 inhibitors
  - Annual insurance premium increase
    - $124 per person in the insurance pool


### Lomitapide (Juxtapid®) – Approved Dec 2012

- **MOA**: Microsomal triglyceride transfer protein (MTP) Inhibitor

http://www.pace-cme.org/d/443/mtp-inhibitors

- **Indication**: Homozygous Familial Hypercholesterolemia
- **FDA required REMS Program**
  - Dosing: 5mg by mouth once daily
  - Titrate every 2 weeks to a maximum dose of 60mg once daily
  - Metabolized via CYP3A4

**Black Box Warning!**
- Transaminase Elevations
- Steatohepatitis

Lomitapide Package insert

http://www.biotechduediligence.com/mipomersen-liver-safety.html

### Mipomersen (Kynamro®) – Approved Jan 2013

- **MOA**: antisense therapy that prevents formation of Apo B

http://www.pace-cme.org/d/443/mtp-inhibitors

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Mipomersen (Kynamro)

Indication: Homozygous Familial Hypercholesterolemia

- FDA required REMS Program
  - Dosing: 200mg once weekly (SQ injection)
  - Not metabolized by the liver

LDL-C TG apo B

\[ \downarrow 25\% \downarrow 18\% \downarrow 27\% \]

Nicotinic Acid: Niacin

<table>
<thead>
<tr>
<th>Niacin</th>
<th>Study</th>
<th>Event risk reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>IR Niacin (crystalline)</td>
<td>Coronary Drug Project</td>
<td>27% non-fatal MI (5 years)</td>
</tr>
<tr>
<td>IR Niacin + Colestipol</td>
<td>FATS</td>
<td>78% composite</td>
</tr>
<tr>
<td>Sis-Niacin or IR + Simvastatin</td>
<td>HATS</td>
<td>61% composite</td>
</tr>
</tbody>
</table>

- Preferred second agent (added to statin therapy)
- Mechanism not fully understood
- Reducing hepatic synthesis of triglycerides and secretion of VLDL
- Inhibit conversion of VLDL to LDL
- Side effects:
  - Flushing (common), alleviated by aspirin or food
  - Reducing hepatic synthesis of triglycerides and secretion of VLDL
  - Inhibit conversion of VLDL to LDL
  - Inhibit FA release from adipose tissue
  - Transaminase Elevations
  - Gout – increased uric acid levels
  - PUD – prostaglandin mediated vasodilation
  - Diabetes – impairs glucose tolerance (doses >1500 mg/day)

LDL Reduction (1.5 g/day) Max Dose Risk of Flushing Risk of Hepatotoxicity

- Niacin IR (OTC) 13% 6 g/day ++ +
- Niacin SR (OTC) 2 g/day + ++
- Sis-Niacin (OTC) 12% 2 g/day ++ +
- Naspan (RX) 13% 2 g/day ++ +

- USE Immediate Release Niacin
  - Squibb (or other pharmaceutical manufacturers who abide by good manufacturing practices)
  - Twin Labs (crystal niacin from health food stores)

- USE with caution Sis-Niacin
  - Upsher-Smith Laboratories, Inc.

HPS2-Thrive: ER Niacin + Laropiprant for Vascular Risk Reduction

- 25,673 patients with Prior history of: myocardial infarction; ischaemic stroke or TIA; peripheral arterial disease; or diabetes with other CHD
- Randomized to ER niacin 2g + laropiprant 40mg daily, or placebo
  - Background simvastatin 40mg or ezetimibe/simvastatin 10/40mg therapy

- Primary endpoint: time to first major vascular event – composite of CHD death, nonfatal MI, stroke, or arterial revascularization
  - ER Niacin 282 (16.4%) vs. 274 (16.25%)

- Trial was stopped after a mean follow-up period of 3.9 years due to significant adverse events, principally myopathy with niacin


LDL particles: Baseline Mean Mean at 4-years

- HDL 44 mg/dL 50 mg/dL
- Triglycerides 125 mg/dL 94 mg/dL
- LDL 63 mg/dL 56 mg/dL

Summary of Recent Trials

<table>
<thead>
<tr>
<th>Study (intervention)</th>
<th>Achieved LDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIM-HIGH (Niacin ER vs. Placebo)</td>
<td>62 mg/dL</td>
</tr>
<tr>
<td>plus ezetimibe 10 mg as needed</td>
<td></td>
</tr>
<tr>
<td>HPS2-Thrive (Niacin ER + laropiprant)</td>
<td>56 mg/dL</td>
</tr>
<tr>
<td>ACCORD-Lipid (Fenofibrate vs. Placebo)</td>
<td>81 mg/dL</td>
</tr>
<tr>
<td>simvastatin 40mg</td>
<td></td>
</tr>
<tr>
<td>or ezetimibe/simvastatin 10/40mg</td>
<td></td>
</tr>
</tbody>
</table>
Comparison of LDL-C Lowering, NNT and CVD Prevention Costs

<table>
<thead>
<tr>
<th>Study</th>
<th>Therapy</th>
<th>Time (yrs)</th>
<th>Relative Risk</th>
<th>Absolute Risk Difference</th>
<th>NNT</th>
<th>2016 Cost (S)</th>
<th>Annual Cost per Event Prevented (S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WOSCOPS</td>
<td>Pravastatin vs. Placebo</td>
<td>4.8</td>
<td>0.69</td>
<td>2.4%</td>
<td>42</td>
<td>50</td>
<td>2,083</td>
</tr>
<tr>
<td>TNT</td>
<td>Hi Atorvastatin vs. Lo Atorvastatin</td>
<td>6.0</td>
<td>0.78</td>
<td>2.2%</td>
<td>45</td>
<td>50</td>
<td>2,273</td>
</tr>
<tr>
<td>IMPROVE-IT</td>
<td>Statin + ezetimibe vs. Statin</td>
<td>7.0</td>
<td>0.94</td>
<td>2.0%</td>
<td>50</td>
<td>1000</td>
<td>50,000</td>
</tr>
<tr>
<td>ODYSSEY (HeFH)</td>
<td>Statin + alirocumab vs. Statin</td>
<td>1.5</td>
<td>0.52</td>
<td>1.6%</td>
<td>63</td>
<td>12,000</td>
<td>756,000</td>
</tr>
<tr>
<td>OSLER (HeFH)</td>
<td>Statin + evolocumab</td>
<td>1.0</td>
<td>0.47</td>
<td>1.2%</td>
<td>81</td>
<td>12,000</td>
<td>972,000</td>
</tr>
</tbody>
</table>

Wilson, PW. Presented at National Lipid Association Meeting, Pittsburgh, PA. 9/18/2015.

CON PCSK9 – Summary Points

- PCSK9 inhibitors effectively lower LDL-C but their true impact on CV events is uncertain
- Post hoc analyses and meta-analyses of phase II and phase III trials are promising
- Four clinical outcomes trials are ongoing
- High annual acquisition cost is problematic
  - $600 annual cost savings
  - Potential increase in insurance premiums for entire pool
  - Cost effectiveness studies comparing options are needed
- Combination drug therapy with niacin or ezetimibe should be considered before PCSK9 inhibitors

According to the National Lipid Association (NLA), which of following is the most appropriate goal of therapy for a patient with very high ASCVD risk?

A. LDL-C <130 mg/dL
B. Non-HDL-C <100 mg/dL
C. 30% LDL-C reduction from baseline
D. 50% reduction in hs-CRP from baseline

Which of the following is true regarding the Proprotein convertase subtilisin/kexintype 9 (PCSK9) inhibitors?

A. PCSK9 inhibitors work by blocking cholesterol absorption in the intestines
B. Alirocumab is dosed orally every 2 weeks
C. Evolocumab is indicated for both heterozygous and homozygous familial hypercholesterolemia
D. PCSK9 inhibitors on average lower LDL-C by same amount as titrating a statin from the lowest dose to the highest dose (i.e. – atorvastatin 10mg to 80mg)
In the IMPROVE-IT trial, which endpoint was significantly lower in patients treated with ezetimibe/simvastatin combination therapy compared to simvastatin alone?

A. All-cause mortality
B. Stroke
C. CVD/MI/Stroke
D. All of the above

Which of the following is most appropriate initial therapy for a patient at very high ASCVD risk?

A. Alirocumab
B. Rosuvastatin
C. Ezetimibe
D. Lomitapide