Optimizing Outcomes in Lipid Management: Focusing on LDL-C Reduction

Spring Managed Care Forum
National Association of Managed Care Physicians
Gaylord alms Resort and Convention Center
Kissimmee, Florida
Friday, April 22, 2016
10:50-11:50 AM

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Seinsheimer Cardiovascular Health Program
Professor of Medicine
Medical University of South Carolina
Charleston, South Carolina
<table>
<thead>
<tr>
<th>DISCLOSURE OF FINANCIAL RELATIONSHIPS</th>
</tr>
</thead>
</table>

**Jan N. Basile, MD**

<table>
<thead>
<tr>
<th>Grant/Research support:</th>
<th>NHLBI (SPRINT), REWIND Eli-Lilly</th>
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</thead>
<tbody>
<tr>
<td>Consultant or Advisory Panel:</td>
<td>Amgen, Eli-Lilly, Allergan, Janssen, Novartis</td>
</tr>
<tr>
<td>Speakers Bureau:</td>
<td>Amgen, Janssen</td>
</tr>
<tr>
<td>Major stock shareholder:</td>
<td>None</td>
</tr>
<tr>
<td>Other:</td>
<td>None</td>
</tr>
</tbody>
</table>
Learning Objectives:

Upon completion of this lecture, learners should be better prepared to:

1) Recognize the 4 patient populations who benefit most from statin-based therapy according to the ACC/AHA 2014 guidelines and the controversies surrounding targeting LDL-C as a treatment goal

2) Define the population where additional lipid-lowering agents with or without a background of statin-therapy have further improved CV outcomes

3) Define the role of the PCSK9 inhibitors to further lower LDL-cholesterol in the hopes of improving CV outcome
Pre-test Question

On a scale of 1 to 5, please rate how confident you would be in treating your patients with Hypercholesterolemia?

1. Not at all confident
2. Slightly confident
3. Moderately confident
4. Pretty much confident
5. Very confident
Statin Evidence: Landmark Statin Trials
The Greater the Risk The Greater the Benefit
The Lower the LDL-C, The Greater the Benefit

Adapted from Kastelein JP. Atherosclerosis. 1999;143(suppl 1):S17-S21.
Relationship Between LDL-C Levels and CHD Events in Secondary Prevention Statin Trials: The Lower the LDL-C, the Fewer the Events

Primary Endpoint-Composite of CV death, MI, coronary revascularization, hospitalization for UA, or UA.

Based on this, the LDL-C goal was lowered in the highest risk group to < 70 mg/dL.

Wiviott SD et al., J Am Coll Cardiol 2005: 1411-1416.
Meta-Analysis: 90,056 Individuals in 14 Randomized Clinical Trials of Statins

423,000 Patient Years of Follow-up

Per a 39 mg/dL (1 mmol/L) absolute reduction in LDL with Statin Rx

- 23% reduction in major cardiac events
- 20% reduction in CHD mortality
- 22% reduction in ischemic strokes
- Benefit entirely in proportion to LDL reduction
- No influence of baseline LDL on level of benefit
- No effect of sex, age, or other risk factors on benefit
- Similar relative risk reduction in all subgroups
- No increase in non-cardiovascular mortality

CTT  Lancet 2005;366:1266-1278
## Effects on MAJOR VASCULAR EVENTS

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Treatment</th>
<th>Control</th>
<th>Rate Ratio (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-fatal MI</td>
<td>2001 (4·4)</td>
<td>2769 (6·2)</td>
<td>0·74 (0·70 – 0·79)</td>
</tr>
<tr>
<td>CHD death</td>
<td>1548 (3·4)</td>
<td>1960 (4·4)</td>
<td>0·81 (0·75 – 0·87)</td>
</tr>
<tr>
<td>Any major coronary event</td>
<td>3337 (7·4)</td>
<td>4420 (9·8)</td>
<td>0·77 (0·74 – 0·80)</td>
</tr>
<tr>
<td>CABG</td>
<td>713 (3·3)</td>
<td>1006 (4·7)</td>
<td>0·75 (0·69 – 0·82)</td>
</tr>
<tr>
<td>PTCA</td>
<td>510 (2·4)</td>
<td>658 (3·1)</td>
<td>0·79 (0·69 – 0·90)</td>
</tr>
<tr>
<td>Unspecified</td>
<td>1397 (3·1)</td>
<td>(3·9)</td>
<td>0·76 (0·69 – 0·84)</td>
</tr>
<tr>
<td>Any coronary revascularization</td>
<td>2620 (5·8)</td>
<td>3434 (7·6)</td>
<td>0·76 (0·73 – 0·80)</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>105 (0·2)</td>
<td>99 (0·2)</td>
<td>1·05 (0·78 – 1·41)</td>
</tr>
<tr>
<td>Presumed ischaemic stroke</td>
<td>1235 (2·8)</td>
<td>1518 (3·4)</td>
<td>0·81 (0·74 – 0·89)</td>
</tr>
<tr>
<td>Any stroke</td>
<td>1340 (3·0)</td>
<td>1617 (3·7)</td>
<td>0·83 (0·78 – 0·88)</td>
</tr>
<tr>
<td>Any major vascular event</td>
<td>6354 (14·1)</td>
<td>7994 (17·8)</td>
<td>0·79 (0·77 – 0·81)</td>
</tr>
</tbody>
</table>

CTT. Lancet 2008 371: 117-125
2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults

Neil J. Stone, MD, MACP, FAHA, FACC, Chair
Jennifer Robinson, D, MPH, FAHA, Vice Chair
Alice H. Lichtenstein, DSc, FAHA, Vice Chair

Anne C. Goldberg, MD, FACP, FAHA
Conrad B. Blum, MD, FAHA
Robert H. Eckel, MD, FAHA
Daniel Levy, MD*
David Gordon, MD*
C. Noel Bairey Merz, MD, FAHA, FACC

Donald M. Lloyd-Jones, MD, ScM, FACC, FAHA
J. Sanford Schwartz, MD
Patrick McBride, MD, MPH, FAHA
Sidney C. Smith, Jr, MD, FACC, FAHA
Karol Watson, MD, PhD, FACC, FAHA
Susan T. Shero, MS, RN*
Peter W.F. Wilson, MD, FAHA

LDL-C Goals for High-Risk Patients Have Become More Intensive Over Time

- As part of therapeutic lifestyle changes, including diet, LDL-C treatment goals for high-risk patients have been lowered over time.

<table>
<thead>
<tr>
<th>Year</th>
<th>ATP I II III Update</th>
<th>2006 AHA/ACC</th>
<th>2010 ADA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1988</td>
<td>Goal: &lt;130 mg/dL¹</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1993</td>
<td>Goal: &lt;100 mg/dL²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2001</td>
<td>Goal: &lt;100 mg/dL³</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2004</td>
<td>Goal: &lt;100 mg/dL⁴</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Optional goal: &lt;70 mg/dL⁴</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>High-risk pts</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Very-high-risk pts⁵</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Goal: &lt;100 mg/dL⁶</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reasonable goal: &lt;70 mg/dL⁶</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Goal: &lt;70 mg/dL⁶</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Overt CVD</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Definition of high-risk or highest-risk patient:
- ATP I: definite CHD or 2 other CHD risk factors¹
- ATP II: prior CHD or other atherosclerotic disease²
- ATP III and the 2004 update: CHD or CHD risk equivalents³,⁴
- 2° AHA/ACC 2006: established coronary and other atherosclerotic disease⁵
- ADA 2010: overt CVD⁶

Factors that place a patient at very high risk:
- Multiple components of the metabolic syndrome, established CVD plus any of the following: multiple major risk factors (especially diabetes), severe and poorly controlled risk factors (eg, cigarette smoking), multiple components of the metabolic syndrome (especially TG ≥200 mg/dL + non–HDL-C ≥130 mg/dL with HDL-C <40 mg/dL), and recent acute coronary syndromes.⁴

References:
2013 ACC/AHA Expert Panel Recommendation

A New Perspective on LDL-C and/or non-HDL Goals

- There is no RCT evidence to support continued use of specific LDL–C and/or non-HDL–C treatment targets.

- The appropriate intensity of statin therapy should be used to reduce ASCVD risk in those most likely to benefit.

- Non-statin therapies, whether used alone or in addition to statins, do not provide acceptable ASCVD risk reduction benefits compared to their potential for adverse effects in the routine prevention of ASCVD.
2013 ACC/AHA Expert Panel

- **TLC**: Still an integral part of CHD risk management
- **LDL-C**: No longer a primary target of lipid-modifying therapy
- **Non-HDL-C**: No longer a secondary target of therapy in patients with hypertriglyceridemia (≥200 mg/dL)
- **HDL-C**: No treatment goals are identified for HDL-C
  - Low HDL-C (<40 mg/dL) as positive CHD risk factor
  - High HDL-C (≥60 mg/dL) as negative CHD risk factor
- **TG**: No treatment goals are identified for TG
  - Treat if levels >500 mg/dL where risk of pancreatitis is still high

TLC = Therapeutic Lifestyle Change

LDL-C Reduction Remains Fundamental to Major Cholesterol Treatment Guidelines

Recommendations for Patients With Clinical ASCVD

ASCVD = atherosclerotic cardiovascular disease; ACC = American College of Cardiology; AHA = American Heart Association; ADA = American Diabetes Association; NLA = National Lipid Association; AACE = American Association of Clinical Endocrinologists; IAS = International Atherosclerosis Society; ESC = European Society of Cardiology; EAS = European Atherosclerosis Society.

*Percent LDL-C reduction defines treatment intensity and assesses adherence;† also includes percent LDL-C reduction as an efficacy metric.

**ADA: Recommendations for Statin And Combination Treatment in People with Diabetes**

<table>
<thead>
<tr>
<th>Age</th>
<th>Risk Factors</th>
<th>Statin Intensity*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40 years</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>ASCVD risk factor(s)**</td>
<td>Moderate or high (C)</td>
</tr>
<tr>
<td></td>
<td>ASCVD</td>
<td>High</td>
</tr>
<tr>
<td>40–75 years</td>
<td>None</td>
<td>Moderate (A)</td>
</tr>
<tr>
<td></td>
<td>ASCVD risk factors</td>
<td>High (B)</td>
</tr>
<tr>
<td></td>
<td>ACS &amp; LDL &gt;50 who can’t tolerate high dose statin</td>
<td>Moderate + ezetimibe (A)</td>
</tr>
<tr>
<td>&gt;75 years</td>
<td>None</td>
<td>Moderate (B)</td>
</tr>
<tr>
<td></td>
<td>ASCVD</td>
<td>Moderate or high (B)</td>
</tr>
<tr>
<td></td>
<td>ACS &amp; LDL &gt;50 who can’t tolerate high dose statin</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>ACS &amp; LDL &gt;50 who can’t tolerate high dose statin</td>
<td>Moderate + ezetimibe (A)</td>
</tr>
</tbody>
</table>

* In addition to lifestyle therapy.
** LDL cholesterol ≥100 mg/dL (2.6 mmol/L), high blood pressure, smoking, overweight or obesity, and family hx of premature ASCVD.

American Diabetes Association Standards of Medical Care in Diabetes. *Diabetes Care* 2016; 39 (Suppl. 1): S60-S71
# High- and Moderate-Intensity Statin Therapy*

<table>
<thead>
<tr>
<th>High Intensity Statin Therapy</th>
<th>Moderate-Intensity Statin Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lowers LDL by ≥50%</td>
<td>Lowers LDL by 30 - &lt;50%</td>
</tr>
<tr>
<td>Atorvastatin 40-80 mg</td>
<td>Atorvastatin 10-20 mg</td>
</tr>
<tr>
<td>Rosuvastatin 20-40 mg</td>
<td>Rosuvastatin 5-10 mg</td>
</tr>
<tr>
<td></td>
<td>Simvastatin 20-40 mg</td>
</tr>
<tr>
<td></td>
<td>Pravastatin 40-80 mg</td>
</tr>
<tr>
<td></td>
<td>Lovastatin 40 mg</td>
</tr>
<tr>
<td></td>
<td>Fluvastatin XL 80 mg</td>
</tr>
<tr>
<td></td>
<td>Pitavastatin 2-4 mg</td>
</tr>
</tbody>
</table>

* Once-daily dosing

American Diabetes Association Standards of Medical Care in Diabetes. *Diabetes Care* 2016; 39 (Suppl. 1): S60-S71
### 2014 National Lipid Association Guidelines: Criteria for ASCVD Risk Assessment, LDL-C Treatment Goals, and When to Consider Drug Therapy

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Criteria</th>
<th>Treatment Goal</th>
<th>Consider Drug Therapy</th>
</tr>
</thead>
</table>
| Low           | ▪ 0-1 major ASCVD risk factors  
                  ▪ Consider other risk indicators, if known | <130 Non-HDL-C mg/dL  
                                          <100 LDL-C mg/dL | ≥190  
                                          ≥160 |
| Moderate      | ▪ 2 major ASCVD risk factors  
                  ▪ Consider quantitative risk scoring  
                  ▪ Consider other risk indicators | <130 Non-HDL-C mg/dL  
                                          <100 LDL-C mg/dL | ≥160  
                                          ≥130 |
| High          | ▪ ≥3 major ASCVD risk factors  
                  ▪ Diabetes mellitus* (Type 1 or 2)  
                        ▪ 0-1 other major ASCVD risk factors, and  
                        ▪ No evidence of end organ damage  
                  ▪ Chronic kidney disease stage 3B or 4  
                  ▪ LDL-C ≥190 mg/dL (severe hypercholesterolemia)  
                  ▪ Quantitative risk score reaching the high-risk threshold | <130 Non-HDL-C mg/dL  
                                          <100 LDL-C mg/dL | ≥130  
                                          ≥100 |
| Very High     | ▪ ASCVD*  
                  ▪ Diabetes mellitus* (Type 1 or 2)  
                        ▪ ≥2 other major ASCVD risk factors or  
                        ▪ Evidence of end organ damage | <100 Non-HDL-C mg/dL  
                                          <70 LDL-C mg/dL | ≥100  
                                          ≥70 |

*For patients with ASCVD or diabetes mellitus, consideration should be given to use of moderate- or high-intensity statin therapy, irrespective of baseline atherogenic cholesterol levels.*

Despite Treatment Many US Adults With CHD* Are Not Achieving Prespecified LDL-C Levels

NHANES = National Health and Nutrition Examination Survey.
*NHANES defined CHD based on answers to questions about CHD, angina, and MI (patient survey).

Early Nonstatin Trials of Lowering Cholesterol Levels

LRC-CPPT\(^a\): 3806 asymptomatic men
- Cholestyramine + diet vs diet alone
- \(\Delta\) LDL-C: 23-40 mg/dL

- Placebo
- Cholestyramine resin

19\% reduction
\(P < .05\)

Helsinki Heart\(^b\): 4081 asymptomatic men
- Gemfibrozil vs placebo
- \(\Delta\) LDL-C: 21 mg/dL

- Placebo
- Gemfibrozil

34\% reduction
\(P < .02\)

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# Niacin as Monotherapy: Secondary Prevention Studies

<table>
<thead>
<tr>
<th>Trial</th>
<th>Design/Duration</th>
<th>Drug(s)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary Drug Project 1975</td>
<td>2° prevention</td>
<td>Niacin</td>
<td>5 yrs – nonfatal MI ↓27%; stroke/TIA ↓24%; 15 yrs – total mortality ↓11%</td>
</tr>
<tr>
<td>Stockholm IHD Study 1988</td>
<td>2° prevention</td>
<td>Niacin, clofibrate</td>
<td>Total mortality ↓26%; Ischemic heart disease mortality ↓36%</td>
</tr>
<tr>
<td></td>
<td>5 yrs.</td>
<td></td>
<td></td>
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</tbody>
</table>
Fibrates: Cardiovascular Outcome Data Shows Mixed Results Based on Mono vs Additive Rx

Table 1. Cardiovascular Outcomes in Fibrate Trials.*

<table>
<thead>
<tr>
<th>Trial</th>
<th>Fibrate</th>
<th>Follow-up yr</th>
<th>Patient Population</th>
<th>Primary End Point</th>
<th>Absolute Event Rate (%)</th>
<th>Risk Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HHS (1982)</td>
<td>Gemfibrozil, 1200 mg</td>
<td>5.0</td>
<td>4081 men with non-HDL cholesterol ≥200 mg/dl (primary prevention)</td>
<td>Fatal or nonfatal MI, or CAD death</td>
<td>84/2030 (4.1)</td>
<td>56/2051 (2.7)</td>
<td>0.66 (0.47–0.92)</td>
</tr>
<tr>
<td>VA-HIT</td>
<td>Gemfibrozil, 1200 mg</td>
<td>5.1</td>
<td>2531 men with CAD and HDL cholesterol &lt;40 mg/dl (secondary prevention)</td>
<td>Nonfatal MI or CAD death</td>
<td>275/1267 (21.7)</td>
<td>219/1264 (17.3)</td>
<td>0.78 (0.65–0.95)</td>
</tr>
<tr>
<td>BIP (1990–1992)</td>
<td>Bezaefibrate, 400 mg</td>
<td>6.2</td>
<td>3090 men and women with previous MI or angina (secondary prevention)</td>
<td>Fatal or nonfatal MI or sudden death</td>
<td>232/1542 (15.1)</td>
<td>211/1548 (13.6)</td>
<td>0.91 (0.76–1.08)</td>
</tr>
<tr>
<td>FIELD</td>
<td>Fenofibrate, 200 mg</td>
<td>5.0</td>
<td>9795 men and women with type 2 diabetes (primary and secondary prevention)</td>
<td>Nonfatal MI or CAD death</td>
<td>288/4900 (5.9)</td>
<td>256/4895 (5.2)</td>
<td>0.89 (0.75–1.05)</td>
</tr>
<tr>
<td>ACCORD</td>
<td>Fenofibracid, 160 mg</td>
<td>4.7</td>
<td>5518 men and women with type 2 diabetes on statin therapy (primary and secondary prevention)</td>
<td>Nonfatal MI, nonfatal stroke, or death from cardiovascular causes</td>
<td>310/2765 (11.2)</td>
<td>291/2753 (10.6)</td>
<td>0.92 (0.79–1.08)</td>
</tr>
</tbody>
</table>

* ACCORD denotes Action to Control Cardiovascular Risk in Diabetes trial, BIP Bezaefibrate Infarction Prevention study, CAD coronary artery disease, FIELD Fenofibrate Intervention and Event Lowering in Diabetes study, HHS Helsinki Heart Study, MI myocardial infarction, and VA-HIT Veterans Affairs High-Density Lipoprotein Intervention Trial.
When to Consider Statins in Combination with:

Niacin
- No use: AIM HIGH, HPS THRIVE-2

Fenofibrate
- No use: FIELD, ACCORD

Fish Oil
- No use: NO STUDIES

Ezetimibe
- Can use: NOW PROOF:
  (The IMPROVE IT trial)

Bile Acid Resin
- No use: NO STUDIES
Combination therapy (statin/fibrate) doesn’t improve ASCVD outcomes and is generally not recommended. Consider therapy with statin and fenofibrate for men with both trigs ≥204 mg/dL (2.3 mmol/L) and HDL ≤34 mg/dL (0.9 mmol/L).

Combination therapy (statin/niacin) hasn’t demonstrated additional CV benefit over statins alone, may raise risk of stroke & is not generally recommended.

Statin therapy is contraindicated in pregnancy.
IMPROVE-IT Study Design

Patients stabilized post ACS ≤ 10 days:

LDL-C 50 – 125 mg/dL (or 50-100 mg/dL if prior lipid-lowering Rx)
-34% on statins upon entering trial
-mean age 64, 1147 sites in 39 countries

Standard Medical & Interventional Therapy

N= 18, 144

Simvastatin
40 mg

Uptitrated to Simva 80 mg if LDL-C > 79
(adapted per FDA label 2011)
-27% mono, 6% combo

Ezetimibe / Simvastatin
10 / 40 mg

Follow-up Visit Day 30, every 4 months

Duration: Minimum 2 ½-year follow-up (at least 5250 events)

Primary Endpoint: CV death, MI, hospital admission for UA, coronary revascularization (≥ 30 days after randomization), or stroke

Cannon CP AHJ 2008;156:826-32
### IMPROVE-IT

#### LDL-C and Lipid Changes

<table>
<thead>
<tr>
<th></th>
<th>1 Yr Mean</th>
<th>LDL-C</th>
<th>TC</th>
<th>TG</th>
<th>HDL</th>
<th>hsCRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simva</td>
<td></td>
<td>69.9</td>
<td>145.1</td>
<td>137.1</td>
<td>48.1</td>
<td>3.8</td>
</tr>
<tr>
<td>EZ/Simva</td>
<td></td>
<td>53.2</td>
<td>125.8</td>
<td>120.4</td>
<td>48.7</td>
<td>3.3</td>
</tr>
<tr>
<td>Δ in mg/dL</td>
<td></td>
<td>-16.9</td>
<td>-19.3</td>
<td>-16.7</td>
<td>+0.6</td>
<td>-0.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time since randomization (months)</th>
<th>Mean LDL-C (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>QE</td>
<td>93</td>
</tr>
<tr>
<td>R</td>
<td>82</td>
</tr>
<tr>
<td>1</td>
<td>66</td>
</tr>
<tr>
<td>4</td>
<td>71</td>
</tr>
<tr>
<td>8</td>
<td>69</td>
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<tr>
<td>12</td>
<td>68</td>
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<td>16</td>
<td>66</td>
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<td>24</td>
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<td>72</td>
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</tr>
<tr>
<td>84</td>
<td>60</td>
</tr>
<tr>
<td>96</td>
<td>59</td>
</tr>
</tbody>
</table>

Number at risk:
- EZ/Simva: 8990, 8889, 8230, 7701, 7264, 6864, 6583, 6256, 5734, 5354, 4508, 3484, 2608, 1078

IMPROVE-IT vs. CTT: Ezetimibe vs. Statin Benefit

CTT Collaboration.
Lancet 2005; 366:1267-78;
Lancet 2010;376;1670-81.

IMPROVE-IT (cont)

Safety of Very Low Achieved LDL-C Levels

- AE rates similar with very low, low, medium, and higher achieved LDL-C levels in patients treated with simvastatin/ezetimibe

<table>
<thead>
<tr>
<th>AE Leading to Discontinuation</th>
<th>AST or ALT ≥ 3x ULN</th>
<th>Myalgia With CK Elevation per Investigator</th>
<th>Myopathy per CEC</th>
<th>Rhabdomyolysis per CEC</th>
<th>Memory Impairment or Altered Mental Status</th>
<th>Hemorrhagic Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>P = .38</td>
<td>P = .68</td>
<td>P = .90</td>
<td>P = .41</td>
<td>P = .16</td>
<td>P = .97</td>
<td>P = .57</td>
</tr>
<tr>
<td>6.9</td>
<td>4.6</td>
<td>9.7</td>
<td>0.1</td>
<td>0.1</td>
<td>2.1</td>
<td>0.3</td>
</tr>
<tr>
<td>6.9</td>
<td>4.5</td>
<td>8.8</td>
<td>0.1</td>
<td>0.2</td>
<td>2.5</td>
<td>0.8</td>
</tr>
<tr>
<td>6.5</td>
<td>4.4</td>
<td>9.2</td>
<td>0.1</td>
<td>0.1</td>
<td>2.9</td>
<td>0.4</td>
</tr>
<tr>
<td>6.5</td>
<td>4.4</td>
<td>9.2</td>
<td>0.1</td>
<td>0.1</td>
<td>2.3</td>
<td>0.6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients by LDL-C Level at 1 mo</th>
<th>&lt; 30 mg/dL</th>
<th>30- &lt; 50 mg/dL</th>
<th>50- &lt; 70 mg/dL</th>
<th>≥ 70 mg/dL</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>969</td>
<td>4755</td>
<td>5482</td>
<td>3989</td>
<td></td>
</tr>
<tr>
<td>Randomized to simvastatin + ezetimibe, %</td>
<td>85</td>
<td>72</td>
<td>44</td>
<td>22</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>

IMPproved Reduction of Outcomes: Vytorin Efficacy International Trial
IMPROVE-IT

• Re-affirms the LDL hypothesis
• Lower LDL-C is Better (achieved mean LDL-C was 70 mg/dL vs 54 mg/dL at 1 year)
• Hs-CRP was 0.5 lower with combination Rx
• ITT [intention-to-treat] patients followed for 7 years all did better (pre-specified endpoint)
• All safety endpoints for cancer, myopathy, and liver side effects were met (not different from statin-alone Rx)

CLINICAL PEARL

Addition of non-statin cholesterol-lowering drug(s) may be considered if the ASCVD risk-reduction benefits outweigh the potential for adverse effects.
AHA/ACC Cholesterol Treatment Guidelines


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AHA = American Heart Association; ACC = American College of Cardiology.
The 4 Statin Benefit Groups

- **Clinical ASCVD***

- **LDL-C ≥190 mg/dL, Age ≥21 years**

- **Primary prevention – Diabetes**: Age 40-75 years, LDL-C 70-189 mg/dL

- **Primary prevention - No Diabetes†**: ≥7.5%‡ 10-year ASCVD risk, Age 40-75 years, LDL-C 70-189 mg/dL

*Atherosclerotic cardiovascular disease
†Requires risk discussion between clinician and patient before statin initiation
‡Statin therapy may be considered if risk decision is uncertain after use of ASCVD risk calculator

ASCVD Statin Benefit Groups

Adults >20 years of age and a candidate for statin therapy

Clinical ASCVD and Age ≤75

LDL–C ≥190 mg/dL

Diabetes type 1 or 2 and age 40–75

>7.5% 10-year ASCVD risk and age 40 to 75

Measure risk factors every 4-6 years and recalculate 10-year ASCVD risk in those without ASCVD, diabetes, and with LDL-C <190 mg/dl

Global CV Risk Assessment Score

- 10-year ASCVD risk
  - Nonfatal or fatal MI; and nonfatal or fatal stroke

- [http://my.americanheart.org/cvriskcalculator](http://my.americanheart.org/cvriskcalculator)

- App-AHA CV Risk Calculator-Free download
# ACC AHA Risk Calculator

## Risk Factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Units</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>M (for males) or F (for females)</td>
<td>m</td>
</tr>
<tr>
<td>Age</td>
<td>years</td>
<td>48</td>
</tr>
<tr>
<td>Race</td>
<td>AA (for African Americans) or WH (for whites or others)</td>
<td>aa</td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td>mg/dL</td>
<td>160</td>
</tr>
<tr>
<td>HDL-Cholesterol</td>
<td>mg/dL</td>
<td>50</td>
</tr>
<tr>
<td>Systolic Blood Pressure</td>
<td>mm Hg</td>
<td>130</td>
</tr>
<tr>
<td>Treatment for High Blood Pressure</td>
<td>Y (for yes) or N (for no)</td>
<td>y</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Y (for yes) or N (for no)</td>
<td>n</td>
</tr>
<tr>
<td>Smoker</td>
<td>Y (for yes) or N (for no)</td>
<td>n</td>
</tr>
</tbody>
</table>

## Risk Results

- **Your 10-Year ASCVD Risk (%):** 7.7
- **10-Year ASCVD Risk (%) for Someone Your Age with Optimal Risk Factor Levels:** 3.5
Coronary Artery Calcium (CAC) Scores Predict the Need for Statin Therapy

On the basis of current guidelines from both NCEP and ACC/AHA:

- CAC scores < 75th percentile \textit{and} < 300 are to be treated with low- to moderate-dose statins.\(^1,2\)
- CAC scores > 75th percentile \textit{or} \(\geq 300\) are to be treated with high-dose statins.\(^1,2\)
- CAC score of zero should be considered for lifestyle modification, unless a compelling indication for statin already exists as CAC=0 resulted in the largest, most accurate downward risk reclassification of tests done\(^3\)

Inter-individual variability in response to statins

Subjects participating in clinical trials of statin therapy, display impressive average reductions in LDL-C. An individual patient’s response to statin therapy, however, can be very variable. The graph below shows dramatic inter-individual variability in response to Atorvastatin 10 mg daily. This has also been observed with other statins.
Statin Intolerance (SI)

- An estimated 5–20% cannot tolerate statin treatment
- Statin intolerance (most commonly muscle pain, aching, and weakness) commonly leads to discontinuation
- Intolerance may be the result of perception or expectation (clipping the package insert on the Rx)
- Most statin-intolerant patients can be successfully re-challenged (occurs when patients are blinded in studies)
- A subset of patients are truly statin intolerant but it is much smaller than we believe it is with the exact number unclear.
- The FDA defines SI as patients who have either been optimized on a statin or unable to tolerate any statin type or dose

Abramson JD, et al. BMJ. 2013;347:f6123

De Vera MA, et al. BJCP. 2014;78(4):684-698
What Does the 2013 ACC/AHA Guideline Say?  
Monitoring Statin Therapy

- Initial fasting lipid panel
- Second panel 4-12 weeks later to determine adherence to therapy
- Every 3-12 months as clinically indicated

CASE PRESENTION

• 51 year-old male
  - at age 41 treated with PCI for LAD occlusion
  - at age 49 further development of coronary disease resulting in three-vessel CABG

• PMHx-hasn’t smoked in 20 years, drinks a couple of beers on the weekend

• No hx of diabetes, hypertension, thyroid or liver disease
CASE PRESENTATION

- Fam Hx: - brother died of an MI at age 43
  - sister had angioplasty at age 52.
- Meds: On atorvastatin 80 mg and ezetimibe 10 mg
- Did not tolerate bile acid sequestrants (constipation and bloating) or niacin (bad flushing)
- TC=276 mg/dL, LDL-201 mg/dL, TGs 125 mg/dL and HDL 45 mg/dL. Lp(a)-56 mg/dL.
- BMI 24.6 kg/m2, BP 126/74 mm Hg
- Corneal Arcus and Achilles xanthoma found on exam
2013 ACC/AHA Cholesterol Guidelines

Recommend high-intensity statin therapy for patients at high risk

- Age $\geq$ 21 y and a candidate for statin therapy
- Clinical ASCVD
  - Yes
    - LDL-C $\geq$ 190 mg/dL
      - Yes
        - High-intensity statin
        - (moderate-intensity statin if not candidate for high-intensity statin)
      - No
        - Diabetes
          - LDL-C 70-189 mg/dL Age 40-75 y
            - Yes
              - Moderate-intensity statin
            - No
              - Estimated 10-y ASCVD risk $\geq$ 7.5%
                - Yes
                  - High-intensity statin
                - No
                  - Moderate-intensity statin

Definitions of High- and Moderate-Intensity Statin Therapy

- High
  - Daily dose lowers LDL-C by $\sim \geq 50\%$
- Moderate
  - Daily dose lowers LDL-C by $\sim 30\%$ to $< 50\%$

Regularly monitor adherence to lifestyle and drug therapy with lipid and safety assessments

FH: Most Common Inherited Disorder

Heterozygous FH is found in 1:250-300 patients

FH: Most Common Inherited Disorder

FH
Dominant otosclerosis
Adult PCKD
Sickle cell Disease
Multiple Exostoses
Huntington’s Disease
Fragile X
Neurofibromatosis
Cystic fibrosis
Duchenne’s muscular dystrophy

PCKD = polycystic kidney disease.

FH
1.0
0.8
0.5
0.5
0.5
0.5
0.4
0.4
0.3

4x more common
5x more common

What Is Clinical ASCVD and FH?

Clinical ASCVD\(^1\)
- Defined in 2013 ACC/AHA guidelines as one or more of the following:\(^1,2\)
  - Coronary heart disease (CHD)
    - Acute coronary syndrome
    - History of myocardial infarction (MI)
    - Stable or unstable angina (UA)
    - Coronary or other arterial revascularization
  - Stroke or transient ischemic attack
  - Peripheral arterial disease

Familial Hypercholesterolemia (FH)\(^2-4\)
- Inherited conditions characterized by elevated LDL-C and mutations in genes involved in LDL metabolism\(^3\)
  - Heterozygous FH
    - LDL-C \(\geq 190\) mg/dL\(^3,*\)
    - Identification\(^4\)
      - Elevated LDL-C with physical findings or family history of early MI
      - DNA-based evidence
  - Homozygous FH
    - LDL-C > 500 mg/dL\(^5,*\)
    - CVD diagnosis on average at 20 years\(^3\)


DNA = deoxyribonucleic acid.
\(^*\)Typical levels when untreated;
\(^\dagger\)LDL-C level indicative of HoFH, lower levels do not exclude HoFH.

Simon Broome criteria in adults include an LDL-C of > 190 mg/dL (without therapy) plus clinical criteria (including patient or family history of tendon xanthomas, family history of early CAD, or family history of TC > 290 mg/dL).\(^2,3\)
Familial Hypercholesterolemia (FH)

- Inheritable, almost always autosomal dominant disorder\(^1,4\)
- Due to mutations that result in decreased clearance of LDL particles from plasma\(^1\)
  - Usually loss of function (LOF) mutation in LDL receptor gene (FH1)\(^2,3\)
  - Other mutations include LOF in Apo B (FH2) and gain of function mutations in the PCSK9 genes (FH3)\(^4\)
- Clinical manifestations include\(^1,2,4\)
  - Severe hypercholesterolemia due to accumulation of plasma LDL
  - Often accompanied by cholesterol deposition in tendons and skin (xanthomas) and in the eyes (corneal arcus)
  - Evidence of CVD early in life, aortic stenosis (HoFH)

New LDL-C Lowering Drugs For The Treatment of Hypercholesterolemia
## Currently Used Therapies for HoFH and HeFH

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Major Effect</th>
<th>LDL-lowering Response</th>
<th>HoFH</th>
<th>HeFH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-Chol Diet</td>
<td>↑ LDLR activity</td>
<td></td>
<td>&lt;10%</td>
<td>10-25%</td>
</tr>
<tr>
<td>Statins</td>
<td>↑ LDLR activity</td>
<td>&lt;10%</td>
<td>&lt;10%</td>
<td>&gt;25%</td>
</tr>
<tr>
<td>Resins</td>
<td>↑ LDLR activity</td>
<td>&lt;10%</td>
<td>&lt;10%</td>
<td>10-25%</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>↓ chol absorp + ↑ LDLRa</td>
<td>&lt;10%</td>
<td>&lt;10%</td>
<td>10-25%</td>
</tr>
<tr>
<td>Stanol Esters</td>
<td>↓ chol absorp + ↑ LDLRa</td>
<td>&lt;10%</td>
<td>&lt;10%</td>
<td>10-25%</td>
</tr>
<tr>
<td>Nicotinic Acid</td>
<td>↓ VLDL synthesis</td>
<td>&lt;10%</td>
<td>&lt;10%</td>
<td>&gt;25%</td>
</tr>
<tr>
<td>LDL apheresis</td>
<td>Removes LDL-C</td>
<td>&gt;25%</td>
<td>&gt;25%</td>
<td>&gt;25%</td>
</tr>
</tbody>
</table>
# Novel Targets for Lipid Management

## Drugs that block Lipoprotein Assembly

1. **ApoB Antisense (Mipomersen)**
   - trade name **KYNAMRO™**

2. **MTP Inhibition (Lomitapide)**
   - trade name **JUXTAPID™**

Both drugs are only available under a REMS program *(Risk Evaluation & Mitigation Strategies)*

## Drugs that Increase Lipoprotein Clearance

1. **PCSK9 Inhibitors** *(At least 8 in development, 2 Already FDA approved)*
## Novel LDL-Lowering Approaches for Familial Homozygous Hypercholesterolemia

<table>
<thead>
<tr>
<th>Mechanism of action</th>
<th>Mipomersan Kynamro™</th>
<th>Lomitapide Juxtapid™</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antisense oligonucleotide</td>
<td>MTTP inhibitor</td>
<td></td>
</tr>
<tr>
<td>T 1/2</td>
<td>1-2 months</td>
<td>39.7 hours</td>
</tr>
<tr>
<td>Administration</td>
<td>Injection, weekly</td>
<td>Oral, daily</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Tissues</td>
<td>Liver</td>
</tr>
<tr>
<td>Approval</td>
<td>January 2013</td>
<td>December 2012</td>
</tr>
<tr>
<td>Comments</td>
<td>Black Box Warning for Risk of hepatotoxicity</td>
<td>Black Box Warning for Risk of Hepatotoxicity</td>
</tr>
</tbody>
</table>

- Only certified HCPs and pharmacies may prescribe and distribute drug via a restricted REMS program.

REMS = Risk Evaluation Mitigation Strategy.
Novel LDL-Lowering Approaches for Familial Homozygous Hypercholesterolemia

<table>
<thead>
<tr>
<th></th>
<th>Anti-Sense ApoB inhibitor Mipomersan (FDA: HoFH) (Injectable)</th>
<th>MTTP-inhibitor Lomitapide (FDA: HoFH) Less VLDL in liver and chlyomicron in gut (oral)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expected LDL-C Reduction</td>
<td>25%-37% on top of statins +/- other LLT</td>
<td>40-50% on top of statins +/- other LLT</td>
</tr>
<tr>
<td>Lp(a) Reduction</td>
<td>-20-30%</td>
<td>-1-19%</td>
</tr>
<tr>
<td>GI Side Effects</td>
<td>Mild</td>
<td>Moderate-to-severe</td>
</tr>
<tr>
<td>Transaminitis</td>
<td>Mild</td>
<td>Moderate-to-severe</td>
</tr>
<tr>
<td>Compliance</td>
<td>80-90%</td>
<td>80-90%</td>
</tr>
<tr>
<td>Long Term Safety</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>Quality of Life</td>
<td>Fatty liver Injection reactions Flu-like symptoms</td>
<td>Fatty liver</td>
</tr>
</tbody>
</table>

Proprotein Convertase Subtilisin/Kexin type 9 (PCSK9)

- A protein (serine protease) secreted by the liver which acts as a chaperone for the LDL receptor targeting the receptor for degradation.
- Patients with hyperactive PCSK9 (Gain of function mutations) have fewer LDL receptors and higher circulating LDL-C levels leading to premature atherosclerosis.
- Loss of function mutations assoc. with low LDL-C.
- Monoclonal antibodies against the PCSK9 protein block this “vacuum effect” on the LDL receptor leading to re-circulation and expression of a greater # of LDL receptors thereby lowering LDL-C levels.
PCSK9

- A secreted protein which targets the LDL receptor for degradation
- Up-regulated by statin therapy
- Gain of function mutations cause high LDL-C
- Loss of function mutations cause low LDL-C
- Inhibition lowers LDL-C levels
PCS9 Regulates LDLR Turnover Through Increased Intracellular Degradation
Blocking PCSK9 Activity Inhibits Intracellular Degradation of LDLR
PCSK9 Monclonal Antibodies Have Been Studied in…

- Monotherapy
- Add on to Low or High-Dose Statin +/- Ezetimibe
- Statin Intolerance
- Familial Heterozygote Hypercholesterolemia
- Familial Homozygous Hypercholesterolemia (most variants)
- Long Term
# PCSK9-Directed Therapies Approved or In Development

<table>
<thead>
<tr>
<th>Company</th>
<th>Drug (Alternate Name)</th>
<th>Agent</th>
<th>Indication</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sanofi/Regeneron</td>
<td>Alirocumab Praluent®</td>
<td>Human monoclonal antibody</td>
<td>Hypercholesterolemia</td>
<td>FDA approved</td>
</tr>
<tr>
<td>Amgen</td>
<td>Evolocumab Repatha®</td>
<td>Human monoclonal antibody</td>
<td>Hypercholesterolemia</td>
<td>FDA approved</td>
</tr>
<tr>
<td>Novartis</td>
<td>LGT-209</td>
<td>Monoclonal antibody</td>
<td>Hypercholesterolemia</td>
<td>2</td>
</tr>
<tr>
<td>Pfizer/Rinat</td>
<td>Bococizumab</td>
<td>Monoclonal antibody</td>
<td>Hypercholesterolemia</td>
<td>3</td>
</tr>
<tr>
<td>Genentech</td>
<td>MPSK3169A, RG7652</td>
<td>Monoclonal antibody</td>
<td>Hypercholesterolemia</td>
<td>2</td>
</tr>
<tr>
<td>Alnylam Pharmaceuticals</td>
<td>ALN-PCS02</td>
<td>siRNA oligonucleotide</td>
<td>Hypercholesterolemia</td>
<td>1</td>
</tr>
<tr>
<td>Adnexus Therapeutics/Bristol-Myers Squibb</td>
<td>BMS-962476</td>
<td>Fusion protein using Adnectin technology</td>
<td>Cardiovascular disease</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Idera Pharmaceuticals</td>
<td>TBD</td>
<td>Antisense oligonucleotide</td>
<td>Hypercholesterolemia</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Serometrix</td>
<td>SX-PCK9</td>
<td>Small peptide mimic; LDLR antagonist</td>
<td>Hypercholesterolemia</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Shifa Biomedical Corp.</td>
<td>TBD</td>
<td>Small molecule PCSK9 modulator</td>
<td>Metabolic disorders</td>
<td>Preclinical</td>
</tr>
</tbody>
</table>

Adapted from Brautbar A, Ballantyne CM. Nat Rev Cardiol. 2011;8:253-265.
### 17 Phase 3 Studies of PCSK9 Inhibitors in > 10,000 Patients

- **Monotherapy:**
  - MENDEL-2
  - ODYSSEY MONO

- **In combination with statin:**
  - LAPLACE-2
  - ODYSSEY COMBO II
  - ODYSSEY COMBO I
  - YUKAWA-2

- **In addition to diet alone, statin, or statin + ezetimibe:**
  - DESCARTES
  - ODYSSEY CHOICE I

- **Statin intolerance:**
  - GAUSS-2
  - ODYSSEY ALTERNATIVE
  - ODYSSEY CHOICE II

- **Heterozygous FH:**
  - RUTHERFORD-2
  - ODYSSEY FH I and II

- **Homozygous FH:**
  - TESLA Part B

- **Long-term extension studies:**
  - OSLER-1 and OSLER-2
  - ODYSSEY LONG TERM

---

Evolocumab Program

Phase II
- MONOTHERAPY
  - MENDEL-1 (N=406)
  - LAPLACE-TIMI57 (N=629)
Phase III
- MENDEL-2 (N=614)
- LAPLACE-2 (N=1896)

Eligible if medically stable and on study drug

Irrespective of treatment assignment in parent study

4465 patients (74%) elected to enroll into the OSLER extension program
- 1324 from Phase II trials into OSLER-1
- 3141 from Phase III trials into OSLER-2

2:1

Evolocumab + standard of care (2976)
Standard of care (N=1489)

Median follow-up of 11.1 months (IQR 11.0-12.8)
7% discontinued evolocumab early • 96% completed follow-up

Evolocumab: Add-on to statins – significant LDL-C lowering with QM or Q2W

**LAPLACE-2**

- **Placebo wk10&12**
  - Q2W: +6.8%
  - QM: +3.2%

- **EvoMab wk10&12**
  - Q2W: -62%
  - QM: -64%

**RUTHERFORD-2**

- **Placebo wk10&12**
  - Q2W: -1%
  - QM: +2%

- **EvoMab wk10&12**
  - Q2W: -61%
  - QM: -64%

**Combo with Statin Study** (n = 1,899)
- 1° hypercholesterolemia/mixed dyslipidemia
- Consistent LDL lowering regardless if added to high or moderate intensity statin
- Up to 94% patient reach LDL target

**HeFH Study** (n = 331)
- HeFH patients unable to achieve LDL-C < 2.6 mmol/L despite statin ± EZE
- ~ 60% LDL lowering in this difficult patient group

HeFH: Heterozygous Familial Hypercholesterolemia

† Reflexive LDL-C measurements; Co-primary Endpoints: Mean % change from baseline in LDL at week 10/12

Evolocumab: Significant LDL-C lowering with monthly or bi-weekly Dosing

Statin-Intolerant Study (n = 307)
- Patients intolerant to ≥ 2 statins
- Robust efficacy combined with favourable tolerability at 12 weeks

Evolocumab: Other Lipid Parameters

Week 12 data: values are means except for TG and Lp(a) which are medians; Error bars are 95% CI

- 52% ↓ in Non-HDL-C
  - Standard of Care: 5.9
  - Evolocumab + Standard of Care: -46.1
  - P < 0.001

- 13% ↓ in TG
  - Standard of Care: 3.5
  - Evolocumab + Standard of Care: -9.1
  - P < 0.001

- 47% ↓ in ApoB
  - Standard of Care: 5.5
  - Evolocumab + Standard of Care: -41.7
  - P < 0.001

- 7% ↑ in HDL-C
  - Standard of Care: 8.7
  - Evolocumab + Standard of Care: 1.7
  - P < 0.001

- 26% ↓ in Lp(a)
  - Standard of Care: 0
  - Evolocumab + Standard of Care: -25.5
  - P < 0.001

- 4% ↑ in ApoA1
  - Standard of Care: 2.6
  - Evolocumab + Standard of Care: 6.8
  - P < 0.001

OSLER 1 & 2 Studies
Long Term Extension Studies Use of Evolocumab Or Standard Therapy (Standard therapy in some cases included statin or ezetimibe)

Adverse Event rates similar in both groups except for neurocognitive complaints which were more frequent with evolocumab

No. at Risk
Standard therapy 1489 394 1388 1376 402 1219
Evolocumab 2976 864 2871 2828 841 2508

Absolute reduction (mg/dl) 60.4 73.4 70.4 72.7 70.5
Percentage reduction 45.3 60.9 58.8 54.0 58.4
P value <0.001 <0.001 <0.001 <0.001 <0.001

OSLER 1 & 2 Studies
Effect on CV Events
(Pre-specified Exploratory Analysis)

Hazard ratio, 0.47 (95% CI, 0.28–0.78)
P = 0.003

No. at Risk
Standard therapy 1489 1486 1481 1473 1467 1463 1458 1454 1457 1438 1428 1361 407
Evolocumab 2976 2970 2962 2949 2938 2930 2920 2910 2901 2885 2871 2778 843


**Alirocumab Phase III Clinical Development Program**

<table>
<thead>
<tr>
<th></th>
<th>COMBO II (N=707)</th>
<th>COMBO I (N=311)</th>
<th>FH I (N=485)</th>
<th>FH II (N=247)</th>
<th>HIGH FH (N=106)</th>
<th>LONG TERM (N=2310)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alirocumab 75/150 mg</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LS mean (%) from baseline</td>
<td>-52.0</td>
<td>-50.2</td>
<td>-49.7</td>
<td>-50.1</td>
<td>-61.5</td>
<td></td>
</tr>
<tr>
<td><strong>Alirocumab 150 mg</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-60.7</td>
<td></td>
</tr>
</tbody>
</table>

**LDL-C level lowering effect of alirocumab was consistent across studies regardless of statin dose intensity**

% Change in LDL-C in Alirocumab Groups According to Background Statin Dose Intensity (ITT Analysis)
High-intensity statin=atorvastatin 40–80 mg, rosuvastatin 20-40 mg; Not high-intensity statin=any other dose of atorvastatin or rosuvastatin, or simvastatin.
ITT = Intent to Treat
Alirocumab: ODYSSEY LONG TERM study design

**Patient Characteristics:**
- HeFH or High CV-risk patients
- On high-dose or max-tolerated statin ± other lipid-lowering therapy
- LDL-C ≥1.81 mmol/L
- T2DM = 34%

**Double-blind treatment (18 months)**
- Alirocumab 150 mg Q2W SC (single 1-mL injection using prefilled syringe for self-administration)
- Placebo Q2W SC

**Assessments**
- W0, W4, W8, W12, W16, W24, W36, W52, W64, W78

**Primary efficacy endpoint:**
% change in LDL cholesterol level from baseline

**Safety end points:** AEs occurring after 1st injection to 10 weeks after last injection

71.7% (1113/1553 alirocumab) and 75.5% (595/788 placebo) completed the study. Study completion defined as patient receiving last study-drug injection at week 76, and the end-of-treatment visit (week 78) occurred within 21 days after the last injection and at least 525 days after randomization. Mean treatment duration: 70 weeks

2341 patients on background of high-dose or maximally-tolerated statin ± other lipid-lowering therapy randomized to placebo or 150 mg q 2 weeks for 78 weeks

Intent-to-treat analysis
In a post-Hoc safety analysis, the rate of major adverse CV events was 48% lower among alirocumab than placebo patients.
Alirocumab
LONG TERM: Safety analysis

<table>
<thead>
<tr>
<th>% (n) of patients</th>
<th>Alirocumab (n=1550)</th>
<th>Placebo (n=788)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All on high-dose or max-tolerated statin ± other LLT</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Summary of AEs – %, (no. patients)**

<table>
<thead>
<tr>
<th>Event</th>
<th>Alirocumab</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEAEs</td>
<td>81.0% (1255)</td>
<td>82.5% (650)</td>
</tr>
<tr>
<td>Treatment-emergent SAEs</td>
<td>18.7% (290)</td>
<td>19.5% (154)</td>
</tr>
<tr>
<td>TEAE leading to death</td>
<td>0.5% (8)</td>
<td>1.3% (10)</td>
</tr>
<tr>
<td>TEAEs leading to treatment discontinuation</td>
<td>7.2% (111)</td>
<td>5.8% (46)</td>
</tr>
</tbody>
</table>

**Cardiovascular AEs of interest – %, (no. patients)**

<table>
<thead>
<tr>
<th>Event</th>
<th>Alirocumab</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjudicated major adverse CV events in post hoc analysis*</td>
<td>1.7% (27)</td>
<td>3.3% (26)</td>
</tr>
<tr>
<td>CHD death, including death from unknown cause</td>
<td>0.3% (4)</td>
<td>0.9% (7)</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>0.9% (14)</td>
<td>2.3% (18)</td>
</tr>
<tr>
<td>Fatal + non-fatal ischemic stroke</td>
<td>0.6% (9)</td>
<td>0.3% (2)</td>
</tr>
<tr>
<td>Unstable angina requiring hospitalisation</td>
<td>0</td>
<td>0.1% (1)</td>
</tr>
</tbody>
</table>

*Primary endpoint for the ODYSSEY OUTCOMES trial: CHD death, nonfatal MI, fatal and nonfatal ischemic stroke, and unstable angina requiring hospitalisation. “Unstable angina requiring hospitalisation” is limited to the UA events with definite evidence of progression of the ischemic condition (strict criteria).

## Contrasting the PCSK9 Inhibitors

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Praluent™ Alirocumab</th>
<th>Repatha™ Evolocumab</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FDA Approval</strong></td>
<td>July 2015</td>
<td>August 2015</td>
</tr>
<tr>
<td><strong>Indication: Adjunct to diet and maximally tolerated statin therapy</strong>&lt;sup&gt;*&lt;/sup&gt; for Rx of:</td>
<td>Clinical ASCVD who require additional LDL-C reduction</td>
<td>Clinical ASCVD who require additional LDL-C reduction</td>
</tr>
<tr>
<td>- Heterozygous Hypercholesterolemia</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>- Homozygous Familial Hypercholesterolemia</td>
<td>--</td>
<td>+</td>
</tr>
<tr>
<td><strong>Dosage (SQ)</strong></td>
<td>75 mg q 2 weeks. If inadequate LDL-C, increase to 150 mg</td>
<td>140 mg q 2 weeks 420 mg once monthly-FoH only</td>
</tr>
<tr>
<td><strong>Usage in Adolescents</strong></td>
<td>No</td>
<td>13-17 yrs old</td>
</tr>
<tr>
<td><strong>LDL-C Monitoring</strong></td>
<td>Measure w/in 4-8 weeks to measure response</td>
<td>Only 4-8 weeks post dose FoH</td>
</tr>
<tr>
<td><strong>Storage (time out of refrigerator)</strong></td>
<td>Max 24 hours</td>
<td>Max 30 days</td>
</tr>
</tbody>
</table>

*highest dose of Statin achieved or unable to tolerate any dose of statin
**PCSK9 Inhibitors Furthest along in Development**

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Description</th>
<th>Clinical Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alirocumab</td>
<td>Fully human IgG1 mAb</td>
<td>3*</td>
</tr>
<tr>
<td>Evolocumab</td>
<td>Fully human IgG1 mAb</td>
<td>3*</td>
</tr>
<tr>
<td>Bococizumab</td>
<td>Humanized IgG1 mAb</td>
<td>3</td>
</tr>
</tbody>
</table>

* FDA approved
Clinical Trial Results for the Anti-PCSK9 Monoclonal Antibodies

• Results in LDL Cholesterol level Reductions 40-70%
• Results in triglycerides and Lp(a) Reductions of 30% in various patient populations
  - on or off statins
  - with or w/o Familial Hypercholesterolemia
  - with or w/o clinical ASCVD
• No dose-limiting toxicities have been seen with injection site reactions of 0-5%
• To date over 10,000 patients have received these drugs in clinical trials for up to 1 year
PCSK9 Inhibition: Summary

• Early post-hoc data on CVD events is encouraging;
  
  full CVD Outcome trial results:
  - in late 2016-evolocumab (FOURIER=27,500)
  - early 2018-alirocumab (ODDYYSEY OUTCOME=18,000)
  - 2019-bococizumab (SPIRE I= 12,000 and II=6,300).

• We await the results of these outcome trials
Heterozygous Familial Hypercholesterolemia
Frequency: 1/200-300
USA: 600,000 patients

FINAL OPTION - LDL apheresis
LDL 75-80% acutely (50% over 2-week average)

FDA APPROVAL (HELP, LIPOSORBTER)

- LDL > 200 mg/dL (with CHD)
- LDL > 300 mg/dL (no CHD)
Conclusions

• The ACC/AHA Blood Cholesterol Guidelines deemphasize LDL-C and non-HDL-C thresholds and risk stratified treatment targets and now recommend treating patient risk for CVD with statins of specific dose and potency.

• National Lipid Association Recommendations offer an alternative goal directed strategy focusing on Non-HDL-C as the primary target

• There is some discretion for physicians to discern if LDL-C reduction is adequate. If not, or if the patient is statin intolerant or only tolerates a low dose of a statin, then adjuvant therapy can be used.

• Mipomersen given weekly by SQ injection is an anti-sense molecule that increases degradation of the mRNA for apoB100.

• Lomitapide, given daily, orally is a MTP inhibitor that reduces lipidation and maturation of apoB100 in the endoplasmic reticulum.

• Mipomersen and lomitapide are only indicated for the treatment of HoFH and are available only through a REMS program.

REMS=Risk Evaluation Mitigation Strategy.
Conclusions

- Monoclonal antibodies directed against PCSK9 are a very promising new class of LDL-C lowering agent with 2 already FDA approved. These drugs are being tested in large-scale outcomes trials with and without a statin background in both patients who have stable ischemic heart disease and those who are status post acute coronary syndrome. These drugs reduce the total atherogenic lipoprotein burden by reducing serum LDL-C, VLDL-C, non-HDL-C, apo B, Lp(a), and remnant lipoproteins.
Summary:

You should now be better able to:

1) Recognize the 4 patient populations who benefit most from statin-based therapy according to the ACC/AHA guidelines

2) Define the specific population where an additional lipid-lowering agent on top of a background of statin therapy has further improved cardiovascular (CV) outcome

3) Define the role of the newer LDL-C reducing drugs to further lower LDL-cholesterol in the hopes of improving CV outcome
Post-test Question

On a scale of 1 to 5, please rate how confident you would be in treating your patients with Hypercholesterolemia?

1. Not at all confident
2. Slightly confident
3. Moderately confident
4. Pretty much confident
5. Very confident