How Low Can You Go?
Evaluating the Safety of Low Low-Density Lipoprotein

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Learning Objectives:

1. Summarize current guidelines available for the treatment of dyslipidemia
2. Identify the expected effect of lipid treatment options on low-density lipoprotein
3. Assess the evidence for the safety of low low-density lipoprotein
4. Using a patient case, formulate a treatment plan for a patient with low low-density lipoprotein
The Use of Lipid Lowering Agents

I. Why We Use Lipid Lowering Agents\textsuperscript{1-3}

II. Goals of Lipid Lowering Therapy\textsuperscript{3-7}

\begin{table}[h]
\centering
\begin{tabular}{|l|l|}
\hline
\textbf{Guideline} & \textbf{Goals of therapy} \\
\hline
2017 AACE\textsuperscript{4} & \begin{itemize}
  \item Specific targets based on risk category (see Table 2)
\end{itemize} \\
2017 ACC Update\textsuperscript{5} & \begin{itemize}
  \item Refer to 2013 ACC/AHA goals of therapy
  \item $\geq 50 \%$ LDL reduction
\end{itemize} \\
2015 NLA Part 1\textsuperscript{6} & \begin{itemize}
  \item Specific targets based on risk category (see Table 3)
\end{itemize} \\
2014 VA/DoD\textsuperscript{7} & \begin{itemize}
  \item Do not support the of LDL-C or non-HDL-C goals
\end{itemize} \\
2013 ACC/AHA\textsuperscript{3} & \begin{itemize}
  \item No specific goal of LDL-C or non-HDL-C made
  \item Do not recommend for or against the use of specific levels
\end{itemize} \\
\hline
\end{tabular}
\caption{Goals of Lipid Lowering Therapy}
\end{table}


\begin{table}[h]
\centering
\begin{tabular}{|l|l|}
\hline
\textbf{Risk Category} & \textbf{LDL – C goal} \\
\hline
Extreme Risk & $< 55 \text{ mg/dL}$ \\
\hline
\begin{itemize}
  \item Progressive ASCVD including unstable angina in patients after achieving LDL-C $< 70 \text{ mg/dL}$
  \item Established clinical cardiovascular disease in patients with DM, CKD 3/4, or Heterozygous Familial Hypercholesterolemia (HeFH)
  \item History of premature ASCVD ($<55 \text{ male, } <65 \text{ female}$)
\end{itemize} & $< 70 \text{ mg/dL}$ \\
\hline
Very High Risk & $< 100 \text{ mg/dL}$ \\
\hline
\begin{itemize}
  \item Established or recent hospitalization for ASCVD, coronary, carotid or peripheral vascular disease, 10-year risk $>20\%$
  \item Diabetes or CKD 3/4 with 1 or more risk factor(s)
  \item HeFH
\end{itemize} & $< 100 \text{ mg/dL}$ \\
\hline
High Risk & $< 130 \text{ mg/dL}$ \\
\hline
\begin{itemize}
  \item $\geq 2$ risk factors and 10-year risk 10-20\%
  \item Diabetes or CKD 3/4 with no other risk factors
\end{itemize} & $< 100 \text{ mg/dL}$ \\
\hline
Moderate Risk & $< 100 \text{ mg/dL}$ \\
\hline
Low Risk & $< 130 \text{ mg/dL}$ \\
\hline
\end{tabular}
\caption{2017 AACE LDL-C Treatment Goals\textsuperscript{4}}
\end{table}
III. Effect of Lipid Lowering Agents on LDL

| Table 3: 2015 National Lipid Association LDL-C Treatment Goals
<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Criteria</th>
<th>LDL – C Treatment Goal</th>
</tr>
</thead>
</table>
| Low           | • 0 – 1 major ASCVD risk factors*  
• Consider other risk indicators, if known | < 100 mg/dL |
| Moderate      | • 2 major ASCVD risk factors  
• Consider quantitative risk scoring (Framingham Risk Score)  
• Consider other risk indicators | < 100 mg/dL |
| High          | • ≥ 3 major ASCVD risk factors  
• Diabetes mellitus (type 1 or 2)  
• 0 – 1 other major ASCVD risk factors  
• No evidence of end-organ damage  
• Chronic kidney disease stage 3B or 4  
• LDL-C of ≥ 190 mg/dL (severe hypercholesterolemia)  
• Quantitative risk score reaching the high-risk threshold (Framingham Risk Score) | < 100 mg/dL |
| Very High     | • ASCVD  
• Diabetes mellitus (type 1 or 2)  
• ≥ 2 other major ASCVD risk factors  
• Evidence of end-organ damage** | < 70 mg/dL |

*Risk Factors: Age (male ≥ 45 years old, female ≥ 55 years old); family history of early CHD (≤ 55 years of age in male 1st degree relative, < 65 years of age in female 1st degree relative); current cigarette smoker; high blood pressure (≥ 140/90 mmHg or on blood pressure medication); low HDL (Male < 40 mg/dL; Female < 50 mg/dL)

**Increased albumin to creatinine ratio (≥ 30 mg/g), CKD (eGFR, < 60 mL/min/1.73 m²), or retinopathy

| Table 4: Lipid Lowering Agents Role in Therapy and Predicted Lipid Lowering Effect |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| **Statins**                     | **Ezetimibe**                   | **PCSK-9 Inhibitors**           |
| **Role in Therapy**             | **1st line agent**              | **2nd line agent**              | **2nd line agent**              |
|                                 | • Clinical ASCVD                | • Clinical ASCVD                | • Clinical ASCVD                |
|                                 | • LDL – C ≥ 190 mg/dL          | • LDL – C ≥ 190 mg/dL           | • LDL – C ≥ 190 mg/dL           |
|                                 | • Diabetes + LDL – C 70 to 189 mg/dL | • Diabetes + LDL – C 70 to 189 mg/dL | • Diabetes + LDL – C 70 to 189 mg/dL |
|                                 | • Age 40 – 75 + ASCVD risk S to < 7.5% | • Age 40 – 75 + ASCVD risk ≥ 7.5% | • Age 40 – 75 + ASCVD risk ≥ 7.5% |
|                                 | • Age 40 – 75 + ASCVD risk ≥ 7.5% |                                 |                                 |
| **Expected % Reduction in LDL** | • High: ≥ 50%                   | < 25 %                          | > 25 %                          |
|                                 | • Moderate: 30 to < 50%         |                                 |                                 |
|                                 | • Low: < 30%                   |                                 |                                 |
Clinical Controversy

I. Role of Cholesterol in the Body
   a. Precursor for all steroids in the body
      i. Sex hormones
      ii. Corticosteroids
      iii. Vitamin D
      iv. Bile acids
   b. Essential structure of membranes allows for fluidity and permeability

II. Definition of Low LDL
   a. Currently no universally expected definition of low LDL
   b. 2013 ACC/AHA Guidelines
      i. Consider reducing statin when LDL < 40 mg/dL on two consecutive occasions.
         (Weak recommendation)

III. Concerns of Low LDL
   a. Neurocognitive Issues
      i. Dementia
      ii. Depression
   b. Retinal Disorders
      i. Cataracts
   c. Hemorrhage strokes
   d. Cancers

IV. Clinical Controversy
   a. What do we do with LDL levels < 40 mg/dL?
   b. What are the safety concerns for patients who reach low LDL levels?

<table>
<thead>
<tr>
<th>Objective</th>
<th>Evaluate the safety and efficacy of achieving very low LDL levels with intensive statin therapy</th>
</tr>
</thead>
</table>

**Methods**

**Study Design**
- Treatment groups of original trial: intensive statin therapy (atorvastatin 80 mg daily) vs. standard therapy (pravastatin 40 mg daily)
- Post-hoc analysis that analyzed only patients who received atorvastatin 80 mg
- Subgroups at 4 months: LDL 81-100 mg/dL, 61-80 mg/dL, 41-60 mg/dL, and ≤ 40 mg/dL
- Very low LDL levels defined as LDL < 60 mg/dL

**Patient Selection**

**Inclusion:**
- Within 10 days of ACS
- Patients who achieved LDL < 100 mg/dL at 4 months
- Treated with intensive statin therapy

**Exclusion:**
- Treated with standard therapy
- Patients who did not achieve LDL < 100 mg/dL at 4 months

**Outcomes**

**Efficacy:** composite of death, myocardial infarction (MI), stroke, revascularization, and unstable angina requiring hospitalization
**Safety:** hemorrhage stroke, liver-related events, muscle-related events, and retinal adverse events

**Statistical Analysis**
- 81-100 mg/dL reference group
- Chi-square used for trends for safety, efficacy and baseline characteristics
- Kaplan-Meier used for primary efficacy event rates
- Multivariate analyses accounting for differences in baseline characteristics (age, gender, diabetes, prior history of myocardial infarction (MI), baseline LDL levels and smoking status)

**Results**

**Baseline Characteristics**
- 1,756 patients met treatment goal of LDL < 100 mg/dL
  - 81-100 mg/dL: 256 patients
  - 61-80 mg/dL: 576 patients
  - 41-60 mg/dL: 631 patients
  - ≤ 40 mg/dL: 193 patients

<table>
<thead>
<tr>
<th>Concomitant Medications</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>93</td>
</tr>
<tr>
<td>Warfarin</td>
<td>8</td>
</tr>
<tr>
<td>Clopidogrel or ticlodipine</td>
<td>72</td>
</tr>
<tr>
<td>Beta Blockers</td>
<td>85</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>69</td>
</tr>
<tr>
<td>ARB</td>
<td>14</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Selected Baseline Characteristics Based on Achieved LDL Level in (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristic</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Age, median</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Caucasian</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Prior MI</td>
</tr>
<tr>
<td>Smoker</td>
</tr>
<tr>
<td>Prior statin</td>
</tr>
<tr>
<td>Total cholesterol, baseline median</td>
</tr>
<tr>
<td>LDL, baseline median</td>
</tr>
</tbody>
</table>
### Baseline Characteristics that Influence Achieving Lower LDL Levels

<table>
<thead>
<tr>
<th>More likely to achieve</th>
<th>Less likely to achieve</th>
</tr>
</thead>
</table>
| • Older
• Male
• Diabetic
• Lower baseline total cholesterol and LDL levels | • Prior MI
• Prior coronary artery bypass graft
• Cigarette smoker
• Prior statin before study initiation |

### Study Outcomes

#### Efficacy Outcomes:

<table>
<thead>
<tr>
<th>LDL Level (mg/dL)</th>
<th>Hazard Ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>61-80</td>
<td>0.80</td>
<td>0.59 to 1.07</td>
</tr>
<tr>
<td>41-60</td>
<td>0.67</td>
<td>0.50 to 0.92</td>
</tr>
<tr>
<td>≤40</td>
<td>0.61</td>
<td>0.40 to 0.91</td>
</tr>
</tbody>
</table>

- Rate of MI was lower in patients with LDL < 80 mg/dL when compared to patients with LDL ≥ 80 mg/dL (p < 0.01)

#### Safety Outcomes:

- No significant difference in adverse events between LDL groups including muscle side effects, liver side effects, hemorrhagic stroke, retinal adverse effects, suicide/trauma death

### Author’s Conclusion

- Not necessary to lower the dose of statin based on LDL levels
- No association between the achieved LDL level and adverse events of statins over a 2-year period.

### Critique

#### Strengths:

- Assessed efficacy and safety outcomes
- Variety of LDL levels evaluated
- Endpoints were adjudicated by an independent committee

#### Limitations:

- Small number of patients experience side effects, lack of power to determine difference
- Applies to secondary prevention only
- Distribution of LDL in the LDL < 40 group
- Did not assess neurocognitive changes
- Post-hoc analysis – results only exploratory
- Only evaluated LDL levels 4 months post ACS

Duration of follow-up is 2 years

### Take away summary

- No difference in safety or efficacy regardless of LDL level
- Additional efficacy does not appear to be present when comparing patients those who achieved a LDL of 41-60 mg/dL to those who achieved a LDL < 40 mg/dL
Table 6: Everett BM, Mora S, Glynn RJ, et al. Safety Profile of Subjects Treated to Very Low Low-Density Lipoprotei
Cholesterol Levels (< 30 mg/dL) with Rosuvastatin 20 mg daily (from JUPITER)\textsuperscript{11}

| Objective | Evaluate the safety achieving very low LDL levels, either LDL – C < 30 mg/dL or ≥ 70% reduction in
LDL-C, while on rosvastatin 20 mg |

| Methods |
| Study Design | Post-hoc analysis, double-blind, placebo controlled |

| Patient Selection | Inclusion: |
| | • Men ≥ 50 years and women ≥ 60 years |
| | • No history of diabetes |
| | • No history of cardiovascular disease |
| | • LDL-C < 130 mg/dL |
| | • C-reactive protein ≥ 2.0 mg/L |

| Exclusion: |
| | • Pre-existing diabetes |
| | • Previous use of lipid lowering medications |
| | • SBP > 180 mmHg or DBP > 100 mmHg |
| | • Cancer (except basal or squamous cell carcinoma of the skin) in the last 5 years |
| | • TSH > 1.5 x ULN or ALT > 2 x ULN, CK > 3 x ULN, Cr > 2.0 mg/dL |
| | • Recent alcohol or drug abuse |
| | • Inflammatory conditions |
| | • Use of immunosuppressants |

| Outcomes | Primary Outcome: Adverse reaction, hemorrhagic stroke was the only adverse drug reaction that was adjudicated. |

| Statistical Analysis | Cox proportional hazard for propensity - adjusted analysis |

| Results |
| 16, 304 participants |

<p>| Baseline Characteristics | Selected Baseline Characteristics |</p>
<table>
<thead>
<tr>
<th></th>
<th>Characteristic</th>
<th>LDL &lt; 30 mg/dL (N = 767)</th>
<th>LDL ≥ 30 mg /dL (N = 7387)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>66 (61-72)</td>
<td>66 (60-71)</td>
<td>0.62</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>32.2 %</td>
<td>38.9%</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>69.6%</td>
<td>72.6%</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>29.3 (26.2-33.2)</td>
<td>28.2 (25.2-31.9)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Systolic BP</td>
<td>136 (125-148)</td>
<td>134 (124-145)</td>
<td>0.047</td>
<td></td>
</tr>
<tr>
<td>Metabolic Syndrome</td>
<td>51.6%</td>
<td>40.3%</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Impaired fasting glucose</td>
<td>36.3%</td>
<td>30.6%</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Adherence to study medication</td>
<td>97.8%</td>
<td>89.0%</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>166 (146-186)</td>
<td>187 (171-201)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Triglycerides</td>
<td>134 (93-206)</td>
<td>118 (84-166)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>HDL</td>
<td>46 (38-56)</td>
<td>49 (41-60)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>LDL</td>
<td>86 (70-100)</td>
<td>109 (97-120)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin A1C</td>
<td>5.7 (5.4-5.9)</td>
<td>5.7 (5.4-5.9)</td>
<td>0.29</td>
<td></td>
</tr>
</tbody>
</table>
Characteristics that Influence Achieving LDL < 30 mg/dL

- Men
- Black
- Have metabolic syndrome or its components
  - Impaired fasting glucose
  - Higher triglycerides
  - Higher BMI
  - Lower high-density lipoprotein (HDL) levels

Study Outcomes

- No difference in nervous system disorders (i.e. memory impairment, fatigue or hemorrhage stroke) and cancer when comparing those who achieved LDL < 30 mg/dL to those who achieved > 30 mg/dL
- No difference in adverse events when comparing patients who achieved ≥ 70 % reduction in LDL to those who achieved < 70 % reduction in LDL

<table>
<thead>
<tr>
<th>Selective Adjusted Adverse Events</th>
<th>LDL &lt; 30 mg/dL compared to LDL ≥ 30 mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse Event</td>
<td>LDL &lt; 30 mg/dL (N = 767) (Incidence Rate)</td>
</tr>
<tr>
<td>Any</td>
<td>620 (103)</td>
</tr>
<tr>
<td>Hepatobiliary Disorders</td>
<td>30 (1.7)</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td>69 (4.0)</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>107 (6.4)</td>
</tr>
<tr>
<td>Physician-reported hematuria</td>
<td>34 (1.9)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>27 (1.5)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>47 (2.6)</td>
</tr>
</tbody>
</table>

Author’s Conclusion

- Suggests statin therapy overall is well tolerated at concentrations as low as 30 mg/dL
- Increased risk of diabetes in patients with LDL-C < 30 mg/dL compared to LDL-C > 30 mg/dL
- Question of whether very low levels of LDL puts patients at an increased risk of hematuria.

Critique

**Strengths**
- Assessed cognitive function, hemorrhagic stroke and cancer
- Large sample size
- Patients without clinical ASCVD or diabetes

**Limitations**
- Post-hoc analysis
- Did not assess incidence of cataracts
- Efficacy was not addressed in terms of LDL level
- Limited number of LDL levels evaluated
- Distribution of LDL levels achieved in each group not specified
- Large number of statistical tests preformed
- Only adjudicated 1 ADR endpoint

Duration of follow-up is 1.9 years

Take away summary

- Compared to adverse events of patients who achieved LDL levels > 30 mg/dL, those that achieved LDL levels < 30 mg/dL had more incidence of diabetes, insomnia and physician-reported hematuria. However, there was no difference seen in incidence rates of memory impairment and hemorrhagic stroke, which are potential safety concerned of achieving low levels of LDL.
- The safety concern is with the achieved LDL level rather than the percentage of LDL reduction.
Table 7: Giugliano RP, Wiviott SD, Blazing MA et al. Long-term Safety and Efficacy of Achieving Very Low Levels of Low-Density Lipoprotein Cholesterol A Prespecified Analysis of the IMPROVE-IT Trial

<table>
<thead>
<tr>
<th>Objective</th>
<th>Evaluate the safety and efficacy of very low achieved LDL levels in patients receiving combination therapy with ezetimibe and simvastatin</th>
</tr>
</thead>
</table>
| Methods   | • Randomized, double-blind, placebo controlled  
• Pre-specified safety analysis  
• Post-hoc analysis for incidence of cataracts  
• Intervention group: ezetimibe 10 mg daily plus simvastatin 40 mg daily  
• Comparator group: placebo plus simvastatin 40 mg daily  
• No medication adjustments made if patient’s LDL was low  
• Patients with a LDL drawn at 1 month and who did not have an efficacy or prespecified safety event prior to the 1-month visit were included in the analysis  
• Pre-specified groups based on LDL: ≥ 70 mg/dL; 50 – 69 mg/dL; 30 – 49 mg/dL; < 30 mg/dL |
| Patient Selection | **Inclusion:**  
• ACS within the preceding 10 days  
• LDL level of 50 to 100 mg/dL (if taking a prior lipid lowering therapy)  
• LDL level of 50 to 125 mg/dL (if not on prior lipid lowering therapy)  
| **Exclusion:**  
• CrCl < 30 mL/min  
• Active liver disease  
• Clinical instability  
• On other lipid lowering agents more potent than simvastatin 40 mg |
| Outcomes | • **Safety:** elevated liver enzymes, creatinine kinase levels, myopathy, rhabdomyolysis, adverse hepatobiliary events, cancer, adverse event leading to study drug discontinuation, heart failure leading to hospitalization, non-cardiovascular death, neurocognitive effects and a post-hoc analysis of cataract – related adverse event  
• **Efficacy:** composite of cardiovascular death, myocardial infarction, unstable angina requiring hospitalization, coronary revascularization after 30 days, stroke (hemorrhagic and ischemic)  
• Efficacy endpoints (except revascularization), muscle-related events and cancer were the only endpoints adjudicated by independent committee |
| Statistical Analysis | • Cox proportional hazard ratio to determine independent risk factors  
• Kaplan-Meier used for the rate of primary outcome at 7 years  
• Cochran-Armitage to trend independent risk factors among LDL groups |
| Results | 15,281 included in analysis |

<table>
<thead>
<tr>
<th>Concomitant Medications</th>
<th>&lt; 30 (971)</th>
<th>30 – 49 (4780)</th>
<th>50 – 69 (5504)</th>
<th>≥ 70 (4026)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEi or ARB</td>
<td>437 (45.0)</td>
<td>1944 (40.7)</td>
<td>2210 (40.2)</td>
<td>1604 (39.9)</td>
<td>0.03</td>
</tr>
<tr>
<td>ASA</td>
<td>392 (40.4)</td>
<td>1910 (40.7)</td>
<td>2244 (40.8)</td>
<td>1830 (45.5)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>B blocker</td>
<td>334 (34.4)</td>
<td>1550 (32.40)</td>
<td>1872 (34.0)</td>
<td>1497 (37.2)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Statin</td>
<td>217 (22.3)</td>
<td>1352 (28.3)</td>
<td>1958 (35.6)</td>
<td>1723 (42.8)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Characteristic</td>
<td>&lt; 30 (971)</td>
<td>30 – 49 (4780)</td>
<td>50 – 69 (5504)</td>
<td>≥ 70 (4026)</td>
<td>p value</td>
</tr>
<tr>
<td>----------------</td>
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<td>----------------</td>
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<td>---------</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>824 (84.9)</td>
<td>3433 (71.8)</td>
<td>2414 (43.9)</td>
<td>878 (21.8)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Age (IQR)</td>
<td>64.5 (57.9-71.5)</td>
<td>63.9 (57.9-71.5)</td>
<td>62.9 (57.4-71.7)</td>
<td>61.7 (55.8-69.3)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Male</td>
<td>773 (79.6)</td>
<td>3746 (78.4)</td>
<td>4190 (76.1)</td>
<td>2936 (72.9)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>White</td>
<td>769 (79.2)</td>
<td>3980 (83.3)</td>
<td>4645 (84.4)</td>
<td>3431 (85.2)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>BMI (IQR)</td>
<td>28.4 (25.8-32.0)</td>
<td>27.7 (25.0-31.2)</td>
<td>27.5 (24.8-30.8)</td>
<td>27.2 (24.7-30.5)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DM</td>
<td>403 (41.5)</td>
<td>1432 (30.0)</td>
<td>1327 (24.1)</td>
<td>940 (23.3)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>HTN</td>
<td>642 (66.1)</td>
<td>2944 (61.6)</td>
<td>3251 (59.1)</td>
<td>2443 (60.7)</td>
<td>0.006</td>
</tr>
<tr>
<td>Current Smoker</td>
<td>272 (28.0)</td>
<td>1384 (29.0)</td>
<td>1799 (32.7)</td>
<td>1568 (39.0)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>MI Hx</td>
<td>169 (17.5)</td>
<td>866 (18.1)</td>
<td>1137 (20.7)</td>
<td>979 (24.3)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>PCI Hx</td>
<td>156 (16.1)</td>
<td>810 (16.9)</td>
<td>1055 (19.2)</td>
<td>928 (23.1)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>CABG Hx</td>
<td>57 (5.9)</td>
<td>376 (7.9)</td>
<td>522 (9.5)</td>
<td>423 (10.5)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>PAD Hx</td>
<td>45 (4.6)</td>
<td>243 (5.10)</td>
<td>287 (5.2)</td>
<td>258 (6.4)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

### Baseline Lipid Panel

<table>
<thead>
<tr>
<th></th>
<th>TC</th>
<th>LDL</th>
<th>HDL</th>
<th>Triglycerides</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>155 (136-174)</td>
<td>85 (70-100)</td>
<td>38 (32-46)</td>
<td>141 (95-204)</td>
</tr>
<tr>
<td></td>
<td>160 (141-178)</td>
<td>93 (77-108)</td>
<td>39 (33-48)</td>
<td>120 (86-172)</td>
</tr>
<tr>
<td></td>
<td>163 (145-181)</td>
<td>96 (80-112)</td>
<td>40 (33-49)</td>
<td>117 (83-168)</td>
</tr>
<tr>
<td></td>
<td>168 (151-186)</td>
<td>97 (85-113)</td>
<td>41 (34-50)</td>
<td>122 (85-174)</td>
</tr>
</tbody>
</table>

### Abbreviations:
- BMI, body mass index; DM, diabetes; HTN, hypertension; MI Hx, myocardial infarction history; PCI Hx, percutaneous coronary intervention; CABG Hx, coronary artery bypass surgery; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ASA, aspirin; TC, total cholesterol; LDL, low density lipoprotein; HDL, high density lipoprotein

### Characteristics that Influence Achieving LDL Levels < 30 mg/dL

- More likely to Achieve
- Less Likely to Achieve
- Male
- Non-white
- Higher BMI
- Pre-existing diabetes
- Treated with statin prior to ACS
- Smoker
- Have prior myocardial infarction, percutaneous coronary intervention, or coronary artery bypass graft
### Study Outcomes

#### Selected Prespecified Safety Events by Achieved LDL Level (mg/dL) at 1 month

<table>
<thead>
<tr>
<th>Safety Endpoint HR (95% CI)</th>
<th>&lt; 30</th>
<th>30 – 49</th>
<th>50 – 69</th>
<th>p value (Trend)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurocognitive events (all)</td>
<td>0.913 (0.545-1.529)</td>
<td>1.045 (0.772-1.414)</td>
<td>1.204 (0.92-1.574)</td>
<td>0.84</td>
</tr>
<tr>
<td>Hemorrhagic Stroke</td>
<td>0.36 (0.11-1.26)</td>
<td>1.05 (0.6-1.84)</td>
<td>0.58 (0.33-1.04)</td>
<td>0.69</td>
</tr>
<tr>
<td>Cancer</td>
<td>1.18 (0.91-1.53)</td>
<td>1.12 (0.95-1.33)</td>
<td>1.11 (0.96-1.29)</td>
<td>0.14</td>
</tr>
</tbody>
</table>

#### Rate of Primary Efficacy Endpoint at 7 years by Achieved LDL Level (mg/dL)

<table>
<thead>
<tr>
<th>LDL Level</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 30</td>
<td>31.9%</td>
</tr>
<tr>
<td>30 – 49</td>
<td>29.9%</td>
</tr>
<tr>
<td>50 – 69</td>
<td>30.8%</td>
</tr>
<tr>
<td>≥ 70</td>
<td>36%</td>
</tr>
</tbody>
</table>

#### Incidence of Cataract-Related Events by Achieved LDL Level (mg/dL) at 1 month

<table>
<thead>
<tr>
<th>LDL Level</th>
<th>Odds Ratio</th>
<th>95 % Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 30</td>
<td>1.12</td>
<td>0.78-1.62</td>
</tr>
<tr>
<td>30 – 49</td>
<td>1.20</td>
<td>0.96-1.50</td>
</tr>
<tr>
<td>50 – 69</td>
<td>1.08</td>
<td>0.86-1.34</td>
</tr>
</tbody>
</table>

#### Time Weighted Mean LDL Levels

<table>
<thead>
<tr>
<th>1 - month LDL Level (mg/dL)</th>
<th>LDL C Level 4-72 months (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 70</td>
<td>79.9</td>
</tr>
<tr>
<td>50-69</td>
<td>63.3</td>
</tr>
<tr>
<td>30-49</td>
<td>48.3</td>
</tr>
<tr>
<td>&lt; 30</td>
<td>34.4</td>
</tr>
</tbody>
</table>

#### Author’s Conclusion
- Patients with LDL level of < 30 mg/dL at one month had a similar safety profile over a median follow-up over 6 years when compared to patients who achieved a LDL > 30 mg/dL.
- Overall patients who achieved LDL < 70 mg/dL had fewer efficacy outcomes.
- Numerically the risk of an efficacy outcome was lowest in patients who achieved LDL < 30 mg/dL.

#### Critique

**Strengths**
- Randomized
- Evaluated both safety and efficacy
- Safety endpoints of interest included
  (hemorrhagic stroke, cancer, cataracts, neurocognitive events)
- Large sample size
- Study duration longer than others
- Adjudication committee

**Limitations**
- Grouped based on LDL level at one month
- Included only secondary prevention patients
- Excluded patients on other lipid lowering agents
- Distribution of LDL < 30 mg/dL
- Mean LDL level in the < 30 mg/dL was 34.4 mg/dL
- Low event rate for some events therefore power was not met to determine difference
- Post-hoc analysis for incidence of cataracts
- Not all endpoints adjudicated (only efficacy outcomes, muscle-related events and cancer)

Duration of follow-up: median of 6 – years

**Take away summary**
- No significant difference in adverse events regardless of achieved LDL level.
- When comparing efficacy of patients who achieved very low levels of LDL to LDL levels above 30 mg/dL but less than 70 mg/dL, there was not a significant difference. This suggest that there is no benefit of achieving very low LDL levels compared to achieving levels < 70 mg/dL.
### Table 8: Robinson JG, Rosenson RS, Farnier M et al. Safety of Very Low Low-Density Lipoprotein Cholesterol Levels with Alirocumab Pooled Data from Randomized Trials

<table>
<thead>
<tr>
<th>Objective</th>
<th>Evaluate the safety of patients with LDL values &lt; 25 mg/dL or &lt; 15 mg/dL in the ODYSSEY program.</th>
</tr>
</thead>
</table>

#### Methods

**Study Design**
- Pooled data from 14 randomized, double blinded trials
- Analysis of adverse events in patients who had 2 consecutive low LDL levels (defined in objective)
- Consecutive levels defined as ≥ 21 days apart
- Alirocumab dosing was 150 mg every 2 weeks in most trials. Some trials started with 75 mg every 2 weeks and increased to 150 mg every 2 weeks if desired LDL reduction was not achieved by week 8.
- Intervention: alirocumab in addition to stable statin therapy (except ODYSSEY MONO)
- Stable statin therapy: maximally tolerated (defined in 6 of the trials)
- Comparator: placebo or ezetimibe

**Patient Selection**

**Inclusion:**
- Heterozygous familial hypercholesteremia (HeFH)
- High cardiovascular risk
- LDL ≥ 70 mg/dL

**Exclusion:**
- Patients with recent ACS, stroke, or PVD intervention in the previous 3 months
- Prior hemorrhage stroke
- Hemoglobin A1C > 10%
- Homozygous familial hypercholesteremia

**Outcomes**

Treatment-emergent adverse events (TEAEs) that occurred, worsened or became serious following the first LDL value < 25 mg/dL or < 15 mg/dL

**Statistical Analysis**
Cox proportional for propensity analysis

#### Results

**Baseline Characteristics**
- 3,340 patients on alirocumab
  - 1,153 had low levels of LDL on 2 consecutive occasions
    - LDL < 25 mg/dL: 839 (25.1%)
    - LDL < 15 mg/dL: 314 (9.4%)

| Selected Baseline Characteristics from Pooled Data of Patients with Low LDL level |
|-----------------------------|----------------|----------------|----------------|
| Characteristics (pooled from phase 2 and 3) | ≥ 25 (mg/dL) (2187) | < 25 (mg/dL) (839) | < 15 (mg/dL) (314) |
| Age, yrs | 58.6 ± 11.4 | 61.9 ± 9.8 | 61.8 ± 9.9 |
| Male | 57.3 ± 9.8 (1,434) | 75.0 (629) | 74.8 (235) |
| Race, white | 88.5 (2,213) | 91.1 (764) | 89.8 (282) |
| BMI | 30.1 ± 6.0 | 29.7 ± 4.6 | 29.8 ± 4.4 |
| Calculated LDL | 134 ± 48.9 | 100.3 ± 28.5 | 95.7 ± 28.3 |
| HDL | 51.1 ± 14.3 | 46.6 ± 11.0 | 45.1 ± 10.9 |
| Fasting Triglycerides | 122.0 (88.0-170.8) | 146.9 (108.8-206.2) | 168.0 (126.5-231.0) |
| Baseline HbA1C | 5.98 ± 0.84 | 6.17 ± 0.98 | 6.22 ± 0.94 |

**Medical History (pool of phase 3)**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>CHD</th>
<th>CHD risk equivalents</th>
<th>Type 2 Diabetes</th>
<th>HeFH</th>
<th>High-intensity statin</th>
<th>Other lipid lowering therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of patients</td>
<td>60.6 (2,061)</td>
<td>29.9 (709)</td>
<td>27.9 (662)</td>
<td>33.5 (794)</td>
<td>55.9 (1,325)</td>
<td>30.6 (725)</td>
</tr>
<tr>
<td>95% CI</td>
<td>76.9 (624)</td>
<td>40.45 (328)</td>
<td>37.1 (301)</td>
<td>10.2 (83)</td>
<td>53.0 (430)</td>
<td>23.6 (191)</td>
</tr>
<tr>
<td>p value</td>
<td>0.244</td>
<td>0.140</td>
<td>0.128</td>
<td>0.29</td>
<td>0.151</td>
<td>0.71</td>
</tr>
</tbody>
</table>

**Italics:** p < 0.05 for comparison of LDL ≥ 25 mg/dL to < 25 mg/dL in the phase 3 studies
Factors Associated with LDL < 25 mg/dL

- Lower baseline LDL
- Higher triglycerides and lower HDL
- Male, older, with a lower BMI
- Did not have HeFH
- Cardiovascular Disease
- Type II Diabetes and higher hemoglobin A1C
- Use of 150 mg every 2 weeks and baseline LDL < 160 mg/dL

Study Outcomes

<table>
<thead>
<tr>
<th>Selected Treatment Emergent Adverse Events</th>
<th>LDL ≥ 25 mg/dL (2,501)</th>
<th>LDL &lt; 25 mg/dL (839)</th>
<th>LDL &lt; 15 mg/dL (314)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurocognitive disorders</td>
<td>1.0 (26), [0.8]</td>
<td>0.6 (5), [0.5]</td>
<td>0.3 (1), [0.3]</td>
</tr>
<tr>
<td>Amnesia</td>
<td>0.2 (5), [0.2]</td>
<td>0.1 (1), [0.1]</td>
<td>0</td>
</tr>
<tr>
<td>Aphasia</td>
<td>&lt; 0.1 (1), [0.1]</td>
<td>0.1 (1), [0.1]</td>
<td>0</td>
</tr>
<tr>
<td>Confused state</td>
<td>0.3 (7), [0.2]</td>
<td>0.1 (1), [0.1]</td>
<td>0</td>
</tr>
<tr>
<td>Dementia</td>
<td>0</td>
<td>0.1 (1), [0.1]</td>
<td>0</td>
</tr>
<tr>
<td>Frontotemporal Dementia</td>
<td>0</td>
<td>0.1 (1), [0.1]</td>
<td>0.3 (1), [0.3]</td>
</tr>
<tr>
<td>Ophthalmological</td>
<td>1.9 (47), [1.5]</td>
<td>1.5 (13), [1.2]</td>
<td>1.6 (5), [1.3]</td>
</tr>
<tr>
<td>Cataract</td>
<td>0.8 (19), [0.6]</td>
<td>2.5 (21), [2.0] *</td>
<td>2.9 (9), [2.3]</td>
</tr>
</tbody>
</table>

Values reported in % (n) [rate per 100 patient years]
*p=0.0018 when comparing LDL ≥ 25 mg/dL to < 25 mg/dL

Propensity Analysis of Selected Adverse Events in patients with Low LDL

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>LDL ≥ 25 mg/dL (2371)</th>
<th>LDL &lt; 25 mg/dL (811)</th>
<th>Hazard Ratio</th>
<th>95 % Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurocognitive disorders</td>
<td>1.1 (25)</td>
<td>0.6 (5)</td>
<td>0.38</td>
<td>(0.13-1.09)</td>
</tr>
<tr>
<td>Ophthalmologic events</td>
<td>2.0 (47)</td>
<td>1.6 (13)</td>
<td>0.64</td>
<td>(0.31-1.31)</td>
</tr>
<tr>
<td>Cataracts</td>
<td>0.8 (19)</td>
<td>2.6 (21)</td>
<td>3.4</td>
<td>(1.58-7.35) *</td>
</tr>
</tbody>
</table>

Values reported in % (n); *p=0.0018

Author’s Conclusion

- Increased incidence of cataracts in patients with LDL < 25 mg/dL, however this may be due to confounding factors as the patients compared were not randomized.
- Longer term safety of low LDL levels remains unknown, despite not finding a difference in TEAEs in this study.
<table>
<thead>
<tr>
<th>Critique</th>
<th><strong>Strengths</strong></th>
<th><strong>Limitations</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Safety events of interest evaluated</td>
<td>• Limited LDL distribution</td>
<td></td>
</tr>
<tr>
<td>• Evaluated factors that increase risk of low LDL</td>
<td>• Efficacy not addressed</td>
<td></td>
</tr>
<tr>
<td>• Multiple patient populations assessed (primary prevention, secondary prevention, familial, etc.)</td>
<td>• Post-hoc analysis</td>
<td></td>
</tr>
<tr>
<td>• Multiple alirocumab doses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Various background therapies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Appropriate FLP draw (fasting and 6 weeks)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Verified that LDL was low with 2 readings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Used central lab</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Data monitoring committee member and independent physician monitored patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Propensity analysis to account for confounding factors</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Duration of follow-up: 26 months**

<p>| Take away summary | Although overall there was not a significant difference in adverse events regardless of LDL level, efficacy was not evaluated and therefore we do not know if it is efficacious. Thus, we do not know if the risk outweighs the benefits. |</p>
<table>
<thead>
<tr>
<th>Study</th>
<th>Population (P)</th>
<th>Intervention (I)</th>
<th>Comparator (C)</th>
<th>Outcomes (O)</th>
</tr>
</thead>
</table>
| Hsia 2011      | • Patient without clinical ASCVD or diabetes                                                                                                                                  | rosuvastatin 20 mg daily                                                  | Placebo                                                                 | • Significantly higher rate of any adverse drug events in the LDL < 50 mg/dL group compared to > 50 mg/dL group  
• Higher rate of memory impairment and depression in the LDL > 50 mg/dL compared to the < 50 mg/dL group  
• No difference in incidence of cancer or cataracts                                                                                                                                                                                                                                                                   |
| Giugliano 2017 | • 40-85 years old with stable atherosclerotic disease                                                                                                             | evolocumab 140 mg every 2 weeks or 420 mg once monthly + statin therapy        | Placebo + statin therapy                                                | No difference in adverse events including neurocognitive events, cataract related events, new or progressive malignancy and hemorrhagic stroke.                                                                                                                                                                                                 |
| Giugliano 2017 | • 40-85 years old with stable atherosclerotic disease                                                                                                             | evolocumab 140 mg every 2 weeks or 420 mg once monthly + statin therapy        | Placebo + statin therapy                                                | No difference in change of cognitive function when comparing different levels of achieved LDL.                                                                                                                                                                                                                                                                   |
| LaRosa 2007    | • Patients with clinical atherosclerotic disease                                                                                                                                                   | atorvastatin 80 mg daily                                                   | atorvastatin 10 mg daily                                                | No difference in adverse events including death from cancer and hemorrhagic stroke.  
*neurocognitive events and cataracts were not evaluated                                                                                                                                                                                                                                                                                                           |
Conclusions and Recommendations

I. Summary of Primary Literature

<table>
<thead>
<tr>
<th>PROVE-IT TIMI 22 (2005)</th>
<th>JUPITER (2014)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• No difference in safety outcomes</td>
<td></td>
</tr>
<tr>
<td>• Additional benefit is not apparent between achieving LDL of 41-60 mg/dL versus &lt; 40 mg/dL</td>
<td></td>
</tr>
<tr>
<td>Increased incidence in diabetes, insomnia and hematuria in LDL &lt; 30 mg/dL</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>IMPROVE-IT (2017)</th>
<th>ALIROCUMAB POOLED TRIALS (2017)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• No difference in safety outcomes</td>
<td></td>
</tr>
<tr>
<td>• No significant difference in efficacy between LDL &lt; 30 vs. LDL 30 - 70 mg/dL</td>
<td></td>
</tr>
<tr>
<td>• No difference in overall safety outcomes</td>
<td></td>
</tr>
<tr>
<td>• Increase incidence of cataracts in patients with LDL &lt; 25 mg/dL compared to &gt; 25 mg/dL</td>
<td></td>
</tr>
</tbody>
</table>

**Other Studies**

No difference in safety outcomes with the exception of increased rates of memory impairment and depression in patients achieving LDL ≥ 50 mg/dL vs. < 50 mg/dL
II. Recommendations

LDL < 40 mg/dL on two consecutive occasions

Is the patient experiencing side effects?

Yes  
Consider patient specific factors**

No  
Reasonable to continue with current treatment

**ASCVD Risk, ASCVD History, Control of other risk factors, Age
References:


### Appendices

#### A. 2013 ACC/AHA Cholesterol Guideline: Initiation of Statin Therapy\(^3\)

<table>
<thead>
<tr>
<th>Clinical ASCVD</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Age ≤ 75 years: High-intensity statin</td>
<td></td>
</tr>
<tr>
<td>• Age &gt; 75 years: Moderate-intensity statin</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>LDL - C ≥ 190 mg/dL</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• High-intensity statin</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Aged 40 - 75 years + diabetes + LDL- C 70 to 189 mg/dL</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Estimated 10-year ASCVD risk &lt; 7.5 %: Moderate-intensity statin</td>
<td></td>
</tr>
<tr>
<td>• Estimated 10-year ASCVD risk ≥ 7.5 %: High-intensity statin</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No diabetes, LDL - C 70 to 189 mg/dL and not on statin therapy</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Estimated 10-year ASCVD risk ≥ 7.5 %: Moderate to high intensity statin</td>
<td></td>
</tr>
<tr>
<td>• Estimated 10-year ASCVD risk 5 to &lt; 7.5 %: Moderate-intensity statin</td>
<td></td>
</tr>
</tbody>
</table>

#### B. 2017 ACC Focused Update: Initiation of Non-Statin Therapy\(^5\)

<table>
<thead>
<tr>
<th>Clinical ASCVD without comorbidities</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Initial non-statin add on therapy: ezetimibe</td>
<td></td>
</tr>
<tr>
<td>• Second add on or replacement therapy of ezetimibe: PCSK-9 inhibitors</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical ASCVD with comorbidities</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Consider either ezetimibe or PCSK-9 inhibitor as initial non-statin add on therapy</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Baseline LDL - C ≥ 190 mg/dL</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Consider either ezetimibe or PCSK-9 inhibitor as initial non-statin add on therapy</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>40 - 75 years + diabetes + LDL- C 70 to 189 mg/dL</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Consider ezetimibe</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>A 40 - 75 years + LDL - C 70 to 189 mg/dL + 10-year ASCVD risk of ≥ 7.5%</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Consider ezetimibe</td>
<td></td>
</tr>
</tbody>
</table>