Improving Outcomes for Patients with Severe Hypercholesterolemia

A CME-certified, MOC-eligible Activity

Jointly provided by and

This activity is supported by educational funding provided by Amgen.

Educational Objectives

At the conclusion of this activity, participants should be able to:

• Evaluate the extent of residual CVD risk to which ASCVD patients are exposed, and treat additional CVD risk elements as appropriate
• Conduct appropriate diagnosis of familial hypercholesterolemia and implement appropriate treatment and rationale for cascade screening of the families
• Differentiate the clinical properties of new and emerging pharmacologic approaches to reduce LDL-C and lower CVD risk
• Analyze the potential utility of new LDL-C lowering agents used in combination with statins to reduce CVD risk in patients who have ASCVD

Hypercholesterolemia

Support for LDL-C Causality

• Four compelling lines of evidence
  – Experimental models
  – Observational human data
  – Genetic studies
  – Interventional human trials

Disease Trajectories and CVD Risk Reduction

Familial Hypercholesterolemia (FH)

Diagnostic Categories

<table>
<thead>
<tr>
<th>ICD-10 Category</th>
<th>Clinical Criteria</th>
<th>With Genetic Testing Performed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heterozygous FH</td>
<td>LDL-C &gt;160 mg/dL, for children and &gt;190 mg/dL, for adults and 1 first-degree relative similarly affected or with premature CAD or with positive genetic testing for LDL-C–raising gene defect</td>
<td>Presence of 1 abnormal LDL-C–raising (LDL receptor, apoB, or PCSK9) gene defect</td>
</tr>
<tr>
<td></td>
<td>Diagnosed as heterozygous FH if LDL-C–raising defect and LDL-C &lt;190 mg/dL.</td>
<td>Diagnosed as heterozygous FH if LDL-C–raising defect</td>
</tr>
<tr>
<td></td>
<td>Occasionally, heterozygotes will have LDL-C &gt;400 mg/dL, they should be treated similarly to homozygotes.</td>
<td>Occasionally, heterozygotes will have LDL-C &gt;400 mg/dL, they should be treated similarly to homozygotes.</td>
</tr>
<tr>
<td></td>
<td>Presence of both abnormal LDL-C–raising (LDL receptor, apoB or PCSK9) gene defects and LDL-C–lowering gene variant(s) with LDL-C &lt;190 mg/dL.</td>
<td>Presence of both abnormal LDL-C–raising (LDL receptor, apoB or PCSK9) gene defects and LDL-C–lowering gene variant(s) with LDL-C &lt;190 mg/dL.</td>
</tr>
</tbody>
</table>

Substantial CVD Risk Remains after ACS

43,810 Patients with ACS in GRACE Registry: 6-month Death Rate

GrACE = global registry of acute coronary events

Funding by: Circulation 2016;134;2167-2192.
Improving Outcomes for Patients with Severe Hypercholesterolemia

Men and Women with Familial Hypercholesterolemia
Rates of CHD Death or Nonfatal MI per 1,000 Person-years and Underlying Observed Event Numbers

FH Confers Greater CAD Risk
Especially when Baseline LDL-C Level ≥190 mg/dL

Monogenic Drivers of Coronary Artery Disease Risk
Familial Hypercholesterolemia
- Implicated genes
  - LDLR, APOB, PCSK9
- Prevalence
  - ~1 in 211
- CAD risk
  - ~4-fold increase
- Targeted therapies to reduce LDL-C
  - Statins, ezetimibe, PCSK9 inhibitors

30-year Survival Rates in Patients with FH

LDL-C Reduction
Cardiovascular Benefits

LDL-C and ASCVD
Statement from the European Atherosclerosis Society Consensus Panel
- Cumulative LDL arterial burden is a central determinant for the initiation and progression of ASCVD
- The lower the LDL-C level attained by agents that primarily target LDL receptors, the greater the clinical benefit
- Both relative risk reduction and absolute risk reduction relate to the magnitude of LDL-C reduction
- Lowering LDL-C in individuals at high cardiovascular risk earlier rather than later appears advisable, especially in those with familial hypercholesterolemia
Improving Outcomes for Patients with Severe Hypercholesterolemia

Treatments for Hypercholesterolemia

- Lifestyle Change
  - Physical activity
  - Medical nutrition therapy
  - Smoking cessation

- Pharmacologic Therapy
  - Statins
  - Cholesterol absorption inhibitors
  - Bile acid sequestrants
  - Fibrates
  - Omega-3 fish oil
  - PCSK9 inhibitors
  - MTP inhibitors
  - Antisense apo B oligonucleotide
  - Combination therapies

Therapies That Lower LDL-C

Statins

The Gold Standard for LDL-C Reduction and ASCVD Prevention

Primary Prevention Statin Trials

CHD Event Rates

Secondary Prevention Statin Trials

CHD Event Rates

Patients with Homozygous FH

Efficacy of LDL-C Lowering Therapies


Patients with Homozygous FH
CHD Risk According to Statin Treatment


Lower On-treatment LDL-C with Statins Predicts Lower ASCVD Risk


≥175
150-175
125-150
100-125
75-100
50-75
<50

Adjusted Hazard Ratio 95% Cl

0.25 0.5 0.75 1

LDL-C (mg/dL)

Lower On-treatment LDL-C with Statins Predicts Lower ASCVD Risk

2013 ACC/AHA Guidelines
Four Statin Benefit Groups

• Clinical ASCVD "secondary prevention"
• LDL-C >190 mg/dL without secondary cause
• Primary prevention with diabetes
  – Age 40-75 years; LDL-C 70-189 mg/dL
• Primary prevention without diabetes
  – Age 40-75 years, LDL-C 70-189 mg/dL; Estimated ASCVD risk >7.5%


Intensive Statin Therapy Reduces MACE
PROVE IT - TIMI 22: Study Design

2x2 factorial: gatifloxacin vs placebo
Double-blind

ASA + Standard Medical Therapy
“Standard Statin Therapy” pravastatin 40 mg

“Intensive Statin Therapy” atorvastatin 80 mg

223 patients; gatifloxacin or placebo
Duration: mean 2-year follow-up (>925 events)
Primary Endpoint: death, MI, documented UA requiring hospitalization, revascularization (>30 days after randomization), or stroke


Intensive Statin Therapy: PROVE IT-TIMI 22
All-Cause Death or Major CV Events

4,162 patients with an acute coronary syndrome <10 days
ASA + Standard Medical Therapy
“Standard Statin Therapy” pravastatin 40 mg
“Intensive Statin Therapy” atorvastatin 80 mg

Duration: mean 2-year follow-up (>925 events)
Primary Endpoint: death, MI, documented UA requiring hospitalization, revascularization (>30 days after randomization), or stroke


Intensive Statin Therapy Reduces MACE
PROVE IT - TIMI 22: Study Design

2013 ACC/AHA Guideline
Treatment of Blood Cholesterol to Reduce ASCVD Risk in Adults

• High-intensity statins recommended for: clinical ASCVD; LDL-C >190 mg/dL; DM with high-risk; 10-year ASCVD risk >7.5%
• Moderate-intensity possible for patients at less-elevated risk or prone to statin intolerance
• Low-intensity statins recommended only in patients with history of/at risk for adverse drug effects
• Monitoring LDL-C was recommended to assess compliance and response to therapy, but no guidance given for LDL-C goals on-treatment
• Shared decision making (doctor with patient) recommended for all treatment choices.

National Lipid Association Recommendations

Initiate Therapy Based on Risk and Lipid Levels then Treat to Specific Goal

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Criteria</th>
<th>Initiate Drug Therapy</th>
<th>Treatment Goal Non-HDL-C (LDL-C) (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0-1 major risk factors (RF)*</td>
<td>Non-HDL-C (LDL-C) &gt;190 (&gt;160)</td>
<td>&lt;130 (&lt;100)</td>
</tr>
<tr>
<td>Moderate</td>
<td>At least 2 major RF and 10-year risk &lt;15%*</td>
<td>Non-HDL-C (LDL-C) &gt;160 (&gt;130)</td>
<td>&lt;130 (&lt;100)</td>
</tr>
<tr>
<td>High</td>
<td>At least 2 major RF and 10-year risk &gt;15%*</td>
<td>Non-HDL-C (LDL-C) &gt;190 mg/dL</td>
<td>&lt;130 (&lt;100)</td>
</tr>
<tr>
<td>Very High</td>
<td>Established ASCVD</td>
<td>Non-HDL-C (LDL-C) &gt;190 (mg/dL)</td>
<td>&lt;130 (&lt;100)</td>
</tr>
</tbody>
</table>

*Consider other risk markers

Efficacy of Statin Treatment to Lower LDL-C

Only about 1/3 of High Risk Patients Achieve LDL-C Goal

Ezetimibe: IMPROVE IT Trial Design

Patients stabilized post-ACS ≤10 days
LDL-C ≤125 mg/dL or ≤100 mg/dL if prior statin

Duration: minimum 2.5-year follow-up (5250 events)

Primary Endpoint: CV death, MI, hospitalization for UA, revascularization (>30 days after randomization), or stroke
IMPROVE-IT Trial
LDL-C and Other Lipid Effects with Ezetimibe

<table>
<thead>
<tr>
<th></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>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>53.2</td>
<td>125.8</td>
<td>120.4</td>
<td>48.7</td>
<td>3.3</td>
</tr>
<tr>
<td>Δ</td>
<td>-16.7</td>
<td>-19.3</td>
<td>-16.7</td>
<td>+0.6</td>
<td>-0.5</td>
</tr>
</tbody>
</table>

Median Time avg 60.5 vs. 51.7 mg/dL


IMPROVE IT Trial: Ezetimibe + Simvastatin
Lowers ASCVD More than Simvastatin Alone

Primary endpoint: cardiovascular death, nonfatal myocardial infarction, stroke, hospitalization for unstable angina, coronary revascularization


Primary endpoint: cardiovascular death, nonfatal myocardial infarction, stroke, hospitalization for unstable angina, coronary revascularization


Non-statin Add-on

LDL-lowering Therapies

PCSK9 Inhibitors

Rationale Behind PCSK9 as a Therapeutic Target

Physiology of PCSK9

Proprotein Convertase Subtilisin/Kexin Type 9

PCSK9 retains LDL-R in endosome → LDL-R destruction → ↓ LDL removal → ↑ plasma LDL-C

PCSK9 Mutations and Effect on LDL Metabolism

Gain of Function

↓ LDL-R levels

↑ LDL clearance

Loss of Function

↑ LDL-R levels

↓ LDL clearance

LDL = Low-density lipoprotein

Improving Outcomes for Patients with Severe Hypercholesterolemia

PCSK9 Loss-of-Function Mutations
Resulted in Lower LDL-C Levels and Reduced CHD Rates

- Wild-type PCSK9 degrades LDL receptors
- 1% to 3% of population have a loss-of-function (LOF) mutation
- LOF mutations increase hepatic LDL receptor expression, reducing LDL-C levels by 15%-40%
- CHD incidence was reduced 47%-88% in PCSK9 loss-of-function mutation carriers compared with normal individuals


PCSK9 Inhibition
Enhanced LDL-C Reduction and Reduced CVD Risk

LDL-C Lowering Efficacy Dose-Response of Alirocumab and Evolocumab*

<table>
<thead>
<tr>
<th>ALIROCUMAB</th>
<th>% Change LDL-C</th>
<th>EVOLOCUMAB</th>
<th>% Change LDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 mg Q2W</td>
<td>-35%</td>
<td>70 mg Q2W</td>
<td>-42%</td>
</tr>
<tr>
<td>100 mg Q2W</td>
<td>-55%</td>
<td>105 mg Q2W</td>
<td>-69%</td>
</tr>
<tr>
<td>150 mg Q2W</td>
<td>-67%</td>
<td>140 mg Q2W</td>
<td>-66%</td>
</tr>
<tr>
<td>300 mg Q4W</td>
<td>-83%</td>
<td>350 mg Q4W</td>
<td>-58%</td>
</tr>
<tr>
<td>420 mg Q4W</td>
<td>-93%</td>
<td>420 mg Q4W</td>
<td>-50%</td>
</tr>
</tbody>
</table>

* Added to Stable Statin Therapy - Week 12

Clinical Outcomes of PCSK9 Inhibitors
Meta-analysis of 35 Randomized Clinical Trials

<table>
<thead>
<tr>
<th>End Point</th>
<th>Fixed-effects Odds Ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial Infarction</td>
<td>0.72 (0.64-0.81)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.81 (0.69-0.97)</td>
<td>0.002</td>
</tr>
<tr>
<td>Coronary Revascularization</td>
<td>0.79 (0.70-0.89)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>All-Cause Mortality*</td>
<td>1.00 (0.88-1.14)</td>
<td>0.999</td>
</tr>
<tr>
<td>Cardiovascular Mortality</td>
<td>1.01 (0.85-1.19)</td>
<td>0.936</td>
</tr>
<tr>
<td>Neurocognitive Adverse Events</td>
<td>1.12 (0.94-1.33)</td>
<td>0.218</td>
</tr>
</tbody>
</table>

* A significant association was shown between LDL-C and benefit in all-cause mortality

Clinical Data on Alirocumab

Alirocumab: ODYSSEY Outcomes
Evaluation of Alirocumab After ACS

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Improving Outcomes for Patients with Severe Hypercholesterolemia

**ODYSSEY Outcomes Design: Alirocumab Dose Adjustments to Stay within LDL-C Target Range**

- **Undesirably high baseline range**
- **Target range**
- **Below target**
- **Above target**
- **Alirocumab**

We attempted to maximize the number of patients in the target range and minimize the number below target by blindly titrating alirocumab (75 or 150 mg SC Q2W) or blindly switching to placebo.

Approximately 75% of months of active treatment were at the 75 mg dose.

**ODYSSEY Outcomes: Alirocumab Lowers LDL-C**

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

Excludes LDL-C values after premature treatment discontinuation or blinded switch to placebo.

Approximately 75% of months of active treatment were at the 75 mg dose.

**Alirocumab: ODYSSEY Outcomes**

Alirocumab reduces MACE

<table>
<thead>
<tr>
<th>Endpoint, n (%)</th>
<th>Alirocumab (N=9462)</th>
<th>Placebo (N=9462)</th>
<th>HR (95% CI)</th>
<th>Log-rank P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE</td>
<td>903 (9.5)</td>
<td>1052 (11.1)</td>
<td>0.85 (0.78, 0.93)</td>
<td>0.0003</td>
</tr>
<tr>
<td>CHD death</td>
<td>295 (2.2)</td>
<td>222 (2.3)</td>
<td>0.92 (0.76, 1.11)</td>
<td>0.38</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>626 (6.6)</td>
<td>722 (7.1)</td>
<td>0.86 (0.77, 0.96)</td>
<td>0.006</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>113 (1.2)</td>
<td>152 (1.6)</td>
<td>0.73 (0.57, 0.93)</td>
<td>0.01</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>37 (0.4)</td>
<td>60 (0.6)</td>
<td>0.61 (0.41, 0.92)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

*Based on cumulative incidence.
Improving Outcomes for Patients with Severe Hypercholesterolemia

**Alirocumab Effects on Main Secondary Efficacy Endpoints: Hierarchical Testing in ODYSSEY Outcomes**

<table>
<thead>
<tr>
<th>Endpoint, n (%)</th>
<th>Alirocumab (N=9462)</th>
<th>Placebo (N=9462)</th>
<th>HR (95% CI)</th>
<th>Log-rank P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD event</td>
<td>1199 (12.7)</td>
<td>1349 (14.3)</td>
<td>0.88 (0.81, 0.95)</td>
<td>0.001</td>
</tr>
<tr>
<td>Major CHD event</td>
<td>793 (8.4)</td>
<td>899 (9.5)</td>
<td>0.88 (0.80, 0.96)</td>
<td>0.006</td>
</tr>
<tr>
<td>CV event</td>
<td>1301 (13.7)</td>
<td>1674 (15.6)</td>
<td>0.87 (0.81, 0.94)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Death, MI, ischemic stroke</td>
<td>973 (10.3)</td>
<td>1126 (11.9)</td>
<td>0.86 (0.79, 0.93)</td>
<td>0.0003</td>
</tr>
<tr>
<td>CHD death</td>
<td>205 (2.2)</td>
<td>222 (2.3)</td>
<td>0.92 (0.76, 1.11)</td>
<td>0.38</td>
</tr>
<tr>
<td>CV death</td>
<td>240 (2.5)</td>
<td>273 (2.9)</td>
<td>0.88 (0.74, 1.05)</td>
<td>0.15</td>
</tr>
<tr>
<td>All-cause death</td>
<td>334 (3.5)</td>
<td>392 (4.1)</td>
<td>0.85 (0.73, 0.98)</td>
<td>0.026*</td>
</tr>
</tbody>
</table>

*Nominal P-value

**Alirocumab: ODYSSEY Outcomes**

**Alirocumab May Reduce Total Mortality**

ARR† 0.6%

*Nominal P-value

†Based on cumulative incidence

**Clinical Data on Evolocumab**

**Evolocumab: FOURIER**

**Primary Efficacy Endpoint**

Improving Outcomes for Patients with Severe Hypercholesterolemia

Evolocumab: FOURIER
Key Secondary Endpoint

Lowest LDL-C is Best for ASCVD Prevention
Evolocumab (FOURIER) Key Endpoint (CV Death, MI, or Stroke)

Evolocumab: FOURIER
Landmark Analysis

Evolocumab Appears Effective (CVD) and Safe (SAE, D/C) to LDL-C < 10 mg/dL

Ebbinghaus: Evolocumab
Evaluation of Cognition with Aggressive LDL-C Lowering

New Guidance for PCSK9 Inhibitors and Ezetimibe
In Light of Cardiovascular Outcomes Data
Improving Outcomes for Patients with Severe Hypercholesterolemia

2016 ACC/AHA Expert Consensus Decision Pathway

Bottom Line
1. LDL-C goals approved:
   a. <70 for 2o prevention
   b. <100 for HR 1o prev.
2. For PCSK9, LDL-C Threshold = Goal

2017 NLA Expert Panel PCSK9-inhibitor Recommendations

<table>
<thead>
<tr>
<th>Prohibit</th>
<th>LDL-C&lt;70 mg/dl</th>
<th>Strength of evidence</th>
<th>Quality of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASCVD + additional risk factors</td>
<td>≥70 / &lt;100</td>
<td>A</td>
<td>High</td>
</tr>
<tr>
<td>Preexisting ASCVD</td>
<td>≥70 / &lt;100</td>
<td>B</td>
<td>Moderate</td>
</tr>
<tr>
<td>LDL-C ≥ 100, age 64–75</td>
<td>≥50 / &lt;100</td>
<td>B</td>
<td>Moderate</td>
</tr>
<tr>
<td>LDL-C ≤ 100, age 64–75</td>
<td>≥50 / &lt;100</td>
<td>B</td>
<td>Moderate</td>
</tr>
<tr>
<td>LDL-C ≥ 100, age 64–75</td>
<td>≥30 / &lt;100</td>
<td>B</td>
<td>Moderately</td>
</tr>
<tr>
<td>Hemorrhagic stroke history</td>
<td>≥30 / &lt;100</td>
<td>B</td>
<td>Moderate</td>
</tr>
<tr>
<td>ASCVD + Statin intolerance</td>
<td>Clinical judgment</td>
<td>C</td>
<td>Low</td>
</tr>
</tbody>
</table>

2017 Focused Update: ACC Expert Consensus Decision Pathway on Therapies for LDL-C Lowering in Management of ASCVD*

* Patients ≥ 18 years of age with stable clinical ASCVD without ACS, on statin for secondary prevention.

2017 ESC/EAS Task Force on Practical Clinical Guidelines

2017 ESC/EAS Task Force on Practical Clinical Guidelines

PCSK9 Inhibition in Patients with Familial Hypercholesterolemia

<table>
<thead>
<tr>
<th>Response</th>
<th>0%</th>
<th>1%–2%</th>
<th>2%–4%</th>
<th>5%–10%</th>
<th>&gt;10%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Successful approvals, %</td>
<td>70.0</td>
<td>80.0</td>
<td>60.0</td>
<td>40.0</td>
<td>20.0</td>
</tr>
</tbody>
</table>

Approval/Reimbursement Barriers Faced by Patients

©2018 PCME Activity Slides
Defining a “Reimbursement Roadmap”
To Address Cumbersome Approval/Reimbursement Process

- More consistent criteria by payers and checklists, algorithms, apps, sharing of best practices which:
  - Improve patient selection
  - Help to assure that required documentation is submitted
  - Reduce wasted time
  - Avoid frustration by health care providers and patients in the approval/denial process

CME/MOC Credit

- Post-activity Survey and CME Evaluation
  - If you’re seeking only CME credit, please take a moment to answer the Post-activity survey questions on your form
  - Your answers are important and will help us identify remaining educational gaps and shape future CME activities
  - After the post-activity survey, please complete the rest of the Evaluation form and ensure you fill in your name and demographic information after the questions
  - Return all forms to on-site CME staff

- MOC Evaluation
  - MOC seekers do not need to complete the remainder of the paper form. Instead, follow the instructions at the top of the form to complete the online MOC evaluation.

Thank you for joining us today!