Adverse Impacts of Severe ASCVD

Is PCSK9 Inhibition the Key to Improving Patient Outcomes?

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Salt Lake City, Utah
Past President, American Board of Clinical Lipidology

Educational Objectives

At the conclusion of this activity, participants should be able to:
- Evaluate the extent of residual CVD risk to which high-risk patients are exposed
- Analyze the potential strengths and weaknesses of new approaches to reduce CVD risk
- Incorporate insights about new LDL-lowering agents in combination with statin therapy into more comprehensive clinical treatment strategies
- Discuss strategies to improve the knowledge, skills, or performance of the healthcare team

Elevated LDL-C Cardiovascular Pathobiology

Support for LDL Causality in ASCVD

- Four Compelling Lines of Evidence:
  - Observational data
  - Interventional data
  - Genetic studies
  - Experimental data

Impact of Hypercholesterolemia Mutation Status on CAD According to LDL-C Level

ASCVD = atherosclerotic cardiovascular disease

ARIC Study: Relationship of LDL-C to CHD

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Unadjusted Rates of CHD Death or Nonfatal MI per 1000 Person-years and Underlying Observed Event Numbers in Men and Women with FH

LDL-C Reduction: Cardiovascular Benefits

Mean Attained LDL-C on Statin Therapy and Risks of Secondary Cardiovascular Events

Genetically and Pharmacologically Mediated Reduction of LDL-C Lowers Risk of CHD

Patients who Achieve Very Low LDL-C Levels have Lower Risk For MACE

LDL-C and Atherosclerotic Cardiovascular Disease

- Cumulative LDL arterial burden is a central determinant for the initiation and progression of atherosclerotic cardiovascular disease
- The lower the LDL-C level attained by agents that primarily target LDL receptors, the greater the clinical benefit
- Both relative 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
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**Statin Therapy: The Gold Standard for LDL-C Reduction**


**CHD Events Are Reduced Proportional to LDL-C Lowering with Statins**

*Equation: CHD Events = 0.1629 ∙ LDL_C - 4.6776

R² = 0.9029

P < 0.0001

<table>
<thead>
<tr>
<th>LDL Cholesterol (mg/dL)</th>
<th>CHD Events (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>5%</td>
</tr>
<tr>
<td>150</td>
<td>10%</td>
</tr>
<tr>
<td>200</td>
<td>15%</td>
</tr>
<tr>
<td>250</td>
<td>20%</td>
</tr>
<tr>
<td>300</td>
<td>25%</td>
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</table>

**ASCVD Statin Benefit Groups**

- High-intensity Statin Therapy
- Moderate-intensity Statin Therapy
- Low-intensity Statin Therapy

**2013 ACC/AHA Guideline: Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults**

- Low-intensity statins are recommended only in patients with history of or at risk for adverse drug effects
- Moderate-to-high-intensity statins recommended for patients with clinical ASCVD and those with diabetes
- High-intensity statins recommended for patients with LDL-C >190 mg/dL
- Did not find evidence to support LDL-C thresholds or targets of therapy. No evidence was found that titration or combination drug therapy to achieve specific LDL-C or non-HDL-C levels or percent reduction improved ASCVD outcomes. No dose titration recommended.

- Monitor LDL-C to assess compliance and response to therapy

**High, Moderate, and Low-intensity Statin Therapy Used in Clinical Trials**

<table>
<thead>
<tr>
<th>Statin</th>
<th>Dose (mg)</th>
<th>Clinical Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>10* (20**)</td>
<td>PROVE-IT-A2Z</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>10* (20**)</td>
<td>TNT (S20)</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>10**</td>
<td>TNT (A80)</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>40* (80**)</td>
<td>ACC/AHA Guidelines (LIPID-P)</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>40*</td>
<td>ASCVD-P</td>
</tr>
</tbody>
</table>
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### NLA Recommendations: Initiate Therapy Based on Risk and Lipid Levels and Treat to Specific Goal

| Risk Category | Criteria | Initiating Therapy | Treatment Goal
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>≤ 20% 5-year risk</td>
<td>&gt;130 mg/dL (3.4 mmol/L)</td>
<td>&lt;100 mg/dL (2.6 mmol/L)</td>
</tr>
<tr>
<td>Moderate</td>
<td>&gt;20% 5-year risk</td>
<td>&gt;190 mg/dL (5.0 mmol/L)</td>
<td>&lt;100 mg/dL (2.6 mmol/L)</td>
</tr>
<tr>
<td>High</td>
<td>&gt;20% 5-year risk</td>
<td>&gt;250 mg/dL (6.5 mmol/L)</td>
<td>&lt;&lt;130 mg/dL (3.4 mmol/L)</td>
</tr>
<tr>
<td>Very High</td>
<td>&gt;20% 5-year risk</td>
<td>&gt;&gt;300 mg/dL (&gt;8.0 mmol/L)</td>
<td>&lt;&lt;130 mg/dL (3.4 mmol/L)</td>
</tr>
</tbody>
</table>

*Consider other risk factors.
*Complete cessation of high-intensity statin in patients with ASCVD or DM regardless of baseline lipid levels.

### Residual CHD Risk Despite Statin Therapy

#### Major Statin Trials: Despite Benefit, Substantial Residual CV Risk Remains

<table>
<thead>
<tr>
<th>LDL-C (mg/dL)</th>
<th>Placebo</th>
<th>Statin</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C Change</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>15.9</td>
<td>11.8</td>
</tr>
<tr>
<td>Secondary</td>
<td>16.0</td>
<td>12.4</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40</td>
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</tbody>
</table>

Change in LDL-C on Statin and MACE Event Rates

Statin-Treated CHD Patients Achieving LDL-C <100 mg/dL and <70 mg/dL

Cumulative Incidence for Recurrent MI, CHD Events, and All-Cause Mortality

Statin Intolerance and Risk of Coronary Events


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### Disease Trajectories and CVD Risk Reduction

**Non-Statin LDL-Lowering Therapies: Ezetimibe**

**Ezetimibe: IMPROVE IT Trial Design**

- Patients stabilized post-ACS ≤10 days
- LDL-C ≤125 mg/dL (or ≤100 mg/dL if prior statin)
- ASA + Standard Medical Therapy
- Simvastatin 40 mg* + Ezetimibe 10/40 mg*
- Follow-up visit day 30, every 4 months
- Duration: Minimum 2.5 year follow-up (2520 events)

**IMPROVE IT Trial: Effect on LDL-C**

- Ezetimibe (EZ) + Simvastatin vs Simvastatin Alone
- Study drug is administered once daily in the evening

**IMPROVE IT Trial: Ezetimibe + Simvastatin vs Simvastatin Alone**

- Reduction in Rate of Major Vascular Events (%)
  - Reduction in LDL Cholesterol: mmol/L (mg/dL)
    - 2.0 (77.2)
    - 1.5 (57.9)
    - 1.0 (38.6)
    - 0.5 (19.3)

**IMPROVE-IT: Ezetimibe vs Statin Benefit – Change in LDL-C vs Clinical Benefit**

- Ezetimibe/Simvastatin – 32.7%
- Simvastatin – 34.7%
- NNT = 50
- HR 0.936 CI (0.887, 0.988)

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Non-Statin LDL-Lowering Therapies: PCSK9 Inhibitors

PCSK9 Physiology: Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9)

- Chaperones LDL-R to destruction → ↑ circulating LDL-C
- Loss-of-fxn genetic variants → ↓ LDL-R → ↓ LDL-C & ↓ risk of MI

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

- Wild-type PCSK9 degrades LDL receptors.1,2
- Loss-of-function (LOF) mutations increase hepatic LDL receptor expression, reducing LDL-C levels by 15%-40%.2,3
- CHD incidence was reduced 47%-88% in PCSK9 loss-of-function mutation carriers compared with normal individuals.3

Alirocumab: ODYSSEY Long-Term Stable LDL-C Reduction

- Cox model analysis: HR = 0.52 (95% CI 0.31 to 0.90)
- Nominal P-value = 0.02

Alirocumab: ODYSSEY Long-Term MACE Rate by Average LDL-C During Treatment Period

- Based on primary endpoint for the ODYSSEY Long-Term trial, including CHD death, non-fatal MI, non-fatal stroke, non-fatal ischemic stroke, and unstable angina requiring hospitalization for coronary revascularization.


This analysis was based on pooled data from the Phase 3 trials of Alirocumab: ODYSSEY ABLE and ODYSSEY LITMUS.
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**Evolocumab: The GLAGOV Trial**

Progression of Coronary Atherosclerosis on Statin +/- Evolocumab

- **Nicholls SJ et al.**
- **JAMA.** 2016;316:2373-2384.

**Effect of Evolocumab on Progression of Coronary Artery Disease in Statin-treated Patients**

The GLAGOV Randomized Double-Blind Clinical Trial

- **Nicholls SJ et al.**
- **JAMA.** 2016;316:2373-2384.

**Randomized Open-Label Extension of OSLER-1 & OSLER-2 (RDBCTs): Evolocumab vs Placebo on MACE**

Open label study of 4465 pts randomized to evolocumab 140 mg SC Q2W or 420 mg SC QM + standard of care (SOC) for 48 wks

- **CV Events**
  - Death
  - MI
  - UA requiring hospitalization
  - CVA
  - TIA
  - Hosp w CHF

CV Events

Evolocumab: FOURIER Trial Design

27,664 high-risk, stable patients with established CV disease (prior MI, prior stroke, or symptomatic PAD)

Screening, Lipid Stabilization, and Placebo Run-in

High or moderate intensity statin therapy (± ezetimibe)

27,564 high-risk, stable patients with established CV disease (prior MI, prior stroke, or symptomatic PAD)

Randomized Open-Label Extension of OSLER-1 & OSLER-2 (RDBCTs): Evolocumab vs Placebo on MACE

Follow-up 12 wks (over 2.2 y median f/u)

**Evolocumab: FOURIER Trial Design**

- LDL-C ≥ 100 mg/dL or non-HDL-C ≥ 110 mg/dL
- Follow-up Q 12 wks (over 2.2 y median f/u)

**Evolocumab: FOURIER–LDL Cholesterol**

- Placebo
- Evolocumab

55% mean reduction (95% CI 30.6-68.4, P=0.00001)

Absolute reduction: 54 mg/dL (95% CI 35.5-73.5)

**Evolocumab: FOURIER– Primary Efficacy Endpoint**

- Hazard ratio 0.85 (95% CI 0.79-0.92) P=0.0001
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Evolocumab: FOURIER—Landmark Analysis


PCSK9 Inhibition: LDL-C Lowering Efficacy in Long-term Studies

<table>
<thead>
<tr>
<th>Patients</th>
<th>% LDL-C ≤ 35% wks</th>
<th>% LDL-C ≤ 40% wks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evolocumab 140 mg SC Q2W or 420 mg SC QM (baseline LDL-C = 120 mg/dL)</td>
<td>-61% (P&lt;0.001)</td>
<td>-61% (P&lt;0.001)</td>
</tr>
<tr>
<td>Alirocumab 150 mg SC Q2W (baseline LDL-C = 123 mg/dL)</td>
<td>-62% (P&lt;0.001)</td>
<td>-56% (P&lt;0.001)</td>
</tr>
</tbody>
</table>

- Osler1: Open label study of 4485 pts randomized to evolocumab 140 mg SC Q2W or 420 mg SC QM + standard of care (SOC) vs SOC for 48 weeks
- Odyssey Long Term2: Blinded study of 2341 high risk pts on max-tolerated statin with LDL-C > 70 randomized to alirocumab 150 mg or placebo SC Q2W for 78 wks

*Proportion of patients with LDL-C = 70 mg/dL = 74%
ƚProportion of patients with LDL-C = 70 mg/dL = 79%


2016 ESC/EAS Guidelines on Dyslipidemias: Pharmacological Treatment of Hypercholesterolemia

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prescribe statin to the highest recommended dose or highest tolerated dose to reach the goal</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>In the case of statin intolerance, ezetimibe or bile acid sequestrants, or these combined, should be considered</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>If the goal is not reached, statin combination with a cholesterol absorption inhibitor should be considered</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>If the goal is not reached, statin combination with a bile acid sequestrant may be considered</td>
<td>IIb</td>
<td>C</td>
</tr>
<tr>
<td>In patients at very high risk, with persistent high LDL-C despite treatment with maximal tolerated statin dose, in combination with ezetimibe or in patients with statin intolerance, a PCSK9 inhibitor may be considered</td>
<td>IIb</td>
<td>C</td>
</tr>
</tbody>
</table>

Class of Recommendation: 1 = strong 2 = moderate 3 = weak

Level of Evidence: A = strong B = moderate C = limited

2016 ACC/AHA Expert Consensus Decision Pathway

Determining When to Add Nonstatin Therapy
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LDL-C Response Variability to High-Intensity Statin Therapy and Implications for the Allocation of PCSK9 Inhibitors


The Gap Between What We Know and What We Do

“Drugs don’t work in patients who don’t take them.”

– C. Everett Koop
Former US Surgeon General

Barriers to Medication Adherence

Benefits of Shared Decision-making

- Learn about their health
- Recognize a decision is necessary
- Understand pros and cons
- Have the information and tools needed to evaluate
- Are better prepared to talk
- Collaborate with their healthcare team
- Are more likely to follow through with the decision
- Builds a lasting and trusting relationship

Simulation of Lipid-Lowering Therapy Intensification in ASCVD

- Large gaps exist between recommendations and current practice
- Model assumes no lipid lowering therapy (LLT) intolerance and full adherence
- Intensification of oral LLT could achieve an LDL-C level of less than 70mg/dL in most patients, with only a modest percentage requiring a PCSK9 inhibitor.
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- In a contemporary US population with ASCVD, only 53.2% received a statin at baseline
- Only 15.3% received a high-intensity statin
- This treatment 25.2% achieving LDL-C levels of less than 70mg/dL


Interventions to Improve Adherence

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<th>P</th>
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</thead>
<tbody>
<tr>
<td>Study the regimen</td>
<td>Advisor during frequent, small change</td>
<td>Tailored education, patient-centered care, self-care, and peers</td>
<td>Patient monitor, medication management</td>
<td>Provider, pharmaceutical, patient, provider, patient</td>
<td>Education, health literacy, provider, provider, provider</td>
</tr>
</tbody>
</table>

Conclusions

- People with lifetime low LDL-C are at low risk for ASCVD; those with high LDL-C have increased risk
- Despite significant reduction in LDL-C and CVD risk associated with statin use, considerable residual risk persists.
- High-risk patients remain untreated to LDL goals for many reasons, including statin intolerance
- The addition of ezetimibe to statins yields incremental but modest improvements in CVD risk.
- PCSK9 inhibitors represent the most promising new class of LDL-C lowering therapy and ongoing outcomes trials will help to determine the clinical utility of these agents.
- Lipid-lowering therapies improve outcomes of patients with ASCVD, but to be effective, they must be taken as prescribed.

Thank you!