PCSK9 Inhibitors: For Whom, When, and Why

Leslie Cho, MD
Section Head, Preventive Cardiology and Rehabilitation
Director, Women’s Cardiovascular Center
Cleveland Clinic
Cleveland, OH
Steven Nissen, MD
Professor of Medicine
Cleveland Clinic Lerner College of Medicine of
Case Western Reserve University
Chairman, Robert and Suzanne Tomsich
Department of Cardiovascular Medicine
Cleveland Clinic
Cleveland, OH

PCSK9 Inhibitors Inactivate PCSK9 \(\rightarrow\) Increase LDL-Receptor Expression \(\rightarrow\) ↓ LDL-C Levels

**LDL-C–Lowering Efficacy of PCSK9 Inhibitors**

**Monotherapy**

- **Ezetimibe**
  - 20%
- **Alirocumab**
  - 75/150 mg
  - 53%
- **Ezetimibe**
  - 18%
- **Evolocumab**
  - 140 mg q2W
  - 57%
- **Evolocumab**
  - 420 mg q4W
  - 56%

*LDL level is from week 12 of trial, prior to increase to alirocumab 150 mg.*

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**LDL-C–Lowering Efficacy of PCSK9 Inhibitors***

**Background Statin Therapy**

- **Alirocumab**
  - 75 mg q2W
  - -48% -47%
- **Alirocumab**
  - 75/150 mg q2W
  - -54% -46%
- **Alirocumab**
  - 150 mg q2W
  - -63% -62%
- **Evolocumab**
  - 140 mg q2W
  - -61% -71%
- **Evolocumab**
  - 420 mg q4W
  - -60% -63%

*Alirocumab data are from week 24; evolocumab data are from week 12.*

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*LDL-C level is from week 12 of trial, prior to increase to alirocumab 150 mg.*

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Indications for PCSK9 Inhibitors Approved by US FDA in 2015

Alirocumab & Evolocumab

• Use as an adjunct to diet and maximally tolerated statin therapy in patients who require additional LDL-C lowering:
  – Adults with HeFH
  – Adults with clinical CVD

Evolocumab

• Patients with HoFH on statins, ezetimibe, and/or LDL apheresis

• The FDA further noted as a limitation of use that the effect of alirocumab or evolocumab on CV morbidity and mortality has not yet been determined.
PCSK9 Inhibitors in FH

Evolocumab
• TESLA study
• Patients with HoFH on statins and/or ezetimibe

TESLA B: Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Placebo Group (n = 16)</th>
<th>Evolocumab Group (n = 33)</th>
<th>All patients (N = 49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>32 (14)</td>
<td>30 (12)</td>
<td>31 (13)</td>
</tr>
<tr>
<td>Age range (years)</td>
<td>14-57</td>
<td>13-51</td>
<td>13-57</td>
</tr>
<tr>
<td>Female sex</td>
<td>8 (50%)</td>
<td>16 (48%)</td>
<td>24 (49%)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- White</td>
<td>15 (94%)</td>
<td>29 (88%)</td>
<td>44 (90%)</td>
</tr>
<tr>
<td>- Asian</td>
<td>1 (6%)</td>
<td>1 (3%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Clinically evident CAD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Previous coronary artery bypass surgery</td>
<td>6 (38%)</td>
<td>15 (46%)</td>
<td>21 (43%)</td>
</tr>
<tr>
<td>- Aortic valve replacement</td>
<td>4 (25%)</td>
<td>8 (24%)</td>
<td>12 (25%)</td>
</tr>
<tr>
<td>Lipid parameters</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- LDL-C, ultracentrifugation (mmol/L)</td>
<td>8.7 (3.8)</td>
<td>9.2 (3.5)</td>
<td>9.0 (3.5)</td>
</tr>
<tr>
<td>- LDL-C, calculated (mmol/L)</td>
<td>8.7 (3.7)</td>
<td>9.2 (3.5)</td>
<td>9.0 (3.6)</td>
</tr>
<tr>
<td>- apoB (g/L)</td>
<td>2.1 (0.8)</td>
<td>2.1 (0.7)</td>
<td>2.1 (0.7)</td>
</tr>
<tr>
<td>- Lp(a) (mmol/L)</td>
<td>128 (60-201)</td>
<td>76 (26-145)</td>
<td>101 (31-146)</td>
</tr>
<tr>
<td>- apoA1 (g/L)</td>
<td>1.1 (0.4)</td>
<td>1.1 (0.2)</td>
<td>1.1 (0.3)</td>
</tr>
<tr>
<td>- HDL-C (mmol/L)</td>
<td>1.0 (0.4)</td>
<td>1.0 (0.3)</td>
<td>1.0 (0.3)</td>
</tr>
<tr>
<td>- Triglycerides (mmol/L)</td>
<td>1.3 (0.7)</td>
<td>1.2 (0.6)</td>
<td>1.2 (0.6)</td>
</tr>
<tr>
<td>- Free PCSK9 (nmol/L)</td>
<td>9.4 (2.5)</td>
<td>8.9 (2.9)</td>
<td>9.0 (2.7)</td>
</tr>
</tbody>
</table>
TESLA B: Genotype

<table>
<thead>
<tr>
<th></th>
<th>Placebo Group (n = 16)</th>
<th>Evolocumab Group (n = 33)</th>
<th>All Patients (N = 49)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LDL-R mutations</strong></td>
<td>14 (88%)</td>
<td>31 (94%)</td>
<td>45 (92%)</td>
</tr>
<tr>
<td><strong>True homozygous</strong></td>
<td>7 (44%)</td>
<td>15 (45%)</td>
<td>22 (45%)</td>
</tr>
<tr>
<td><strong>Compound heterozygous</strong></td>
<td>7 (44%)</td>
<td>16 (48%)</td>
<td>23 (47%)</td>
</tr>
<tr>
<td><strong>Heterozygous</strong></td>
<td>0</td>
<td>1 (3%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td><strong>apoB</strong></td>
<td>2 (13%)</td>
<td>0</td>
<td>2 (4%)</td>
</tr>
<tr>
<td><strong>Autosomal recessive hypercholesterolaemia</strong></td>
<td>0</td>
<td>1 (3%)</td>
<td>1 (2%)</td>
</tr>
</tbody>
</table>

TESLA B: Change in LDL-C

- Placebo group (n = 16)
- Evolocumab group (n = 33)

Number of patients analyzed at each visit:

- Placebo: 16, 16, 15, 16, 15
- Evolocumab: 33, 32, 28, 32, 29

*Adjusted.*
Statin Intolerant

• GAUSS 1—*JAMA* 2012 (Sullivan D, et al)
• GAUSS 2—*JACC* 2014 (Stroes E, et al)
• GAUSS 3—*JAMA* 2016 (Nissen SE, et al)
• ODYSSEY ALTERNATIVE—AHA 2014 (Moriarty PM, et al)

Study Design:
Two Double-Blind Phases—GAUSS 3

Phase A
- 511 patients enrolled at 53 centers with a history of intolerance to multiple statins due to muscle-related adverse effects
- 10 weeks: Atorvastatin 20 mg or Placebo
- 10 weeks: Atorvastatin 20 mg or Placebo

Phase B
- Patients proceeded to phase B only if they had intolerable muscle symptoms on atorvastatin, but not placebo, or CK ≥ 10 x ULN during prior statin treatment
- 24 weeks: Monthly SC evolocumab 420 mg or Daily oral ezetimibe 10 mg

Select Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Phase A (N = 491)</th>
<th>Phase B (N = 218)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>61</td>
<td>59</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ezetimibe (n = 73)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Evolocumab (n = 145)</td>
</tr>
<tr>
<td>Male gender</td>
<td>50%</td>
<td>47%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>54%</td>
</tr>
<tr>
<td>CHD</td>
<td>35%</td>
<td>29%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>33%</td>
</tr>
<tr>
<td>NCEP-ATP III high risk</td>
<td>63%</td>
<td>52%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>58%</td>
</tr>
<tr>
<td>Intolerance to ≥ 3 statins</td>
<td>82%</td>
<td>82%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>82%</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>301</td>
<td>308</td>
</tr>
<tr>
<td></td>
<td></td>
<td>307</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>212</td>
<td>222</td>
</tr>
<tr>
<td></td>
<td></td>
<td>219</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>51</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50</td>
</tr>
</tbody>
</table>
Phase A: Study Drug Discontinuation Events

<table>
<thead>
<tr>
<th>Intolerable Muscle Symptoms</th>
<th>N = 491</th>
</tr>
</thead>
<tbody>
<tr>
<td>On atorvastatin, but not placebo</td>
<td>209 (42.6%)*</td>
</tr>
<tr>
<td>On placebo, but not atorvastatin</td>
<td>130 (26.5%)</td>
</tr>
<tr>
<td>On both placebo and atorvastatin</td>
<td>48 (9.8%)</td>
</tr>
<tr>
<td>No symptoms on either treatment</td>
<td>85 (17.3%)</td>
</tr>
<tr>
<td>Did not complete phase A</td>
<td>20 (3.9%)*</td>
</tr>
<tr>
<td>Bypassed phase A due to CK elevation ≥ 10 x ULN</td>
<td>19 (3.9%)**</td>
</tr>
</tbody>
</table>

*N = 511.
**218 of these 228 eligible patients proceeded to phase B.

LDL-C Values Over Time During Phase B

- Mean reduction: 16.7% (LDL-C = 181 mg/dL)
- Mean reduction: 53.0% (LDL-C = 104 mg/dL)

Ezetimibe
Evolocumab

P < .001

Phase B: Adverse Effects and Drug Discontinuations

<table>
<thead>
<tr>
<th></th>
<th>Ezetimibe (n = 73)</th>
<th>Evolocumab (n = 145)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total muscle-related events</strong></td>
<td>21 (28.8%)</td>
<td>30 (20.7%)</td>
</tr>
<tr>
<td>Myalgia, muscle pain, or weakness</td>
<td>17 (23.3%)</td>
<td>25 (17.2%)</td>
</tr>
<tr>
<td><strong>Investigator-reported CK increase</strong></td>
<td>1 (1.4%)</td>
<td>4 (2.8%)</td>
</tr>
<tr>
<td><strong>Discontinuation of Treatment for Any Reason</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discontinued oral drug treatment</td>
<td>14 (19.2%)</td>
<td>23 (15.9%)</td>
</tr>
<tr>
<td>Discontinued SC drug treatment</td>
<td>4 (5.5%)</td>
<td>7 (4.8%)</td>
</tr>
<tr>
<td><strong>Discontinuation of Treatment for Muscle Symptoms</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discontinued oral drug treatment</td>
<td>5 (6.8%)</td>
<td>11 (7.6%)</td>
</tr>
<tr>
<td>Discontinued SC drug treatment</td>
<td>0 (0%)</td>
<td>1 (0.7%)</td>
</tr>
</tbody>
</table>

ODYSSEY ALTERNATIVE

- Patients with statin intolerance (by medical history) with LDL-C > 70 mg/dL at very high CV risk or LDL-C > 100 mg/dL at moderate/high risk; mean baseline LDL-C was 190 mg/dL
- 314 patients were randomized to SC alirocumab 75 mg/150 mg every 2 weeks (n = 126), ezetimibe 10 mg once daily (n = 125), or atorvastatin 20 mg once daily (n = 63)
But What About Everyone Else?

After FOURIER and ODYSSEY, Who Else Should Get PCSK9 Inhibitors?
FOURIER

- Evolocumab vs placebo
- N = 27,564
- CVD “plus”—very high risk
  - 3.4% ASCVD/year
  - 34% 10-year ASCVD risk
- Guideline-based statin
  - High intensity (69%)
  - Moderate intensity (30%)
- Median follow-up: 2.2 years
- LDL-C reduction: 59%


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FOURIER

A. Primary Efficacy Endpoint

**Major CVD**
CVD death, MI, stroke, hospitalized unstable angina, coronary revascularization

**HR, 0.80 (95% CI, 0.79-0.92)**

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Months</th>
<th>Placebo</th>
<th>Evolocumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>11,710</td>
<td>15,315</td>
<td>15,313</td>
</tr>
<tr>
<td>Evolocumab</td>
<td>12,070</td>
<td>15,313</td>
<td>15,313</td>
</tr>
</tbody>
</table>

**RRR, 16%**

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Months</th>
<th>Placebo</th>
<th>Evolocumab</th>
</tr>
</thead>
<tbody>
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<td>15,313</td>
</tr>
<tr>
<td>Evolocumab</td>
<td>12,070</td>
<td>15,313</td>
<td>15,313</td>
</tr>
</tbody>
</table>

B. Key Secondary Efficacy Endpoint

**ASCVD**
CVD death, MI, stroke

**HR, 0.80 (95% CI, 0.73-0.88)**

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Months</th>
<th>Placebo</th>
<th>Evolocumab</th>
</tr>
</thead>
<tbody>
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<td>15,313</td>
</tr>
<tr>
<td>Evolocumab</td>
<td>12,070</td>
<td>15,313</td>
<td>15,313</td>
</tr>
</tbody>
</table>

**RRR, 25%**

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Months</th>
<th>Placebo</th>
<th>Evolocumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>11,710</td>
<td>15,315</td>
<td>15,313</td>
</tr>
<tr>
<td>Evolocumab</td>
<td>12,070</td>
<td>15,313</td>
<td>15,313</td>
</tr>
</tbody>
</table>

ODYSSEY: Study Hypothesis

• Alirocumab, versus placebo, reduces CV morbidity and mortality after recent ACS in patients with elevated levels of atherogenic lipoproteins despite intensive or maximum-tolerated statin therapy

Main Inclusion Criteria

• Age ≥ 40 years
• ACS
  – 1 to 12 months prior to randomization
  – Acute MI or unstable angina
• High-intensity statin therapy*
  – Atorvastatin 40 to 80 mg daily or
  – Rosuvastatin 20 to 40 mg daily or
  – Maximum tolerated dose of one of these agents for ≥ 2 weeks

• Inadequate control of lipids
  – LDL-C ≥ 70 mg/dL (1.8 mmol/L) or
  – Non-HDL-C ≥ 100 mg/dL (2.6 mmol/L) or
  – apoB ≥ 80 mg/dL

*Patients not on statins were authorized to participate if tolerability issues were present and documented.
Primary Efficacy Outcome

- Time of first occurrence of:
  - CHD death or
  - Nonfatal MI or
  - Fatal or nonfatal ischemic stroke or
  - Unstable angina requiring hospitalization*

*Required all of the following:
1. Hospital admission > 23 hours for MI symptoms, ↑ tempo in prior 48 hours, and/or ≥ 20 minutes of chest discomfort at rest
2. New ECG findings consistent with ischemia or infarction
3. Angiographically significant obstructive coronary disease

All outcomes adjudicated by the Clinical Events Committee, under the auspices of the DCRI; members were unaware of treatment assignment and lipid levels

Baseline Lipid Characteristics

<table>
<thead>
<tr>
<th>Characteristic, mg/dL, median (Q1-Q3)</th>
<th>Alirocumab (n = 9,462)</th>
<th>Placebo (n = 9,462)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C</td>
<td>87 (73-104)</td>
<td>87 (73-104)</td>
</tr>
<tr>
<td>Non-HDL-C</td>
<td>115 (99-136)</td>
<td>115 (99-137)</td>
</tr>
<tr>
<td>apoB</td>
<td>79 (69-93)</td>
<td>80 (69-93)</td>
</tr>
<tr>
<td>HDL-C</td>
<td>43 (37-50)</td>
<td>42 (36-50)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>129 (94-181)</td>
<td>129 (95-183)</td>
</tr>
<tr>
<td>lp(a)</td>
<td>21 (7-59)</td>
<td>22 (7-60)</td>
</tr>
</tbody>
</table>

- 92.5% of patients qualified on the basis of LDL-C ≥ 70 mg/dL

**Primary Efficacy Endpoint: MACE**

- MACE: CHD death, nonfatal MI, ischemic stroke, or unstable angina requiring hospitalization

  **ARR**, 1.6%
  
  **HR**, 0.85 (95% CI, 0.78, 0.93)
  
  **P** = .0003

  **No. at Risk**
  
<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Alirocumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 Years</td>
<td>9,462</td>
<td>9,462</td>
</tr>
<tr>
<td>1 Year</td>
<td>8,805</td>
<td>8,846</td>
</tr>
<tr>
<td>2 Years</td>
<td>8,201</td>
<td>8,345</td>
</tr>
<tr>
<td>3 Years</td>
<td>3,471</td>
<td>3,574</td>
</tr>
<tr>
<td>4 Years</td>
<td>629</td>
<td>653</td>
</tr>
</tbody>
</table>

  *Based on cumulative incidence.

Primary Efficacy and Components

<table>
<thead>
<tr>
<th>Endpoint, n (%)</th>
<th>Alirocumab (n = 9,462)</th>
<th>Placebo (n = 9,462)</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>1,052 (11.1)</td>
<td>0.85 (0.78, 0.93)</td>
<td>.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>.38</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>626 (6.6)</td>
<td>722 (7.6)</td>
<td>0.86 (0.77, 0.96)</td>
<td>.006</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>111 (1.2)</td>
<td>152 (1.6)</td>
<td>0.73 (0.57, 0.93)</td>
<td>.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>.02</td>
</tr>
</tbody>
</table>


PCSK9 Inhibitors: Safety

- **FOURIER** (median follow-up of 2.2 years, N = 27,564)\(^1\)
  - Comparable rates of new-onset diabetes, neurocognitive events, cataracts, and allergic reactions for evolocumab and placebo groups
  - Significant increase (2.1% vs 1.6%) in injection-site reactions for evolocumab

- **ODYSSEY OUTCOMES** (follow-up of at least 2 years, N = 18,924)\(^2,3\)
  - Comparable rates of new-onset diabetes, neurocognitive disorders, cataracts, and allergic reactions for alirocumab and placebo groups
  - Significant increase (3.8% vs 2.1%) in injection-site reactions for alirocumab

- **Very low LDL-C\(^4,5\)**
  - ODYSSEY LONG TERM > 18 months: slight excess of cataracts in patients with LDL-C < 25 mg/dL
  - FOURIER: no excess adverse events across range of LDL-C levels to < 20 mg/dL

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When to Add Nonstatins in an Imperfect World

CTT Meta-Analysis of LDL-C and CVD Event Reduction
Statins (5 years)

CTT—↓39 mg/dL (1 mmol/L) in LDL-C associated with ↓21% RRR in MACE

CTT Meta-Analysis of LDL-C and CVD Event Reduction

**Ezetimibe (7 years)**


**IMPROVE-IT ASCVD**

LDL-C 70 → 54 mg/dL (1.8 → 1.4 mmol/L)

RRR 6% MACE

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**FOURIER ASCVD**

92 → 30 mg/dL (2.4 → 0.8 mmol/L)

RRR 19% MACE

CTT Meta-Analysis of LDL-C and CVD Event Reduction

**PCSK9 Inhibitors (11-26 months)**

So Who Should Get PCSK9 Inhibitors?
What Do the Guidelines Tell Us?

2016 ACC Nonstatin Decision Pathway
NET BENEFIT APPROACH
LDL-C reduction to trigger consideration of potential for net benefit from adding ezetimibe or PCSK9 mAb

2016 ACC Consensus Guideline

Patients with clinical ASCVD and baseline LDL-C ≥ 190 mg/dL not due to secondary causes, on statin for secondary prevention

Patient has ≥ 50% LDL-C reduction (may consider LDL-C < 70 mg/dL) on maximally tolerated statin

YES

NO

1. Address statin adherence
2. Intensify lifestyle (may consider phytosterols)
3. Increase to high-intensity statin if not already taking
4. Evaluate for statin intolerance if unable to tolerate moderate-intensity statin; referral to lipid specialist recommended if statin intolerant
5. Control other risk factors
6. Consider referral to lipid specialist and RDN for all patients, especially for homozygous FH

Clinician-Patient Discussion Factors to Consider

1. Potential for additional ASCVD risk reduction from addition of nonstatin therapy to lower LDL-C (see Table 4)
2. Potential for adverse events or drug-drug interactions from addition of nonstatin therapy to lower LDL-C (see Table 3)
3. Patient preferences (see Table 4)

Decision for no additional medication

YES

NO

Patient has ≥ 50% LDL-C reduction (may consider LDL-C < 70 mg/dL) on maximally tolerated statin/other medications

YES

NO

Consider ezetimibe (or BAS second line)

Patient has ≥ 50% LDL-C reduction (may consider LDL-C < 70 mg/dL) on maximally tolerated statin/other medications

YES

NO

Consider PCSK9 Inhibitor

Patient has ≥ 50% LDL-C reduction (may consider LDL-C < 70 mg/dL) on maximally tolerated statin/other medications

YES

NO

Repeat clinician-patient discussion

2. Add other nonstatin medication(s) above
3. Consider referral to lipid specialist and RDN

Guidelines for PCSK9 Inhibitor Consideration in Patients With Very High CV Risk: ESC/EAS

Patients with clinical ASCVD or DM with target organ damage or a major risk factor
- on maximally tolerated statin + ezetimibe

(based on clinical judgment)

ASCVD: acute MI, ACS, coronary revascularization, stroke, TIA, aortic aneurysm, and PAD

Risk factors: smoking, marked hypercholesterolemia, or marked hypertension

LDL-C > 3.6 mmol/L (> 140 mg/dL)

Consider a PCSK9 inhibitor

LDL-C > 2.6 mmol/L (> 100 mg/dL) and rapid progression of ASCVD

Rapid progression of ASCVD: repeated ACS, unplanned coronary revascularizations, or ischemic strokes within 5 years of index event

LDL-C > 2.6 mmol/L (> 100 mg/dL) or HoFH without LDLR-/ mutations

Consider a PCSK9 inhibitor

Patients with severe FH without clinical ASCVD

-HoFH: on maximally tolerated statin + ezetimibe (based on clinical judgment)

-HoFH: maximally lipid-lowering therapy, including LDL apheresis

LDL-C > 5.0 mmol/L (> 200 mg/dL) or LDL-C > 4.5 mmol/L (> 175 mg/dL) and very high CV risk

Risk factors: DM, lp(a) > 50 mg/dL, marked hypertension, premature familial ASCVD (< 55 years in males and < 60 years in females)

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Patient groups with statin indication (high risk):

- Clinical atherosclerosis (MI, ACS, stable angina, documented coronary disease by angiography (>10% stenosis), stroke, TIA, documented carotid disease, PAD, claudication, and/or ABI < 0.9)
- Abdominal aortic aneurysm (>3.0 cm or previous aneurysm surgery)
- DM (age ≥ 40 years, 15-year duration for ≥ 30 years, microvascular disease)
- CKD (>3 months' duration, eGFR < 60 mL/min/1.73 m², or ACR > 3.0 mg/mmol)
- LDL-C ≥ 5.0 mmol/L (193 mg/dL; genetic dyslipidemia) or documented FH, excluding secondary causes

1. Add ezetimibe (or alternatively BAS) to statin therapy (clinical judgement)
2. Add PCSK9 inhibitor to treatment

< 50% reduction in LDL-C or LDL-C > 2.0 mmol/L (77 mg/dL) or non-HDL-C > 2.6 mmol/L (101 mg/dL) or apoB > 0.8 g/L

Extreme High Risk—AACE/ACE 2017

- Progressive ASCVD in patients with LDL-C < 70 mg/dL
- CAD + DM
- CAD + CKD (stage 3 and up)
- CAD + HeFH

- Goal LDL-C < 55 mg/dL, non-HDL-C < 80 mg/dL, apoB < 70 mg/dL
- Based on Framingham, MESA, Reynolds Risk Score, UKPDS Risk Engine
Very High Risk—AACE/ACE 2017

- Established CAD, CVD, PAD with 10-year risk > 20%
- DM or CKD stage 3/4 with one or more risk factor
- HeFH

- Goal LDL-C < 70 mg/dL, non-HDL-C < 100 mg/dL, apoB < 80 mg/dL

Conclusion

- Consider PCSK9 inhibitors
  - FH/HeFH
  - Statin-intolerant patients
  - Very high risk CVD patients
PCSK9 Targets the LDL-Receptor for Lysosomal Degradation

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Contact Information

For questions or comments about this activity or CPE contact hours, please contact Med-IQ. Call (toll-free) 866 858 7434 or email info@med-iq.com.

To contact the CME provider, call 216-444-9990.

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PCSK9 Inhibitors: Abbreviations and Acronyms

ABI = ankle brachial index
ACR = albumin:creatinine ratio
ACS = acute coronary syndrome
apo = apolipoprotein
ASCVD = atherosclerotic cardiovascular disease
BAS = bile acid sequestrant
CAD = coronary artery disease
CHD = coronary heart disease
CK = creatine kinase
CKD = chronic kidney disease
CTT = Cholesterol Treatment Trialists
CV = cardiovascular
CVD = cardiovascular disease
DCRI = Duke Clinical Research Institute
DM = diabetes mellitus
ECG = electrocardiogram
eGFR = estimated glomerular filtration rate
FH = familial hypercholesterolemia
HDL-C = high-density lipoprotein
HeFH = heterozygous familial hypercholesterolemia
HoFH = homozygous familial hypercholesterolemia
ITT = intention to treat
LDL-C = low-density lipoprotein cholesterol
LDL-R = low-density lipoprotein receptor
lp(a) = lipoprotein(a)
mAb = monoclonal antibody
MACE = major adverse cardiac events
MESA = Multi-Ethnic Study of Atherosclerosis
MI = myocardial infarction
NCEP-ATP = National Cholesterol Education Program Adult Treatment Panel
PAD = peripheral artery disease
PCSK9 = proprotein convertase subtilisin-like/kexin type 9
q2W = every 2 weeks
q4W = every 4 weeks
RDN = registered dietitian nutritionist
RRR = relative risk reduction
SC = subcutaneous
SE = standard error
SREBP = sterol regulatory element-binding protein
TIA = transient ischemic attack
UKPDS = United Kingdom Prospective Diabetes Study
ULN = upper limit of normal