Implementing New Therapies for Refractory Dyslipidemia: Practical Considerations for Clinical Practice

Lawrence Herman, PA-C, MPA, DFAAPA
Dean/Program Director
Physician Assistant Studies
Gardner-Webb University
Boiling Springs, North Carolina

Douglas Jacoby, MD
Associate Professor of Clinical Medicine
University of Pennsylvania Health System
Director, Penn Cardiology Preventive Care
Medical Director, Penn Presbyterian Heartland Vascular Pavilion
Penn Presbyterian Medical Center
Philadelphia, Pennsylvania
Faculty Disclosure

Dr Jacoby: consultant/lecturer: Quest Diagnostics.
Learning Objectives

• Implement tailored treatment plans to help patients achieve desired lipid goals and reduce the risk of CV events
• Evaluate the mechanisms of action and clinical efficacy of new lipid-lowering agents
• Counsel patients on PCSK9 inhibitors and other new nonstatin regimens, including their appropriate use, side effects, storage, and handling

CV = cardiovascular; PCSK9 = proprotein convertase subtilisin/kexin type 9.
85.6 Million Adults in the United States Aged ≥20 Years Have CVD: National Health and Nutrition Examination Survey, 2009-2012

CVD = cardiovascular disease.
Residual ASCVD Risk Despite LDL-C–Lowering Therapy

ASCVD Event Reduction in Major Statin Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>End Point Reduction (relative risk reduction)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4S</td>
<td>-30</td>
</tr>
<tr>
<td>WOSCOPS</td>
<td>-31</td>
</tr>
<tr>
<td>CARE</td>
<td>-24</td>
</tr>
<tr>
<td>LIPID</td>
<td>-24</td>
</tr>
<tr>
<td>MIRACL</td>
<td>-16</td>
</tr>
<tr>
<td>PROSPEER</td>
<td>-15</td>
</tr>
<tr>
<td>ASCOT-LLA</td>
<td>-16</td>
</tr>
<tr>
<td>CARDS</td>
<td>-15</td>
</tr>
<tr>
<td>SPARCL</td>
<td>-14</td>
</tr>
<tr>
<td>KLIS</td>
<td>-14</td>
</tr>
<tr>
<td>MEGA</td>
<td>-33</td>
</tr>
</tbody>
</table>

Residual ASCVD Risk ~70%

Atorva = atorvastatin; Prava = pravastatin; Simva = simvastatin.
High Residual CVD Risk Remains Even With High-dose Rosuvastatin (JUPITER)

Primary trial end point: MI, stroke, unstable angina/revascularization, CV death

HR: 0.56; 95% CI, 0.46-0.69
P < .00001
NNT<sub>5</sub> = 25

HR = hazard ratio; MI = myocardial infarction; NNT<sub>5</sub> = number needed to treat for 5 years.

Definition of Non–HDL-C

Non–HDL-C = TC – HDL-C

Apo = apolipoprotein; HDL-C = high-density lipoprotein cholesterol; TC = total cholesterol.

LDL-C and Non–HDL-C as Predictors of CVD Risk

Meta-analysis of 8 Randomized, Controlled Statin Trials of 38,153 Patients

On-Treatment LDL-C, Non–HDL-C, mg/dL

Adjusted Hazard Ratio for CV Event

LDL-C | Non–HDL-C

<50, <75 0.44 0.57
50-74, 75-99 0.51 0.60
75-99, 100-124 0.56 0.64
100-124, 125-149 0.58 0.69
125-149, 150-174 0.64 0.75
150-174, 175-199 0.71 0.89
≥175, ≥200 1.00 1.00

LDL-C and Non–HDL-C as Predictors of CVD Risk

Meta-analysis of 8 Randomized, Controlled Statin Trials of 38,153 Patients

ACTION ITEM:
Consider non–HDL-C as an alternative marker of ASCVD risk

Case: Meet Jerry, 57 Years Old

- Prior coronary artery bypass graft at age 55; taking aspirin
- Smoked 1 pack/d for 35 years; quit 5 years ago
- Body mass index: 32 kg/m\(^2\)
- No regular exercise; sedentary job
- Blood pressure: 138/78 mm Hg (treated with losartan 50 mg/d, metoprolol 100 mg twice daily)
- Dyslipidemia (treated with simvastatin 40 mg/d)
- Type 2 diabetes mellitus (treated with metformin 2000 mg/d)

<table>
<thead>
<tr>
<th>Laboratory Values</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipids (mg/dL)</td>
<td></td>
</tr>
<tr>
<td>TC</td>
<td>187</td>
</tr>
<tr>
<td>TG</td>
<td>285</td>
</tr>
<tr>
<td>HDL-C</td>
<td>27</td>
</tr>
<tr>
<td>LDL-C</td>
<td>82</td>
</tr>
<tr>
<td>Non–HDL-C</td>
<td>160</td>
</tr>
<tr>
<td>Fasting plasma glucose (mg/dL)</td>
<td>137</td>
</tr>
<tr>
<td>A1C (%)</td>
<td>7.2</td>
</tr>
</tbody>
</table>

A1C = glycated hemoglobin; TG = triglycerides.
What change in therapy is appropriate for Jerry, according to the 2013 ACC/AHA cholesterol guidelines?

1. Add fibrate
2. Add niacin
3. High-intensity statin therapy
4. No additional therapy is necessary, as his LDL-C is <100 mg/dL

Use your keypad to vote now!
What change in therapy is appropriate for Jerry, according to the 2013 ACC/AHA cholesterol guidelines?

1. Add fibrate
2. Add niacin
3. High-intensity statin therapy
4. No additional therapy is necessary, as his LDL-C is <100 mg/dL

Use your keypad to vote now!
2013 ACC/AHA Blood Cholesterol Guidelines

- Emphasis is on moderate- to high-intensity statin therapy
- Achieving specific LDL-C and non–HDL-C goals optional
- Clinicians are encouraged to:
  - Assess response and confirm adherence to prescribed therapy
  - Consider additional therapy in individuals with significant residual risk (but no specific guidance given on therapy beyond high-intensity statin)

2013 ACC/AHA Statin Benefit Groups

- **High-intensity statin therapy**
  - Clinical ASCVD
  - Primary elevations of LDL-C $\geq 190$ mg/dL (high-intensity preferred)
  - Aged 40-75 years with diabetes, LDL-C 70-189 mg/dL, without clinical ASCVD but 10-year risk $\geq 7.5\%^a$

- **Moderate-intensity statin therapy**
  - Aged 40-75 years with diabetes, LDL-C 70-189 mg/dL, without clinical ASCVD and 10-year risk $< 7.5\%^a$

---


Using the 2014 National Lipid Association Recommendations for Patient-centered Management of Dyslipidemia, what should be Jerry’s treatment goal?

1. Treat to HDL-C >40 mg/dL
2. Treat to LDL-C <70 mg/dL
3. Treat to non–HDL-C <130 mg/dL
4. Treat to TG <150 mg/dL

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Using the 2014 National Lipid Association Recommendations for Patient-centered Management of Dyslipidemia, what should be Jerry’s treatment goal?

1. Treat to HDL-C >40 mg/dL
2. Treat to LDL-C <70 mg/dL
3. Treat to non–HDL-C <130 mg/dL
4. Treat to TG <150 mg/dL

Use your keypad to vote now!
# NLA ASCVD Risk Category Criteria

<table>
<thead>
<tr>
<th>Category</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very high</td>
<td>• ASCVD</td>
</tr>
<tr>
<td></td>
<td>• Diabetes mellitus (type 1 or 2)</td>
</tr>
<tr>
<td></td>
<td>– $\geq 2$ other major ASCVD risk factors, or</td>
</tr>
<tr>
<td></td>
<td>– Evidence of end-organ damage</td>
</tr>
<tr>
<td>High</td>
<td>• $\geq 3$ major ASCVD risk factors</td>
</tr>
<tr>
<td></td>
<td>• Diabetes mellitus (type 1 or 2)</td>
</tr>
<tr>
<td></td>
<td>– 0-1 other major ASCVD risk factor, and</td>
</tr>
<tr>
<td></td>
<td>– No evidence of end-organ damage</td>
</tr>
<tr>
<td></td>
<td>• Chronic kidney disease stage 3B or 4</td>
</tr>
<tr>
<td></td>
<td>• LDL-C $\geq 190$ mg/dL</td>
</tr>
<tr>
<td>Moderate</td>
<td>• 2 major ASCVD risk factors</td>
</tr>
<tr>
<td></td>
<td>• Specific factors should be considered to reclassify risk, such as risk calculators, atherosclerosis imaging, and/or biomarkers</td>
</tr>
<tr>
<td>Low</td>
<td>• 0-1 major ASCVD risk factor</td>
</tr>
<tr>
<td></td>
<td>• Specific factors should be considered to reclassify risk, such as risk calculators, atherosclerosis imaging, and/or biomarkers</td>
</tr>
</tbody>
</table>

NLA = National Lipid Association.

NLA 2014 Recommendations: Levels for Considering Drug Therapy, Treatment Goals

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Consider Drug Therapy</th>
<th>Treatment Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non–HDL-C and LDL-C</td>
<td>Non–HDL-C and LDL-C</td>
</tr>
<tr>
<td></td>
<td>(mg/dL)</td>
<td>(mg/dL)</td>
</tr>
<tr>
<td>Very high</td>
<td>≥100</td>
<td>&lt;100</td>
</tr>
<tr>
<td></td>
<td>≥70</td>
<td>&lt;70</td>
</tr>
<tr>
<td>High</td>
<td>≥130</td>
<td>&lt;130</td>
</tr>
<tr>
<td></td>
<td>≥100</td>
<td>&lt;100</td>
</tr>
<tr>
<td>Moderate</td>
<td>≥160</td>
<td>&lt;130</td>
</tr>
<tr>
<td></td>
<td>≥130</td>
<td>&lt;100</td>
</tr>
<tr>
<td>Low</td>
<td>≥190</td>
<td>&lt;130</td>
</tr>
<tr>
<td></td>
<td>≥160</td>
<td>&lt;100</td>
</tr>
</tbody>
</table>

- Lifestyle therapy is always advocated as basis for ASCVD prevention
- For patients with ASCVD or diabetes mellitus, consider use of moderate- or high-intensity statins, irrespective of baseline atherogenic cholesterol levels

Dyslipidemia Management Strategies

- Encourage **healthy lifestyle** (dietary measures, aerobic physical activity, healthy body weight, smoking avoidance, controlling hypertension and diabetes when present)
- Implement **patient-centered approach to decision making** before utilizing statin therapy (especially for primary prevention in patients at lower ASCVD risk)
- Start **statins** per ACC/AHA guidelines and NLA recommendations
- **Monitor response** to therapy
  - If suboptimal, increase statin potency (not dose)/add nonstatin in patients receiving maximally tolerated statin
  - **Monitor side effects**

Dyslipidemia Management Strategies

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- Start **statins** per ACC/AHA guidelines and NLA recommendations
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  - If suboptimal, increase statin potency (not dose)/add nonstatin
  - Monitor side effects

**ACTION ITEM:**
Encourage a healthy lifestyle to improve lipid-lowering, involve patients in decision making regarding therapy

Jerry is now taking rosuvastatin 40 mg but complains of muscle weakness after 1 month of therapy, suggesting statin myopathy. How would you address Jerry’s complaints?

1. Consider “holiday” off of statin, then retry at a lower dose
2. Decrease the dose and add a fibrate
3. Discontinue statin immediately
4. Replace high-potency statin with low-potency statin

Use your keypad to vote now!
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Use your keypad to vote now!
Statin-associated Muscle Adverse Events

- Myalgia
- Myopathy
- Myositis
- Myonecrosis
- Rhabdomyolysis
- Risk factors
  - Female sex, older age, diabetes, renal/hepatic dysfunction
  - Concomitant agents that inhibit CYP3A4 or CYP2C9
  - History of myopathy on other lipid-lowering therapy

CYP = cytochrome P450.
Management of Statin Myopathy

- Limit daily dosage, reduce dosing frequency, or institute drug “holidays”\(^1\),\(^2\)
- ACC/AHA guidelines and NLA recommendations
  - Consider nonstatin with or without concomitant statin\(^3\)\(^-\)\(^5\)
    - Ezetimibe, bile acid sequestrants often used\(^1\),\(^2\)
    - Niacin (extended release) and fenofibrate (delayed release) no longer approved in combination with statins\(^6\)
- Newer agents: PCSK9 inhibitors (alirocumab, evolocumab)
- Vitamin D deficiency may contribute to statin myalgia\(^7\); limited evidence that vitamin D repletion improves tolerability\(^7\),\(^8\)
- Measure thyroid stimulating hormone in patients with myalgias/myopathy\(^9\)

Management of Statin Myopathy

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- ACC/AHA guidelines and NLA recommendations
  - Consider nonstatin with or without concomitant statin\(^3-5\)
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**ACTION ITEM:**
Consider strategies to manage muscle symptoms in patients taking statins
Lack of Adherence and Persistence to Statin Therapy Is Common: USAGE Study

Population survey of statin use over 18 months (N = 10,138)
- One-fourth of patients discontinued statin after a month
- Half discontinued within 3 months
- As many as three-fourths discontinued use in first year
  - 57% stopped after an AE and had no further prescriptions filled
  - One-third stopped without asking or telling their clinician
- On average, 2 statins were tried before stopping altogether

AE = adverse event.
Adherence Obstacles and Barriers

**Obstacles**
- Muscle-related AEs of statins is the primary reason for lack of adherence and treatment discontinuation\(^1\)
- More common than reported in clinical trials\(^1\)

**Patient-centered Barriers\(^2\)**
- Lack of knowledge about risks of dyslipidemia
- Lack of motivation
- Lack of confidence in adherence
  - Concerns about cognitive impairment
  - Concerns about diabetes
- Unclear expectations about treatment outcome
- Lack of conviction concerning consequences of poor adherence

**Clinician-centered Barriers\(^3, 4\)**
- Insufficient knowledge and skills
- Insufficient confidence
- Insufficient attention to patient education about dyslipidemia and importance of treatment
- Lack of effective communication with patients to emphasize need for good adherence

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- Muscle-related AEs of statins is the primary reason for lack of adherence and treatment discontinuation
- More common than reported in clinical trials

Patient-centered Barriers
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- Lack of motivation
- Lack of confidence in adherence
  - Concerns about cognitive impairment
  - Concerns about diabetes

Clinician-centered Barriers
- Insufficient knowledge and skills
- Insufficient confidence
- Insufficient attention to patient education about dyslipidemia and importance of treatment
  - Lack of effective communication

ACTION ITEM:
Address obstacles to medication adherence

Case Conclusion: Jerry’s Management

- Jerry’s primary care clinician educates him on the risks of obesity, dyslipidemia, and CVD
- He is referred to a dietitian for counseling and is urged to engage in an exercise he enjoys, such as walking, for 45 minutes 4-5 days per week
- Because Jerry’s non–HDL-C and TG are elevated and his HDL-C is low, ezetimibe is added to his lower dose of statin therapy
- Jerry’s primary care clinician educates him about his new regimen and advises him to notify her immediately if AEs develop
- He makes an appointment for follow-up in 3 months
Case: Meet Jeff, 34 Years Old

- Jeff is a 34-year-old African American man presenting for follow-up.
- No known ASCVD, nonsmoker.
- Despite high-intensity statin therapy with rosvuastatin (40 mg), his lipid levels are poorly controlled, even after ezetimibe (10 mg) and colesevelam (3750 mg/d) were added to his regimen.

<table>
<thead>
<tr>
<th>Lipid Parameter</th>
<th>May 20, 2013</th>
<th></th>
<th>July 20, 2015</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No Lipid Medications</td>
<td></td>
<td>Taking Rosuvastatin/Ezetimibe/Colesevelam</td>
</tr>
<tr>
<td>TC</td>
<td>496</td>
<td></td>
<td>255</td>
</tr>
<tr>
<td>TG</td>
<td>100</td>
<td></td>
<td>110</td>
</tr>
<tr>
<td>HDL-C</td>
<td>49</td>
<td></td>
<td>60</td>
</tr>
<tr>
<td>LDL-C</td>
<td>430</td>
<td></td>
<td>173</td>
</tr>
<tr>
<td>Non–HDL-C</td>
<td>447</td>
<td></td>
<td>195</td>
</tr>
</tbody>
</table>
Jeff consults his clinician to discuss other treatment options to control his dyslipidemia. What additional information is most important at this time?

1. Coronary calcium score
2. Family history of early CVD
3. History of atrial fibrillation
4. Hypothyroidism

Use your keypad to vote now!
Jeff consults his clinician to discuss other treatment options to control his dyslipidemia. What additional information is most important at this time?

1. Coronary calcium score
2. Family history of early CVD
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Use your keypad to vote now!
Familial Hypercholesterolemia

- Autosomal codominant disorder
- Very high levels of LDL-C, TC
- Early CVD
- HeFH – 1:200-1:300
- HoFH – 1:160,000-1:360,000
  - Extreme hypercholesterolemia with rapidly accelerated atherosclerosis
  - Very high mortality rate if left untreated
  - LDL apheresis is a treatment option

HeFH = heterozygous familial hypercholesterolemia; HoFH = homozygous familial hypercholesterolemia.
Traditional Therapies for Elevated LDL-C

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Mechanisms of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statins(^1)</td>
<td>Inhibit 3-hydroxy-3-methyl-glutaryl coenzyme A reductase, the rate-limiting step in cholesterol synthesis. Results in upregulation of LDL receptors and improved LDL clearance from circulation</td>
</tr>
<tr>
<td>Cholesterol absorption inhibitor (ezetimibe)(^2)</td>
<td>Inhibits intestinal sterol absorption</td>
</tr>
<tr>
<td>Bile acid sequestrants(^3)</td>
<td>Interfere with intestinal reabsorption of bile acid by binding these breakdown products of cholesterol in the gut and promoting excretion</td>
</tr>
<tr>
<td>Niacin(^4)</td>
<td>Various mechanisms (eg, inhibition of peripheral mobilization of free fatty acids, reducing hepatic VLDL synthesis/hepatic secretion)</td>
</tr>
</tbody>
</table>

VLDL = very low-density lipoprotein.

# Newer Therapies for Elevated LDL-C

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Mechanisms of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCSK9 inhibitors (alirocumab, evolocumab)(^{1,a})</td>
<td>Block binding of PCSK9 enzyme to LDL receptors on surface of hepatocytes</td>
</tr>
<tr>
<td></td>
<td>• Protect receptors from destruction</td>
</tr>
<tr>
<td></td>
<td>• Increase number of receptors on hepatocytes</td>
</tr>
<tr>
<td></td>
<td>• Facilitate LDL-C clearance from blood</td>
</tr>
<tr>
<td>Microsomal transfer protein inhibitor (lomitapide)(^{2,b})</td>
<td>• Inhibits lipoprotein synthesis (chylomicrons [intestinal] and VLDL [hepatic])</td>
</tr>
<tr>
<td>Antisense oligonucleotide inhibitor of Apo B (mipomersen)(^{2,b})</td>
<td>• Sequence-specific binding to messenger RNA encoding Apo B-100</td>
</tr>
<tr>
<td></td>
<td>• Post-translational interruption of hepatic Apo B interferes with VLDL synthesis/secrecion</td>
</tr>
</tbody>
</table>

\(^{a}\)Approved for HeFH or ASCVD when additional lowering of LDL-C is needed even with maximally tolerated statin therapy; evolocumab also approved for HoFH; \(^{b}\)Approved only for HoFH.

Jeff’s father died of an MI at age 49 years and his brother at age 46 years. Jeff’s diagnosis is FH. What is the *most appropriate* treatment option?

1. Add gemfibrozil
2. Add lomitapide
3. Add PCSK9 inhibitor to regimen
4. Replace statin with PCSK9 inhibitor

*Use your keypad to vote now!*
Jeff’s father died of an MI at age 49 years and his brother at age 46 years. Jeff’s diagnosis is FH. What is the most appropriate treatment option?

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2. Add lomitapide
3. Add PCSK9 inhibitor to regimen
4. Replace statin with PCSK9 inhibitor

Use your keypad to vote now!
Blockade of PCSK9/LDL-R Interaction Lowers LDL-C Levels

LDLR = LDL receptor; SREBP = sterol regulatory element-binding protein.
Adapted from LaGace TA. *Curr Opin Lipidol.* 2014;25:387-393.
ODYSSEY MONO: Change in LDL-C, Alirocumab vs Ezetimibe Monotherapy

% Change From Baseline, On-Treatment Analysis

Week 12
-20.4 Ezetimibe
-53.2 Alirocumab

Week 24
-17.2 Ezetimibe
-54.1 Alirocumab

N = 103.
*P < .0001 vs ezetimibe.

MENDEL-2: Change in LDL-C, Evolocumab Monotherapy vs Ezetimibe or Placebo

<table>
<thead>
<tr>
<th></th>
<th>Biweekly</th>
<th>Monthly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment difference vs placebo*</td>
<td>Average at weeks 10 and 12 -57%</td>
<td>Average at weeks 10 and 12 -57%</td>
</tr>
<tr>
<td></td>
<td>At week 12 -57%</td>
<td>At week 12 -55%</td>
</tr>
<tr>
<td>Treatment difference vs ezetimibe*</td>
<td>Average at weeks 10 and 12 -39%</td>
<td>Average at weeks 10 and 12 -40%</td>
</tr>
<tr>
<td></td>
<td>At week 12 -39%</td>
<td>At week 12 -39%</td>
</tr>
</tbody>
</table>

N = 306.

P < .001, multiplicity adjusted.
ODYSSEY LONG TERM: Alirocumab + Statin in Patients at High Risk

Post-hoc analysis: decrease in major CV events with alirocumab + statin (3.3% vs 1.7%; nominal $P = .02$)

LLT = lipid-lowering therapy.
LAPLACE-2: Evolocumab + Statin

All treatment differences vs placebo and ezetimibe: \( P < .001 \).
No notable differences between the mean of weeks 10 and 12 and week 12 alone.
GAUSS-2: Change in LDL-C, Evolocumab vs Ezetimibe in Patients With Statin Intolerance

<table>
<thead>
<tr>
<th></th>
<th>Biweekly</th>
<th>Monthly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment difference</td>
<td>Average at weeks 10 and 12</td>
<td>Average at weeks 10 and 12</td>
</tr>
<tr>
<td>vs ezetimibe*</td>
<td>-37%</td>
<td>-39%</td>
</tr>
<tr>
<td>At week 12</td>
<td>-38%</td>
<td>-38%</td>
</tr>
</tbody>
</table>

N = 307.
P < .001, multiplicity adjusted.
Bococizumab: Investigational PCSK9 Inhibitor

• Ongoing phase 3 trials
  – SPIRE-LDL (add-on to statin vs placebo)
  – SPIRE-HR (add-on to statin vs placebo)
  – SPIRE-HF (add-on to statin in HeFH)
  – SPIRE-1 and -2 (add-on to statin in patients at high risk)
• CV end points at 5 years
  – SPIRE-SI (patients who are statin intolerant)

Candidates for PCSK9 Inhibitors: Indications

As an adjunct to diet and maximally tolerated statin therapy in adult patients with:

- **ASCVD** (eg, MI, stroke, peripheral artery disease) who require additional lowering of LDL-C
- **HeFH**
- **HoFH** (evolocumab only)

## PCSK9 Inhibitors: Dosing and Administration

<table>
<thead>
<tr>
<th></th>
<th>Alirocumab</th>
<th>Evolocumab</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Route</strong></td>
<td>Subcutaneous</td>
<td>Subcutaneous</td>
</tr>
<tr>
<td><strong>Delivery</strong></td>
<td>Prefilled, single-dose, 1-mL syringe or pen</td>
<td>Prefilled, single-dose, 1-mL syringe or pen</td>
</tr>
<tr>
<td><strong>Recommended starting dose</strong></td>
<td>75 mg every 2 weeks</td>
<td>140 mg every 2 weeks</td>
</tr>
<tr>
<td><strong>Maximum dose</strong></td>
<td>150 mg every 2 weeks</td>
<td>420 mg monthly (recommended dose for HoFH)</td>
</tr>
</tbody>
</table>

Injection: Additional Instructions for Patients

- Do not pull the cap off of syringe/pen until ready to inject the medication
- Rotate injection sites
- Assistance may be needed when injecting into arms
- Make sure the pen or syringe is completely empty before removing needle from skin
- The time required for injection of the entire dose may be longer than that for other injectable medicines
- Alert patients to correct sharps disposal
PCSK9 Inhibitors: Follow-up After Initiating Treatment

- Measure LDL-C levels within 4-8 weeks of initiating or titrating to assess response and adjust the dose if needed.
- If a dose is missed:
  - Instruct patient to administer injection within 7 days of the missed dose, then resume original schedule.
  - If missed dose not administered within 7 days, instruct patient to wait until the next dose on the original schedule.
- If allergic reactions appear, discontinue and treat patient according to standard of care.

## Common AEs Associated With PCSK9 Inhibitors (>5% of Patients)

### Alirocumab
- Nasopharyngitis (11.3%)
- Injection site reactions (7.2%)
- Influenza (5.7%)
- AEs leading to discontinuation: 5.3% (vs 5.1% with placebo)

### Evolocumab
- Nasopharyngitis (10.5%)
- Upper respiratory tract infection (9.3%)
- Influenza (7.5%)
- Back pain (6.2%)
- Injection site reactions (5.7%)
- AEs leading to discontinuation: 2.2% (vs 1% with placebo)

- Serious hypersensitivity reactions requiring hospitalization have occurred with both agents
- Potential for immunogenicity with all therapeutic proteins

Storage and Handling of PCSK9 Inhibitors

- Store unused syringes in refrigerator between 36°F to 46°F in outer carton to protect from light
- Do not freeze
- Do not expose the pen or syringe to extreme heat or direct sunlight
- Do not shake
- Should be warmed to room temperature 30-40 minutes before use
- Do not keep alirocumab at room temperature for more than 24 hours; evolocumab may be stored at room temperature if used within 30 days

Working With Specialty Pharmacies

• PCSK9 inhibitors are specialty drugs and available only through specialty pharmacies

• Services
  – Set up home delivery or select in-store pickup for patients
  – Help clinician office staff with prior authorizations and appeals
  – Train patients to self-inject the medications
  – Send patient reminders
  – Call patients when they need to refill prescriptions
  – Enroll patients in patient assistance programs

Other Agents: Lomitapide and Mipomersen, Approved for HoFH Only

Mechanism of Action

IDL = intermediate-density lipoprotein; MTP = microsomal triglyceride transfer protein.
## Lomitapide and Mipomersen in Patients With HoFH: Phase 3 Trials

<table>
<thead>
<tr>
<th>Lipid</th>
<th>Lomitapide (N = 29)</th>
<th>Mipomersen (N = 34)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LDL-C (mg/dL)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BL</td>
<td>336</td>
<td>440</td>
</tr>
<tr>
<td>End point</td>
<td>190</td>
<td>324</td>
</tr>
<tr>
<td>Mean change (%)</td>
<td>−40</td>
<td>−25</td>
</tr>
<tr>
<td><strong>Non–HDL-C (mg/dL)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BL</td>
<td>386</td>
<td>463</td>
</tr>
<tr>
<td>Mean change (%)</td>
<td>−40</td>
<td>−25</td>
</tr>
<tr>
<td><strong>TC (mg/dL)</strong></td>
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<td></td>
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<tr>
<td>BL</td>
<td>428</td>
<td>502</td>
</tr>
<tr>
<td>Mean change (%)</td>
<td>−36</td>
<td>−21</td>
</tr>
<tr>
<td><strong>Apo B (mg/dL)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BL</td>
<td>260</td>
<td>280</td>
</tr>
<tr>
<td>Mean change (%)</td>
<td>−39</td>
<td>−27</td>
</tr>
<tr>
<td><strong>Lipoprotein(a) (mg/dL)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BL</td>
<td>66</td>
<td>60</td>
</tr>
<tr>
<td>Mean change (%)</td>
<td>−13</td>
<td>−32</td>
</tr>
</tbody>
</table>

Lomitapide and Mipomersen: Special Considerations

- May be used in combination with other LLTs
- Dosage forms
  - Lomitapide: oral capsule taken daily
  - Mipomersen: once-weekly subcutaneous injection
- Pregnancy categories
  - Lomitapide: pregnancy category X
  - Mipomersen: pregnancy category B
- Similar safety concerns
  - Boxed warnings citing risk of hepatotoxicity
  - Risk Evaluation and Mitigation Strategy
    - Only certified healthcare providers can prescribe the drug; only certified pharmacies may dispense it

Case Conclusion: Jeff

- Jeff has residual CVD risk that warrants additional therapy
- Genetic testing confirms a diagnosis of HeFH
- Diagnosis warrants referral to clinical lipidologist
- PCSK9 inhibitor is an option as add-on to current maximal statin therapy
Principles for Collaborating With Patients in Treatment Selection

• Ensure optimal pharmacotherapy through prudent use and monitoring of medications
• Educate patients about treatment options
• Encourage lifestyle changes that can reduce CVD risk
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- Ensure optimal pharmacotherapy through prudent use and monitoring of medications
- Educate patients about treatment options
- Encourage lifestyle changes that can reduce CVD risk

ACTION ITEM:
Collaborate with patients in selection of LLT to improve outcomes
PCE Action Plan
PCE Action Plan

- Consider non–HDL-C as an alternative marker of ASCVD risk
- Encourage a healthy lifestyle to improve lipid-lowering, involve patients in decision making regarding therapy
- Consider strategies to manage muscle symptoms in patients taking statins
- Address obstacles to medication adherence
- Collaborate with patients in selection of LLT to improve outcomes

PCE Promotes Practice Change
Q & A
Does lowering triglyceride levels with omega-3 fatty acids reduce cardiovascular risk?
With regard to LDL-C, how low is too low?
Do PCSK9 inhibitors interact with other drugs?
How do you choose a statin in patients who are statin-naïve?
What is the true risk of statins with regard to memory loss, Alzheimer’s, and the increased development of diabetes?
Does the risk of rhabdomyolysis with statins have a familial component?