PCSK9 Inhibitors: Promise or Pitfall?

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Objectives

Pharmacists
• Summarize current evidence-based guideline recommendations for treatment of hypercholesterolemia to reduce cardiovascular risk
• Review the role of the PCSK9 pathway in atherosclerosis
• Explore the novel mechanism of PCSK9 inhibitors and rationale for their use
• Evaluate evidence for treatment role of PCSK9 based therapies
• Review emerging evidence for PCSK9 inhibitors and cardiovascular outcomes

Technicians
• Review the role of the PCSK9 pathway in atherosclerosis
• Explore the novel mechanism of PCSK9 inhibitors and rationale for their use

Background

Cardiovascular disease
• Leading cause of death in the United States
• 610,000 deaths annually
• 1 in every 4 deaths attributed to heart disease

2013 ACC/AHA Lipid Guidelines

Statin Benefit Groups
• Clinical atherosclerotic cardiovascular disease (ASCVD)
• LDL-C ≥ 190 mg/dL
• Age 40-75 years with diabetes and LDL-C 70-189 mg/dL
• Age 40-75 years without diabetes, LDL-C 70-189 mg/dL, and ASCVD risk ≥ 7.5%

Tracy Harlan does not have any actual or potential conflicts of interest to disclose

Off-label use of medications will not be discussed
Current Guideline Statin Regimens

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<th>High Intensity</th>
<th>Moderate-Intensity</th>
<th>Low-Intensity</th>
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<tbody>
<tr>
<td>Lowers LDL ≥ 50%</td>
<td>Atorvastatin 40-80 mg</td>
<td>Rosuvastatin 20-40 mg</td>
<td>Simvastatin 20-40 mg</td>
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<tr>
<td>Lowers LDL &lt;50%</td>
<td>Atorvastatin 10-20 mg</td>
<td>Simvastatin 5-10 mg</td>
<td>Fluvastatin 80 mg</td>
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<td>Rosuvastatin 20-40 mg</td>
<td>Pravastatin 40 mg</td>
<td>Fluvastatin XL 80 mg</td>
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<td>Lovastatin 40 mg</td>
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<td>Fluvastatin 40 mg BID</td>
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<td>Atorvastatin 10 mg</td>
<td>Pravastatin 10-20 mg</td>
<td>Pitavastatin 2-4 mg</td>
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Adapted from: Circulation. 2014;129:S1-S45

Familial Hypercholesterolemia

- Inherited condition that causes high levels of LDL
- Heterozygous (HeFH)
  - (1 in 250 people)
- Homozygous (HoFH)
  - (1 in 1 million people)

Treatment for Familial Hypercholesterolemia

- High-intensity statin
- Ezetimibe
- Bile acid sequestrant
- Niacin
- Apheresis
- Lomitapide
- Mipomersen
- PCSK9 inhibitor

Proprotein Convertase Subtilisin-Kexin Type 9 (PCSK9)

- Expressed by liver and intestine
- Promotes intracellular degradation of LDL-R
- Reduced LDL-R on cell surface
- Reduces LDL clearance from circulation (results in elevated LDL-C)
**Alirocumab (Praluent®)**

**Indications**
- Adjunct to diet and maximally tolerated statin therapy for treatment of:
  - Heterozygous familial hypercholesterolemia (HeFH)
  - Clinical ASCVD requiring additional lowering of LDL-C

**Dosage**
- 75 mg (1 pen/syringe) subcutaneously every 2 weeks (may increase to 150 mg every 2 weeks)

**Storage**
- Refrigerated

**Cost**
- $14,600/year

**Monitoring**
- LDL within 4 to 8 weeks after initiation/dose changes
- Hypersensitivity reactions

**Adverse Drug Reactions**
- Injection site reaction (7%)
- Diarrhea (5%)
- Elevated LFTs (3%)
- Myalgia (4%)
- Confusion (<1%)

**Patient Counseling**
- Let warm to room temperature for ~30 minutes
- Clean injection area (thigh, stomach, upper arms)
- Rotate injection sites
- Do not use pen/syringe if pen/syringe has been at room temp. for 24 hours or greater
OSLER-1 and OSLER-2 (n=4465)

**Population**
- Patients who have completed one of the “parent trials”

**Intervention**
- Evolocumab 140 mg every 2 weeks or 420 mg monthly plus standard therapy versus standard therapy alone

**Results**
- Similar rates of adverse events (69.2% in treatment group and 64.8% in standard therapy)
- Slightly more neurocognitive events in treatment group (0.9%) versus standard therapy (0.3%)
- LDL reduced from median of 120 mg/dL to 48 mg/dL
- Lower rate of CV events shown in exploratory analysis at 1 year
  - 29 (treatment) versus 31 (standard of care) (hazard ratio 0.47, CI 0.28-0.78)

Sabatine MS. NEJM 2015;372:1500-1509.

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ODYSSEY OUTCOMES

Alirocumab (Praluent®)

**Primary Objective**
- Occurrence of CV events with alirocumab versus placebo in addition to evidence-based medical and dietary management of dyslipidemia in patients with history of acute coronary syndrome

**Estimated Enrollment**
- >18,000 patients

**Estimated completion**: February 2018

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WHAT ABOUT CARDIOVASCULAR OUTCOMES?

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FOURIER

Evolocumab (Repatha®)

**Primary Objective**
- Time to cardiovascular death, myocardial infarction, or stroke in patients with history of CVD with evolocumab versus placebo in addition to effective statin therapy

**Estimated Enrollment**
- >25,000 patients

**Estimated completion**: February 2018

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Summary

- PCSK9 inhibitors represent a novel mechanism in LDL-lowering
- Specific patient groups that may benefit from use
- Overall, well tolerated with minimal adverse effects
- Clinical cardiovascular outcomes are highly anticipated in the next two years
Role of Pharmacist/Technician

- Provide thorough patient counseling
- Identification of appropriate utilization especially given high cost
- Ensure continued adherence to existing evidence based lipid lowering therapy
- Assess laboratory monitoring for safety and efficacy

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