PCSK9 Inhibitors: Innovation or Reservation?
Erika Hellenbart, PharmD, BCPS
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I have no personal or financial conflicts of interest to disclose

Pharmacist Objectives
- Describe the mechanism of PCSK9 inhibitors in lipid management
- Review updates to literature regarding PCSK9 inhibitors
- Select patients in which PCSK9 inhibitor use is appropriate, considering both clinical and financial factors

Technician Objectives
- Describe the mechanism of PCSK9 inhibitors in lipid management
- Explain appropriate storage and administration of PCSK9 inhibitors
- Discuss potential barriers for a patient to access and fill a prescription for a PCSK9 inhibitor

Who’s in the audience?
- Pharmacist
- Technician
- Student

How often have you recommended or dispensed a PCSK9 inhibitor?
- Every month
- Every 3-6 months
- Every 6-12 months
- Never

Pre-Assessment #1
Which of the following best describes the mechanism of action of PCSK9 inhibitors?
- Directly binds to LDL for uptake and metabolism by the liver
- Directly binds to PCSK9 to increase available LDL receptors
- Promotes degradation of LDL receptors
- Directly binds to LDL receptors to facilitate binding of LDL
Pre-Assessment #2

Initial clinical trials with currently available PCSK9 inhibitors showed a further reduction of LDL levels by more than 50%.

a. True
b. False

Pre-Assessment #3

The FOURIER trial with evolocumab was recently published showing a significant reduction of the primary endpoint: CV death, MI, stroke, hospitalization for UA, or coronary revascularization. The composite endpoint was driven by which of the following subgroups?

a. CV death, MI, and coronary revascularization
b. MI, hospitalizations for UA, and coronary revascularization
c. MI, stroke, and hospitalizations for UA
d. MI, stroke, and coronary revascularization

Pre-Assessment #4

In which of the following patients would it be most appropriate to recommend a PCSK9 inhibitor?

a. A 62 yo male with CABG at age 56, LDL of 123 mg/dL on atorvastatin 20mg daily
b. A 46 yo male with HTN, DM with an A1c of 10.3% and LDL of 151 mg/dL on simvastatin 20mg daily
c. A 53 yo female with HTN, MI at age 45 and LDL of 169 mg/dL on rosvastatin 40mg daily
d. A 75 yo female with HTN and LDL of 113 mg/dL currently on ezetimibe 10mg daily

Patient Case

• AB is a 52 yo AAM with HTN, HL, and MI at age 47 with PCI x2 in 2012. AB denies any tobacco, alcohol, illicit drug use.
• Medications include rosuvastatin 20mg, ASA 81mg, lisinopril 20mg, and metoprolol XL 100mg daily.
• FLP 5/2017: TC 205; TG 185; HDL 41; LDL 127
• What are our options at this time?

2013 ACC/AHA Guidelines

• First update since ATP III in 2001
• Changed approach to treating hyperlipidemia
• Focus on ASCVD risk reduction
• Population based
  • Identified four groups that would benefit most from treatment
  • Emphasis on medications proven to decrease ASCVD events
  • Extensive evidence that appropriate INTENSITY of statin therapy should be used to reduce ASCVD risk
• Many limitations
  • Possible overestimation of risk
  • ASCVD risk calculator limited to statin-naive patients
  • Interpreted by some as no longer needing to check LDL levels

Need for Additional Therapy

• Heart disease is the leading cause of mortality in the US
  • 1 in every 4 deaths
• Registry data in US from 2008-2012 showed 32.4% of statin-eligible patients were not receiving statin
• Statin intolerance reported in approximately 15% of patients
• Meta-analysis of statin trials
  • > 40% of patients on high-intensity statin did not reach LDL < 70 mg/dL
  • Significantly lower risk for major CV events
    • LDL < 50 mg/dL vs. LDL 75 – 100 mg/dL (HR 0.81; 95% CI 0.70 – 0.95)
    • CV event rates reduced by > 50% when LDL reduced to < 50 mg/dL.
Alternative Lipid Lowering Therapy

- Many options to decrease LDL
- Lack of evidence proving reduction in CV events
- Niacin: AIM-HIGH
- Fenofibrate: ACCORD-Lipid
- Ezetimibe: ENHANCE (2008)
  - Ezetimibe 10mg + simvastatin 80mg vs simvastatin 80mg + placebo
  - Did not slow progression of atherosclerosis
  - Prescribing rates decreased

**IMPROVE – IT**

- Ezetimibe 10mg + simvastatin 40mg vs. simvastatin 40mg + placebo
- Primary outcome: composite of death from CV cause, major coronary event, or nonfatal stroke
  - In stable patients with recent ACS and LDL within guideline recommendations
- Results:
  - Reduction in primary outcomes (32.7% vs. 34.7%)
  - HR 0.906; 95% CI 0.89–0.92; p = 0.0016
  - No effect on reduction in major coronary events and nonfatal stroke
- Reduction in LDL from baseline of 93.8 mg/dL to:
  - 53.7 mg/dL vs. 69.5 mg/dL (p<0.0001)
  - DRW = 70%; 95% CI 66–73; p = 0.0034

**Limitations:**
- Only moderate intensity statin
- Excluded if on higher potency statin

**PCSK9 - Protein**

- Proprotein convertase subtilisin/kexin type 9
- Binds to LDL-R
- Reduces LDL-R density on hepatocellular surface
- Increases circulating LDL
- Gain of function mutation of PCSK9 gene found to be additional cause of familial hypercholesterolemia in 2003
- Increased by inhibition of HMG-CoA reductase via increased expression of regulatory protein (SREBP-2)
  - Increased with statin use
  - Inhibition of PCSK9 can increase efficacy of statin therapy

**PCSK9 Inhibitors**

- Human monoclonal antibody
- Indirectly decreases LDL levels by regulating available LDL receptors
- Binds to PCSK9
- Prevents PCSK9 from binding to LDL-R
- Increases available hepatic LDL-R
- Decreases circulating LDL

**Available Products**

<table>
<thead>
<tr>
<th>Name</th>
<th>Prescription</th>
<th>Approved Indication</th>
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</thead>
<tbody>
<tr>
<td>Praluent</td>
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<td>Additional LDL lowering as adjunct to diet and maximally tolerated statin therapy in</td>
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<tr>
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<td>HOFH: 420mg once monthly</td>
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**Clinical Trials**

- ODYSSEY LONG TERM
- ODYSSEY

**Dose**

- Praluent (alirocumab): 75mg subcutaneously every 2 weeks;
  - Max: 150mg every 2 weeks if LDL response is inadequate;
  - 300mg once monthly
- Repatha (evolocumab): 140mg every 2 weeks;
  - 420mg once monthly

**Regulation of LDL – Receptors**
**Alirocumab - ODYSSEY**

**Study**

<table>
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<th>Treatment</th>
<th>Efficacy</th>
<th>Safety</th>
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<td>CHD (4/2015)</td>
<td>Age ≥ 18 with CHD, 25% CHD risk equivalent</td>
<td>% LDL change at 24 weeks: 53.6% (ODYSSEY-OUTCOMES)</td>
<td>Time to composite CV endpoint: 40 weeks (ODYSSEY-OUTCOMES)</td>
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**Post-hoc analysis of CV Events:**
- Non-significant when CHF requiring hospitalization and revascularization procedures were included. N Engl J Med. 2015;372(16):1489-99
- 1.7 vs. 3.3% (HR 0.5; 95% CI 0.31-0.90; p=0.02)

**FOURIER Conclusions**
- Similar rates of adverse effects when LDL < 25 mg/dL
- Relatively short follow-up
- Possible bias with evolocumab trial
- Patient populations:
  - FH, CHD, or CHD equivalent on high or maximally-tolerated statin
  - Age >18 with HeFH, (2:1 ratio)
  - N = 2341
  - LDL >70mg/dL
  - FH, CHD, or CHD equivalent on high or maximally-tolerated statin
  - Age 40-85 with ASCVD, 1:1
  - N = 27,564

**Study Inclusion**
- Age ≥ 18 with HeFH, (2:1 ratio)
- N = 2341
- LDL >70mg/dL
- FH, CHD, or CHD equivalent on high or maximally-tolerated statin

**Evolocumab - OSLER**

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<td>LDL &gt;70mg/dL</td>
<td>% LDL change at 24 weeks: 53.6% (OSLER-1)</td>
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**FOURIER Conclusions**
- When added to statin therapy, evolocumab lowered LDL by 59% compared to placebo
- Lowered risk of primary endpoint by 15%
  - Driven by non-fatal MI, stroke, and coronary revascularization
  - Slightly higher rate of CV death and death from any cause
- No significant increase in neurocognitive disorders
- Unclear if 2 years is long enough to monitor
- EBBINGHAUS investigators
  - Cognitive study of FOURIER participants

**Study Inclusion**
- Age ≥ 18 with CHD, ≥ 25% CHD risk equivalent
- LDL >70mg/dL
- FH, CHD, or CHD equivalent on high or maximally-tolerated statin

**Alirocumab – ODYSSEY Outcomes**

**Study**

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**Study Completion ~ Dec 2017**
- Objective: Effect of alirocumab vs. placebo on occurrence of CV events in patients with ACS 4-52 weeks prior
- In addition to evidence based medical and dietary management
- Composite endpoint: death from CHD, non-fatal MI, fatal and non-fatal ischemic stroke, UA requiring hospitalization
- 64 month treatment period and 2 month follow-up
2016 ACC Non-Statin Decision Pathway

- Practical guidance for patients not covered by the 2013 ACC/AHA guidelines
- Provide algorithm for each statin benefit group
  - When and which order should non-statin therapies be added
- Guidance for ezetimibe and PCSK9 inhibitors:
  - Clinical ASCVD with or without comorbidities
  - Baseline LDL ≥ 190 mg/dl with or without ASCVD
- Ezetimibe generally recommended over PCSK9 inhibitors
  - Equal consideration when LDL ≥ 190 mg/dl.

**Published before FOURIER**

J Am Coll Cardiol. 2016; 68(1): 92‐125

Cost – ICER Cost Analysis

- Annual cost:
  - Alirocumab: $14,600
  - Evolocumab: $14,100
- Annual budget of ~$125 billion to treat intended population
- 2015 – Price reduction of 60-63% to make cost effective
- Before FOURIER
- 2017 – C+ rating
  - Increased mortality in second year than first
  - Lower than expected reductions in other endpoints
- ODYSSEY OUTCOMES may change ratings

https://icer-review.org

Access Barriers

- 17% initial approval rates by insurance
- 26% approved after appeal
- 37% of patients do not pick up initial fill
  - Mean 30-day copay ~$250
- 10% using drug company coupon program
- More likely to receive therapy if used
- Restricted to commercial insurance

https://icer-review.org

Other Considerations

- Storage:
  - Must be stored in refrigerator
  - Room temperature: 30 days
- Administration of pre-filled pen:
  - Allow injection to warm to room temp (at least 30-40 min)
  - Wash hands and use alcohol wipe to clean injection area
  - Medicine in window should be clear to slightly yellow
  - Injection sites: thigh, upper arm, stomach (>2” from belly button)
  - Pull off cap and use within 5 minutes
  - Firmly push auto-injector on skin at 90°
  - Push start button until hear click, continue holding pen against skin
  - Injection takes approximately 15 seconds
  - Remove pen once window turns yellow
  - Dispose in sharps container

Role of the Pharmacist

- Educate providers of newly released evidence
- Evaluate appropriateness of therapy
  - All additional lipid lowering therapy
- Assist with access issues
- Coordinate with specialty pharmacy
- Educate patient and family
- Follow up phone calls
- Consider “PCSK9 inhibitor consult service”

Role of the Technician

- Assist with access issues
- Coordinate with specialty pharmacy
- Educate patient and family
- Correct administration technique
- Proper storage
Patient Case

- AB is a 52 yo AAM with HTN, HL, and MI at age 47 with PCI x2 in 2012. AB denies any tobacco, alcohol, illicit drug use.
- Medications include rosvastatin 20mg, ASA 81mg, lisinopril 20mg, and metoprolol XL 100mg daily.
- FLP 5/2017: TC 205; TG 185; HDL 41; LDL 127
- What are our options at this time?

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- AB is a 52 yo AAM with HTN, HL, and MI at age 47 with PCI x2 in 2012. AB denies any tobacco, alcohol, illicit drug use.
- Medications include rosvastatin 20mg, ASA 81mg, lisinopril 20mg, and metoprolol XL 100mg daily.
- FLP 5/2017: TC 205; TG 185; HDL 41; LDL 127
- What are our options at this time? Select all that apply.
  A. Continue rosvastatin 20mg daily, assess adherence and lifestyle
  B. Increase rosvastatin to 40mg daily
  C. Add ezetimibe 10mg daily
  D. Add evolocumab 140mg subcutaneously every 2 weeks

Patient Case

- FLP 5/2017: TC 205; TG 185; HDL 41; LDL 127
- Addressed adherence and lifestyle modifications
- Unable to tolerate rosvastatin 40mg daily
- Baseline LDL 193 mg/dL (LDL lowered by 34%)
- Which of the following options would you recommend in this patient?
  A. Continue rosvastatin 20mg daily alone
  B. Add ezetimibe 10mg daily
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  D. Add colesevelam 1875mg daily

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Conclusions

- PCSK9 inhibitors are extremely effective at lowering LDL
- FOURIER showed significant reduction in composite primary endpoint with evolocumab
  - Driven by non-fatal MI, stroke, and coronary revascularization
  - Slight increase in CV death and death from any cause
- ODYSSEY OUTCOMES data still pending with alirocumab

Conclusions

- Clinical utility in very high risk patients
- Maximally tolerated statin
- Additional risk factors minimized (HTN, tobacco use, etc)
- Ezetimibe currently given higher or equal recommendation
- Current guidance published prior to outcomes data
- Pharmacy can play significant role
  - Appropriate prescribing and access
  - Storage and administration education

Post-Assessment #1

Which of the following best describes the mechanism of action of PCSK9 inhibitors?

a. Directly binds to LDL for uptake and metabolism by the liver
b. Directly binds to PCSK9 to increase available LDL receptors
c. Promotes degradation of LDL receptors
d. Directly binds to LDL receptors to facilitate binding of LDL
Post-Assessment #2

Initial clinical trials with currently available PCSK9 inhibitors showed a further reduction of LDL levels by more than 50%.

a. True
b. False

Post-Assessment #3

The FOURIER trial with evolocumab was recently published showing a significant reduction of the primary endpoint: CV death, MI, stroke, hospitalization for UA, or coronary revascularization. The composite endpoint was driven by which of the following subgroups?

a. CV death, MI, and coronary revascularization
b. MI, hospitalizations for UA, and coronary revascularization
c. MI, stroke, and hospitalizations for UA
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Post-Assessment #4

In which of the following patients would it be most appropriate to recommend a PCSK9 inhibitor?

a. A 62 yo male with CABG at age 56, LDL of 123 mg/dL on atorvastatin 20mg daily
b. A 46 yo male with HTN, DM with an A1c of 10.3% and LDL of 151 mg/dL on simvastatin 20mg daily
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Abbreviations

• ACC/AHA: American College of Cardiology/American Heart Association
• ACS: Acute coronary syndrome
• ASCVD: Atherosclerotic cardiovascular disease
• CHD: Coronary heart disease
• CVD: Cardiovascular disease
• HL: Hyperlipidemia
• MI: Myocardial Infarction
• UA: Unstable angina

References

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1. Which best describes the mechanism of action of PCSK9 inhibitors?
   a. Directly binds to LDL for uptake and metabolism by the liver
   b. Directly binds to PCSK9 to increase available LDL receptors
   c. Promotes degradation of LDL receptors
   d. Directly binds to LDL receptors to facilitate binding of LDL

2. Once out of the refrigerator, evolocumab and alirocumab may be stored at room temperature for:
   a. 7 days
   b. 21 days
   c. 30 days
   d. 60 days

3. Which of the following is FALSE regarding the administration of PCSK9 inhibitors?
   a. Possible injection sites are upper arms, stomach, or thigh
   b. Push injection to skin at 90 degree angle
   c. Release pen from skin as soon as start button is pushed and “click” is heard
   d. Medicine in window should be yellow once dose has been administered

4. Patient access to PCSK9 inhibitors is made difficult by which of the following?
   a. Low initial rates of approval by insurance companies
   b. High copays after insurance approval
   c. Drug company coupon programs are restricted to commercial insurance
   d. All of the above

Key: 1) B, 2) C, 3) C, 4) D
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References
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