PCSK9 Inhibitors: Innovation or Reservation?

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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?

a. Pharmacist
b. Technician
c. Student

How often have you recommended or dispensed a PCSK9 inhibitor?

a. Every month
b. Every 3-6 months
c. Every 6-12 months
d. Never

Pre-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

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 rosuvastatin 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-naïve patients
  - Interpreted by some as no longer needing to check LDL levels

Circulation. 2014; 129(25 Suppl 2): S1-45

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

https://www.cdc.gov/heartdisease/facts.htm
J Am Coll Cardiol. 2014; 64(21): 2183-92
Circulation. 2015; 131: e389-e391
J Am Coll Cardiol. 2014; 64(5): 485-94

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

N Engl J Med. 2011; 365(24): 2255-67
N Engl J Med. 2010; 362(17): 1563-74
N Engl J Med. 2008; 358(14): 1431-43

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 0.936; 95% CI 0.89-0.99; p = 0.016
    - Driven by reduction in major coronary events and nonfatal stroke
    - No difference in death from CV cause
  - Reduction in LDL from baseline of 93.8 mg/dL to:
    - 53.7 mg/dL vs. 69.5 mg/dL (p<0.0001)
- Limitations:
  - Only moderate intensity statin
  - Excluded if on higher potency statin

N Engl J Med. 2015; 372: 2387-97

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

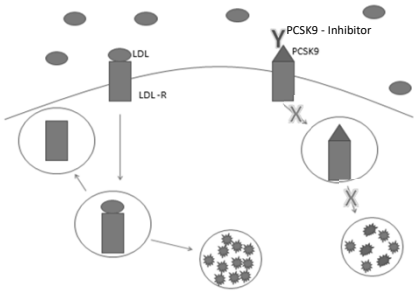
Prog Cardiovasc Dis. 2015; 58(1): 19-31

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 hepatocellular LDL-R
  - Decreases circulating LDL

Prog Cardiovasc Dis. 2015; 58(1): 19-31

Regulation of LDL – Receptors



Available Products

	Alirocumab	Evolocumab
Trade Name	Praluent	Repatha
FDA Approval	July 2015	August 2015
Approved Indication	Additional LDL lowering as adjunct to diet and maximally tolerated statin therapy in adults with: - Heterozygous familial hypercholesterolemia - Clinical atherosclerotic CV disease	Additional LDL lowering as adjunct to diet and maximally tolerated statin therapy in adults with: - Heterozygous familial hypercholesterolemia - Clinical atherosclerotic CV disease Adjunct to diet and other LDL-lowering therapy in adults with: - Homozygous familial hypercholesterolemia
Clinical Trial	ODYSSEY LONG TERM	OSLER
Dose	Self-administered injection 75mg subcutaneously every 2 weeks Max: 150mg every 2 weeks if LDL response is inadequate 300mg once monthly	Self-administered injection 140mg every 2 weeks 420mg once monthly HoFH: 420mg once monthly

Praluent (alirocumab) prescribing information
Repatha (evolocumab) prescribing information

Alirocumab - ODYSSEY

Study	Inclusion	Treatment	Efficacy	Safety
ODYSSEY LONG TERM Efficacy and Safety of Alirocumab in Reducing Lipids and Cardiovascular Events (4/2015)	N = 2341 (2:1 ratio) - Age ≥ 18 with HeFH, CHD, or CHD risk equivalent - LDL ≥ 70mg/dL on max tolerated statin	Alirocumab 150mg q2wks vs. placebo - 78 weeks - Mean study-drug exposure: 70 weeks - 47% on high-dose statin - 28% on other LLT (14% on ezetimibe) - 68-70% with CHD - 18% HeFH - Mean baseline LDL: 122 mg/dL	1°: % LDL change at 24 wks: -61.0 vs +0.8% (p<0.001) ↓LDL to 48 vs 119 mg/dL LDL < 70 at 24 wks 79.3 vs 8% (p<0.001)	86 weeks Myalgias: 5.4 vs. 2.9% (p=0.006) Neurocognitive disorder: 1.2 vs. 0.5% Inj site rxns: 5.9 vs. 4.2% Ophtho: 2.9 vs. 1.9%

Post-hoc analysis of CV Events:
- Composite of death from CHD or unknown cause, nonfatal MI, fatal or nonfatal ischemic stroke, UA requiring hospitalization: 1.7 vs. 3.3% (HR 0.5; 95% CI 0.31-0.90; p=0.02)
- Non-significant when CHF requiring hospitalization and revascularization procedures were included.

N Engl J Med. 2015; 372(16): 1489-99

Evolocumab - OSLER

Study	Inclusion	Treatment	Safety/Efficacy
OSLER Efficacy and Safety of Evolocumab in Reducing Lipids and Cardiovascular Events (4/2015)	N = 4465 (2:1 ratio) - Open label - Patients from phase 2 and 3 parent studies - LDL ≥ 70 to ≥ 100mg/dL on no to high-intensity statin Assigned on last day of parent trial if had not had adverse event leading to study drug d/c	OSLER 1 (N=1324): Evolocumab 420mg monthly + std tx vs. std tx alone for 56 weeks OSLER 2 (N=3141): Evolocumab 140mg q2wks or 420mg monthly for 48 weeks - Median f/u: 44 weeks - 70.3% on statin - 27% on high-intensity - 35% on mod-intensity - 13-15% on ezetimibe - 45% moderate to high risk per NCEP risk factors - 20% CAD - Median baseline LDL: 120-121 mg/dL	1°: Incidence of adverse events: 69.2 vs. 64.8% Muscle-related: 6.4 vs. 6.0% Neurocognitive disorder: 0.9 vs. 0.3% Inj site rxns: 4.3% vs. N/A in std tx 2°: % LDL change at 12 wks: -61.0% (p<0.001) ↓LDL by 73mg/dL to 48 mg/dL LDL < 70 at 12 wks 73.6 vs 3.8%

Post-hoc analysis of CV Events:
- Composite of death, MI, UA requiring hospitalization, coronary revascularization, stroke, TIA, and hospitalization for HF: 1.0% vs. 2.1% (HR 0.47; 95% CI 0.28-0.78; p=0.003)

N Engl J Med. 2015; 372(16): 1500-9

Study Considerations

- Patient populations
  - Alirocumab trial included high-risk patients
    - FH, CHD, or CHD equivalent on high or maximally-tolerated statin
- Possible bias with evolocumab trial
  - Patients had to successfully complete parent trial by tolerating and proving adherence to injections
  - Open – label
- Relatively short follow-up
- Increased rates of neurocognitive events
- Both showed significant decrease in rate of composite CV outcomes
  - Although low overall incidence in both trials
- Similar rates of adverse effects when LDL < 25 mg/dL

Evolocumab - FOURIER

Study	Inclusion	Treatment	Efficacy	Safety
FOURIER Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease (March 2017)	N = 27,564 (1:1) - Age 40-85 with ASCVD, LDL ≥ 70 or non HDL ≥ 100 while taking optimized lipid lowering therapy (high-intensity statin or at least atorva 20 or equivalent) - With or without ezetimibe - Median baseline LDL: 92 mg/dL	Evolocumab 140mg q2wks or 420mg qmonth vs. placebo - Median duration: 26 months (2.2 yrs) - 69.4% on high-dose statin - 30.4% on moderate dose statin - 5.2% on ezetimibe	1°: composite of CV death, MI, CVA, hosp for UA or coronary revasc: - 9.8% vs 11.3% (P<0.001) - NNT = 74 At 48 wks: ↓LDL by 56 mg/mL (92 to 30mg/dL) RRR: 59% LDL < 70 in 87% LDL < 40 in 67% LDL < 25 in 42%	No difference in: - Muscle-related events - Cataract - Neurocognitive events (1.6 vs 1.5%) - Hemorrhagic stroke Inj site rxns: 2.1 vs. 1.6%

- Primary endpoint driven by significant reduction in non-fatal MI (3.4% vs 4.6%; P<0.001) and stroke (1.5% vs. 1.9%; P=0.01) and coronary revascularization (5.5% vs 7.0%; P<0.001)
- Slightly higher rate of CV death (1.8% vs 1.7%; P=0.62) and death from any cause (3.2% vs 3.1%; P=0.54)

N Engl J Med. 2017; 376: 1713-22

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

N Engl J Med. 2017; 376: 1713-22

Alirocumab – ODYSSEY Outcomes

- Completed recruitment
  - 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

ODYSSEY Outcomes NLM Identifier: NCT01663402

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

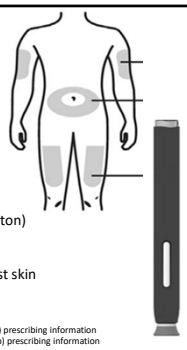
https://icer-review.org

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

Praluent (alirocumab) prescribing information
Repatha (evolocumab) prescribing information

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 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?

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? Select all that apply.
  - A. Continue rosuvastatin 20mg daily, assess adherence and lifestyle
  - B. Increase rosuvastatin 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 rosuvastatin 40mg daily
- Baseline LDL 193 mg/dL (LDL lowered by 34%)
- Which of the following options would you recommend in this patient?
  - A. Continue rosuvastatin 20mg daily alone
  - B. Add ezetimibe 10mg daily
  - C. Add evolocumab 140mg subcutaneously every 2 weeks
  - D. Add colesevelam 1875mg daily

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
d. MI, stroke, and coronary revascularization

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
c. A 53 yo female with HTN, MI at age 45 and LDL of 169 mg/dL on rosuvastatin 40mg daily
d. A 75 yo female with HTN and LDL of 113 mg/dL currently on ezetimibe 10mg 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

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Technician Post-Assessment Questions

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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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1. Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American Collge of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014; 129(25 Suppl 2): S1-45
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