The Role of Non-Statin Therapies for LDL-C Lowering for Management of ASCVD Risk

Maria Thurston, PharmD, BCPS
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**ACTIVITY DESCRIPTION**
A consensus document detailing the management of dyslipidemia with regard to the use of non-statin therapy was recently released in July 2016. New evidence regarding the use of non-statin therapy (i.e., results from IMPROVE IT and HPS2-THRIVE) has been released and new drugs approved (i.e., the PCSK9 inhibitors) since publication of the 2013 ACC/AHA lipid guideline. This has lead to gaps in the guideline regarding clinical decision making surrounding the use of non-statin drugs. It is imperative to disseminate recommendations of this new decision pathway to healthcare practitioners, so that they can provide evidence-based, patient-centered care as members of an interdisciplinary team.

**TARGET AUDIENCE**
The target audience for this activity is pharmacists, pharmacy technicians and nurses in hospital, community, and retail pharmacy settings.

**LEARNING OBJECTIVES**
After completing this activity, the pharmacist will be able to:
- Describe the background of dyslipidemia and atherosclerotic cardiovascular disease (ASCVD)
- Review recommendations from the 2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of ASCVD Risk
- Recognize the role of non-statin pharmacotherapy in dyslipidemia management
- Identify patient-specific pharmacotherapy plans to optimize outcomes for patients with dyslipidemia

After completing this activity, the pharmacy technician will be able to:
- Describe the background of dyslipidemia and atherosclerotic cardiovascular disease (ASCVD)
- Review recommendations from the 2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of ASCVD Risk
- Recognize the role of non-statin pharmacotherapy in dyslipidemia management

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Dr. Maria Thurston graduated with honors from the University of Georgia College of Pharmacy. She completed a PGY-1 pharmacy practice residency with the Atlanta Veterans Affairs Medical Center in Decatur, Georgia and a PGY-2 ambulatory care residency specializing in academia with the University of Georgia/Charlie Norwood Veterans Affairs Medical Center, where she also obtained a Graduate Certificate in Clinical Pharmacy. Dr. Thurston’s areas of interest and expertise include: cardiovascular risk reduction, health coaching, patient education, interprofessional education and professional development. Dr. Thurston achieved the designation of Board Certified Pharmacotherapy Specialist in 2011. She was named the Georgia Society of Health-System Pharmacists Outstanding Young Health-System Pharmacist in 2012 and received the American College of Clinical Pharmacy Ambulatory Care PRN Member Recognition Award in 2016. She is currently serving as a Clinical Assistant Professor in the Department of Pharmacy Practice with Mercer University College of Pharmacy where she coordinates the Nervous Systems Disorders II course and teaches various didactic lectures. She actively practices in a collaborative internal medicine clinic affiliated with Wellstar Atlanta Medical Center, where she precepts both pharmacy students and residents. She serves on committees for multiple regional and national pharmacy organizations and is a peer reviewer for scholarly journals. Her numerous regional and peer-reviewed publications are focused on topics relevant to primary care practice, and she has research and grants in the areas of medication adherence, health literacy, diabetes, heart failure, hypertension, mobile apps, interprofessional education, and professional development.

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Learning Objectives

1. Describe the background of dyslipidemia and atherosclerotic cardiovascular disease (ASCVD)
2. Review recommendations from the 2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of ASCVD Risk
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Background

• Dyslipidemia
  • 73.5 million US adults have high low-density lipoprotein cholesterol (LDL-C)
  • 29.5% have the condition under control
  • < 50% are getting treatment to lower their levels
  • High total cholesterol increases risk for heart disease ~2x

What is ASCVD?

• Atherosclerotic Cardiovascular Disease
  • Myocardial infarction (MI)
  • Stable or unstable angina (ACS)
  • Coronary revascularization
  • Stroke
  • Transient ischemic attack [(TIA)-- of presumed atherosclerotic origin]
  • Peripheral arterial disease (PAD) or revascularization
Therapeutic Options

• Lifestyle modification
  • Heart healthy diet (phytosterols and soluble dietary fibers), regular exercise, tobacco avoidance, and healthy weight maintenance
• 2013 AHA/ACC Lifestyle Management Guideline
• Statin therapy
• Non-statin agents

Cholesterol Guidelines

• ATP III previously “go to” cholesterol guideline
  • Risk assessment with Framingham, CHD risk equivalents & major risk factors
  • LDL & non-HDL goals determined by risk evaluation
• 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol
  • Provides “a strong evidence-based foundation for the treatment of cholesterol for the primary and secondary prevention of ASCVD”
  • New risk assessment tool and elimination of LDL “goals”
  • Focus on appropriate intensity statin therapy according to benefit group

Risk Assessment: ASCVD Risk Score

• Pooled Cohort Equations to predict
  • 10-year risk of first ASCVD event (for patients age 40-79)
  • Used to determine appropriate statin intensity
  • Lifetime risk (for patients age 20-59)
• 9 factors evaluated
  • Sex, age, RACE, total cholesterol, high density lipoprotein, systolic blood pressure, treatment for HTN, PRESENCE OF DIABETES, and smoking status
• Web, computer download, and app!
  • https://my.americanheart.org/

Statin Benefit Groups

- Clinical ASCVD (≥21 years)
  • High-intensity statin

- LDL >190 mg/dL (≥21 years)
  • High-intensity statin

- Diabetes (LDL 70-189 mg/dL; and aged 40-75 years)
  • Moderate or high-intensity statin

- ≥ 7.5% estimated 10-y ASCVD risk (LDL 70-189 mg/dL; and aged 40-75 years)
  • Moderate or high-intensity statin
2013 ACC/AHA Non-Statin Recommendations

- For patients who have failed therapy with multiple statins or have a contraindication to statin use
- Utilize agents that have demonstrated ASCVD risk-reduction
- Insufficient evidence to determine “best” non-statin therapy
- ACC/AHA do not recommend combination therapy
  - Lack of evidence and increased risk of polypharmacy, drug-drug interactions, and adverse effects

HPS2-THRIVE

- Heart Protection Study 2 - Treatment of HDL to Reduce the Incidence of Vascular Events
- Evaluated ER niacin/laropiprant + moderate-intensity statin compared to moderate-intensity statin alone with clinical ASCVD
- No clinical benefit and potential for significant harms, despite further lowering of LDL-C
  - No reduction in risk of heart attacks, strokes and operations to open blocked arteries
  - Increased adverse events

IMPROVE-IT

- CV outcomes trial
- Evaluated addition of ezetimibe (Zetia®) to moderate-intensity statin in patients with recent ACS
  - Resulted in incremental lowering of LDL-C and reduced primary composite endpoint
    - CV death, nonfatal MI, UA requiring re-hospitalization, coronary revascularization [≥ 30 days after randomization], or nonfatal stroke.
    - Over 7 year period
    - 6% RRR and 2% ARR

PCSK9 Inhibitor Trials

- Alirocumab (Praluent®) and evolocumab (Repatha®)
  - Recently gained FDA approval
  - Dramatically reduce LDL-C level over and above statin therapy
  - Favorable short-term outcomes data
- Long-term CV outcomes trials currently in progress
  - Alirocumab—ODYSSEY Outcomes
  - Evolocumab—FOURIER
  - Bococizumab (not yet FDA approved)—SPIRE I and SPIRE II

References:
2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies

• Based on recent clinical trial evidence
  • Rely on the evidence base established by the 2013 guideline
  • Incorporate newer clinical trial data on niacin, ezetimibe, and proprotein convertase subtilisin/kexin 9 (PCSK9) inhibitors
• Created to address current gaps in recommendations for LDL-C lowering to reduce ASCVD in high-risk subsets
  • Provide more detailed recommendations for specific patient scenarios
• Algorithms provide a suggested clinical workflow

3 Key Questions Addressed
1. **In what patient populations** should non-statin therapies be considered?
2. **In what situations** should non-statin therapies be considered, i.e., when is the amount of LDL-C lowering (percent LDL-C reduction or LDL-C range achieved on therapy) less than anticipated, less than desired, or inadequate, and which treatment options should be considered in patients who are truly statin intolerant?
3. If non-statin therapies are to be added, **which agents or therapies** should be considered and in what order

Statin Intolerance

• Most commonly- muscle-related symptoms
• Systematic, multifaceted approach
  • Temporary discontinuation of statin therapy
  • Lower dosing
  • Re-challenge with 2-3 statins of differing metabolic pathways/lipophilicity
  • Intermittent (1-3x weekly) dosing of long half-life statins
• Referral to a lipid specialist and registered dietitian
  • May be considered for higher-risk patients
  • Strongly encouraged for patients with familial hypercholesterolemia (FH)

Familial Hypercholesterolemia (FH)

• **Homozygous** (HoFH) and heterozygous (HeFH)
• Genetic disorder associated with severe hypercholesterolemia
• Management with statins and non-statin
  • Consideration for use of lomitapide (Juxtapid®), mipomersen (Kynamro®), and LDL apheresis as necessary
• Lomitapide and mipomersen only approved first-line treatments for HoFH
  • Evolocumab approved as an adjunct to other LDL-lowering therapies in HoFH
• Referral to a lipid specialist/registered dietitian is often recommended
Factors to Consider

• Absolute and percent reduction in LDL-C level achieved
  • But NOT firm triggers for adding a non-statin
• Extent of available scientific evidence for safety and tolerability
• Potential for drug-drug interactions
• Efficacy of additional LDL-C lowering in ASCVD event reduction
• Cost, convenience, and medication storage
• Pill burden and route of administration
• Potential to jeopardize adherence to evidence-based therapies
• Patient preferences – Important!

Non-Statin Therapy

• Recommendations dependent on stain benefit group
  • Subgroups further delineated

Ezetimibe

• MOA: Reduces cholesterol absorption in small intestine
• Dosing: 10 mg PO daily, with or without food.
  • Take ≥ 2 hours before or ≥ 4 hours after BAS if used in combination
• Efficacy (LDL reduction): Monotherapy—18%, combination therapy with statin (incremental reduction)—25%
• Adverse events/safety
  • Monotherapy—upper respiratory tract infection, diarrhea, arthralgia, sinusitis, pain in extremity; combination with statin—nasopharyngitis, myalgia, upper respiratory tract infection, arthralgia, diarrhea
  • Interacts with cyclosporine, fibrates, BAS

Bile Acid Sequestrants (BAS)

• Colesevelam (Welchol®), Cholestyramine (Questran®), and Colestipol (Colestid®)
• MOA: Bind bile acids to prevent reabsorption in the intestines → Increase LDL-C clearance from the body
• Dosing: Dependent on dosage formulation
  • Tablet, suspension, powder
• Efficacy (LDL reduction): Dependent on the product and formulation
  • Monotherapy—10–27%
  • Combination with statin (incremental reduction)—10–16%
Bile Acid Sequestrants (BAS)

- Adverse events/safety:
  - Constipation, dyspepsia, nausea
  - Increased seizure activity or decreased phenytoin levels
  - Decreased INR in patients receiving warfarin
  - Increased TSH with thyroid hormone replacement therapy
  - Bowel obstruction or fecal impaction
  - Dysphagia or esophageal obstruction
  - Hypertriglyceridemia → pancreatitis
  - Increased transaminases
  - Risk of many drug-drug interactions...

PCSK9 Inhibitors

- Alirocumab and evolocumab
- MOA: Human monoclonal antibody to PCSK9.
  - Binds to PCSK9 and increases the number of LDL receptors available to clear circulating LDL
- Dosing:
  - Alirocumab—initiate 75 mg SQ every 2 weeks, may titrate Q2 weeks
  - Evolocumab—140 mg SQ every 2 weeks or 420 mg SQ once monthly


PCSK9 Inhibitors

- Efficacy (LDL reduction when added to maximally tolerated statin):
  - Alirocumab 75 mg & 150 SQ: 45% & 58% decrease, respectively
  - Evolocumab 140 mg & 420 mg: 64% and 58% decrease, respectively
- Adverse events/safety:
  - Alirocumab—nasopharyngitis, injection site reactions, influenza
  - Evolocumab—nasopharyngitis, upper respiratory tract infection, influenza, back pain, and injection site reactions
  - Increases in self-reported cognitive adverse effects in RCTs with both agents
  - No clinically significant drug-drug interactions

Non-Statin Recommendations– By Group

1. Clinical ASCVD*
   - Subgroups: +/- comorbidities, baseline LDL ≥ 190 mg/dL
   - For secondary prevention
2. Baseline LDL ≥ 190 mg/dL*
3. Diabetes**
4. 10-year risk ≥ 7.5%**
   - Considerations for special populations also included

*Age dependent recommendation
**LDL-range dependent recommendation

Clinical ASCVD Without Comorbidities

- If < 50% LDL-C reduction (and may consider LDL ≥ 100 mg/dL)
- Optimize adherence, lifestyle, statin, and risk factors → Re-evaluate
- Clinician-patient discussion → Re-evaluate
- Non-statin therapy
  - Ezetimibe: First-line
  - Bile Acid Sequestrant: Alternative for ezetimibe intolerant patients
    - Avoid in patients with triglycerides >300 mg/dL
    - No evidence of benefit
  - Consider adding or replacing with PCSK9 inhibitor as second step

Clinical ASCVD With Comorbidities

- If < 50% LDL-C reduction (and may consider LDL ≥ 70 mg/dL or non-HDL ≥ 100 mg/dL in patients with diabetes)
- Same optimization and clinician-patient discussion process
- Non-statin therapy
  - Ezetimibe: First-line
  - Bile Acid Sequestrant: Alternative for ezetimibe intolerant patients
    - Avoid in patients with triglycerides >300 mg/dL
    - Colesevelam may have modest HbA1c lowering effects
  - Consider adding or replacing with PCSK9 inhibitor as “second” step

Clinical ASCVD and LDL-C ≥ 190 mg/dL

- If < 50% LDL-C reduction (and may consider LDL ≥ 70 mg/dL)
- Optimization and clinician-patient discussion process
  - Consider referral to lipid specialist and dietician for all
- Non-statin therapy
  - Ezetimibe (or bile acid sequestrant second line)
  - ADD PCSK9 inhibitor
    - Reasonable to consider as first step
  - May consider mipomersen or lomitapide or LDL apheresis in appropriate patients

Baseline LDL ≥ 190 mg/dL

- If < 50% LDL-C reduction (and may consider LDL ≥ 100 mg/dL)
- Optimization and clinician-patient discussion process
  - Consider referral to lipid specialist and dietician for all
- Non-statin therapy
  - Either ezetimibe or a PCSK9 inhibitor
  - Gap in evidence with ezetimibe in this population
    - Depending on additional % LDL-C reduction desired
    - BAS as second line alternative to ezetimibe
  - May consider mipomersen or lomitapide or LDL apheresis in appropriate patients
### Diabetes

- If < 50% LDL-C reduction (and may consider LDL ≥ 100 mg/dL or non-HDL ≥ 130 mg/dL in patients with diabetes)
- Optimization and clinician-patient discussion process
  - Statin intensification only for small proportion of patients with 10-year ASCVD risk < 7.5% started on moderate-intensity statin therapy
  - Increase to high-intensity statin if 30 to < 50% LDL-C reduction not attained
- Non-statin therapy
  - Ezetimibe first-line
  - Bile acid sequestrant second-line
  - No established role for PCSK9 inhibitors

### 10-Year Risk ≥ 7.5%

- If < 30% LDL-C reduction (and may consider LDL ≥ 100 mg/dL)
- Optimization and clinician-patient discussion process
  - Increase to high-intensity statin
- Non-statin therapy
  - "Limited role" per expert consensus writing committee
  - ≥ 1 high-risk markers
  - Lack of RCT data and lower net ASCVD risk-reduction benefit
  - Routine use NOT recommended if risk 5 to < 7.5%
  - Ezetimibe first-line & bile acid sequestrant second-line if multiple risk factors
  - PCSK9 inhibitors NOT recommended

### Special Populations

- Those not included in one of the four statin benefit groups
  - Patients with heart failure (HF)
    - Equivocal data on use of statins → may consider in symptomatic HF
    - Follow algorithm for patients with ASCVD and comorbidities—but NO PCSK9 inhibitors
  - Patients on maintenance hemodialysis
    - Individualize approach based on longevity and other comorbidities
    - Consider algorithm for patients with ASCVD and comorbidities—but NO PCSK9 inhibitors
  - Women considering pregnancy or already pregnant
    - Statins only in those using effective contraception and who are not nursing
    - Consider bile acid sequestrants and monitor for vitamin K deficiency or LDL apheresis
- Other… beyond the scope of the document

### Monitoring Outcomes

- Fasting lipid panel (LDL-C level) 4-12 weeks after treatment modification and every 3-12 months thereafter
  - Consistent with the recommendations of the 2013 guideline
  - Friedewald equation for LDL-C calculation endorsed
  - LDL-C response to therapy
  - Adherence
- Lifestyle
- Side effects
Patient Counseling

- Shared decision making
  - Patient preferences
    - Perception of benefit, convenience/burden of therapy, cost, quality of life, impact on adherence to evidence-based therapies
- Efficacy and safety of non-statin therapy
  - Additional ASCVD risk reduction
  - Adverse events/drug interactions
- Benefits of drug therapy adherence
- When to make referral to a lipid specialist

Summary

- Dyslipidemia is a prevalent and relevant condition today
- 2016 ACC Expert Consensus Decision Pathway offers guidance on the role of non-statin therapies for LDL-C lowering in the management of ASCVD risk
  - Ensure patient is prescribed maximally tolerated statin therapy, as indicated
  - 2013 ACC/AHA Cholesterol Guideline - 4 statin benefit groups
    - Ezetimibe → first-line
    - Bile acid sequestrant → second-line
    - Consider PCSK9 inhibitors in high risk patients
- Patient education and shared decision making are key!
Exam Questions:

1. What item in a patient’s past medical history is considered to meet the definition of clinical atherosclerotic cardiovascular disease (ASCVD)?
   a. Hypertension 
   b. Diabetes 
   c. Unstable angina 
   d. Pulmonary embolism

2. In regards to the use of non-statin therapy, the 2013 ACC/AHA Blood Cholesterol Guideline recommends:
   a. Combination therapy of a statin and non-statin agent as first-line
   b. Fibrate products as the class of choice for all patients
   c. Non-statin agents first-line in patients less than 40 years of age with a 10-year risk > 7.5%
   d. Non-statin agent use in statin-intolerant patients if benefits outweigh possible adverse effects

3. What tool is recommended to use for estimating a patient’s 10-year ASCVD risk?
   a. Framingham Equation 
   b. Pooled Cohort Equations 
   c. Treating to New Targets Equation 
   d. FRAX Equation

4. What non-statin agent is generally recommended first-line in patients aged 40-75 years without clinical ASCVD and with diabetes and baseline LDL-C 70-189 mg/dL on statin therapy for primary prevention?
   a. Alirocumab 
   b. Ezetimibe 
   c. Colesevelam 
   d. Niacin
5. What clinical feature would preclude the use of a bile acid sequestrant for non-statin management?
   a. Triglyceride level of 330 mg/dL
   b. HbA1c value of 8.8%
   c. Concomitant statin therapy
   d. CrCl = 55 mL/min

6. Which agent is no longer recommended as a non-statin therapy option due to unfavorable results of the HPS2-THRIVE trial?
   a. EPA/DHA
   b. Niacin
   c. Lomitapide
   d. Ezetimibe

7. What should a provider consider prior to the addition of a non-statin agent?
   a. Intensification of lifestyle modifications
   b. Use of maximally tolerated statin therapy
   c. Addressing adherence to statin therapy
   d. All of the above

8. In what patient population can a PCSK9 inhibitor be considered as a “first step” non-statin agent?
   a. Clinical ASCVD and baseline LDL-C > 190 mg/dL
   b. Diabetes and baseline LDL-C = 150 mg/dL
   c. 10-year ASCVD risk = 14% on statin for primary prevention
   d. 55 year old patient with heart failure

9. What is the anticipated percent reduction in LDL-C from maximally tolerated high-intensity statin therapy that is important to consider when assessing the need for non-statin therapy?
   a. Less than 30% LDL-C reduction
   b. Great than or equal to 50% LDL-C reduction
   c. 30-49% LDL-C reduction
   d. Assessment of percent LDL-C reduction is not recommended
10. What is an adverse effect that patients should be counseled on associated with the use of ezetimibe?

   a. Worsening in liver function
   b. Risk of diarrhea
   c. Increase in triglycerides
   d. Decrease in absorption of other medications