The Role of Non-Statin Therapies for LDL-C Lowering for Management of ASCVD Risk in Family Practice
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Michael Cobble, MD, FNLA, has the following relevant financial relationships with commercial interests to disclose:

Consultant – Kowa

Speakers Bureau: Amarin, Amgen, AstraZeneca, Kowa, Sanofi

Louis Kuritzky, MD, has the following relevant financial relationships with commercial interests to disclose:

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Stephen A. Brunton, MD; Paul P. Doghramji, MD, FAAFP; and Penny Tenzer, MD, do not have any relevant financial relationships with commercial interests to disclose.

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This activity is supported by educational funding provided by Amgen.
Educational Objectives

Upon completion of this activity, learners should be able to:

1. **SUMMARIZE** the latest guidelines and recommendations on cholesterol management from major clinical organizations

2. **REVIEW** potential cholesterol-lowering therapies beyond statins and explain when these non-statin therapies should be considered

3. **STATE** the indications in detail for proprotein convertase subtilisin kexin type 9 inhibitor (PCSK9i) therapy
The National Lipid Association (NLA) published recommendations for patient-centered management of dyslipidemia in 2015. Those recommendations propose treatment goals for non–HDL-C and LDL-C based on 4 risk categories: Low, Moderate, High, and Very High. Treatment goals for the Low, Moderate, and High risk categories are the same. Which of the following represents the NLA treatment goals for LDL-C?

A. Low, Moderate, High: <70 mg/mL; Very High: <70 mg/mL
B. Low, Moderate, High: <70 mg/mL; Very High: <100 mg/mL
C. Low, Moderate, High: <100 mg/mL; Very High: <100 mg/mL
D. Low, Moderate, High: <100 mg/mL; Very High: <70 mg/mL
Pre-test Question 2

Statin and non-statin combination therapy may improve lipid-lowering efficacy and may improve cardiovascular outcomes. Which of the following combination therapies was studied in the IMPROVE-IT trial and demonstrated reductions in cardiovascular outcomes?

A. Colestipol and simvastatin  
B. Ezetimibe and simvastatin  
C. Evolocumab and simvastatin  
D. Lomitapide and simvastatin
Pre-test Question 3

Which of the following is TRUE regarding indications for PCSK9 inhibitors?

A. Alirocumab is approved for either monotherapy or combination therapy for patients with heterozygous familial hypercholesterolemia (HeFH), homozygous familial hypercholesterolemia (HoFH), or clinical atherosclerotic cardiovascular disease (ASCVD).

B. Alirocumab is approved for combination therapy with a maximally tolerated statin for patients with HeFH, HoFH, or clinical ASCVD.

C. Evolocumab is indicated to reduce the risk of myocardial infarction, stroke, and coronary revascularization in adults with established CVD.

D. Evolocumab is just approved for combination therapy for patients with HeFH or clinical ASCVD.
Pre-test Question 4

BN is a 27-year-old woman diagnosed at age 13 years with HoFH. Current lipid medications are lovastatin, colesevelam, and ezetimibe. BN adheres to a healthy lifestyle with a low-fat diet and regular exercise. However, BN’s LDL-C levels remain high with the most recent level of 213 mg/dL. With the HoFH diagnosis, her family history of cardiovascular disease, and the recent increase in LDL-C despite high-dose lipid-lowering drugs, BN asks her physician about the new PCSK9 inhibitors. Which of the following would be an appropriate treatment option for BN?

A. Alirocumab 75 mg subcutaneously biweekly (2x/month)
B. Alirocumab 300 mg subcutaneously q4 weeks
C. Evolocumab 300 mg subcutaneously q4 weeks
D. Evolocumab 420 mg subcutaneously q4 weeks
Case Study

• Mark B, a 54-year-old man with familial hypercholesterolemia (FH)
  • BMI: 31.7
  • On treatment LDL-C: ≈220 mg/dL
  • Smoking: 1 pack/day
  • Typical American diet
  • Exercise: walking ≈30 minutes, 1 or 2 days/week
  • Meds: atorvastatin 80 mg qd, lisinopril 20 mg qd

What recommendations for the patient?
Cardiovascular Disease and Hyperlipidemia

• Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of morbidity and mortality in the United States
  • Responsible for 1 of 7 deaths
  • Hyperlipidemia is a major ASCVD risk factor
• Statins are recommended as first-line drug therapy for lowering LDL-C
  • 30% of patients do not achieve lipid-lowering goals, even with maximum statin doses

Familial Hypercholesterolemia (FH)

- Inherit a pathogenic variant in 1 of the key genes involved in lipoprotein metabolism: \textit{APOB}, \textit{LDLR}, or \textit{PCSK9}
- Heterozygous familial hypercholesterolemia (HeFH)
  - Prevalence may be up to 1 of 200 individuals
- Homozygous familial hypercholesterolemia (HoFH)
  - Prevalence rate of up to 1 of 300,000 individuals
- Treatment of HeFH or HoFH typically requires additional pharmacotherapy measures and/or LDL apheresis treatments

FH in Children

- Early diagnosis and treatment can result in normal life expectancy
- Distinguish FH from non-FH via LDL-C screening in childhood
  - Phenotypic diagnosis: LDL-C ≥190 mg/dL, or an LDL-C ≥160 mg/dL with family history of premature coronary heart disease and/or high baseline cholesterol in 1 parent
  - If a parent has a genetic defect, the LDL-C cut-off for the child is ≥130 mg/dL
- Healthy lifestyle and statin treatment (from age 8–10 years) are the foundations of therapy
  - Target LDL-C: <130 mg/dL if >10 years old
    - OR
  - 50% reduction from baseline if 8–10 years old

# How Do I Know When My Patient Has FH?

## (USA: MEDPED Criteria)

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Total cholesterol (and LDL-C) levels, mg/dL</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1st-degree relative</td>
<td>2nd-degree relative</td>
</tr>
<tr>
<td>&lt;18</td>
<td>220 (155)</td>
<td>230 (165)</td>
</tr>
<tr>
<td>20</td>
<td>240 (170)</td>
<td>250 (180)</td>
</tr>
<tr>
<td>30</td>
<td>270 (190)</td>
<td>280 (200)</td>
</tr>
<tr>
<td>≥40</td>
<td>290 (205)</td>
<td>300 (215)</td>
</tr>
</tbody>
</table>

Lipid Guidelines/Recommendations

American Heart Association/American College of Cardiology (AHA/ACC)

• 2013 Cholesterol Management Guidelines

• 2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk

• 2017 Focused Update of 2016 ACC Expert Consensus on the Role of Non-statin Therapies for Low-density Lipoprotein Cholesterol (LDL-C) Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk

• 2018 ACC/AHA Multi-society Guideline on the Management of Blood Cholesterol

Lipid Guidelines/Recommendations

National Lipid Association (NLA)

• 2015 Dyslipidemia Management Recommendations, Parts 1 and 2
• 2017 Recommendations of the NLA Expert Panel on Treatment with PCSK9i
• 2018 Guideline on the Treatment of High Blood Cholesterol

2013 AHA/ACC Guidelines and 2016/2017/2018 ACC Updates

1. Heart-healthy lifestyle habits
2. Appropriate intensity of statin therapy based on ASCVD risk
   → 5 treatment benefit groups
   → Add-on non-statin therapy in very high risk ASCVD
3. Regularly monitor adherence to lifestyle and drug therapy
4. In cases of statin intolerance, use the maximally tolerated intensity of statin (which may be 0)
5. In patients 40-75 years of age being evaluated for primary ASCVD prevention, discuss statin therapy

2018 AHA/ACC Cholesterol Treatment Guidelines

Statin and Non-statin Benefit Groups

Factors to Consider

Optional Interventions to Consider

### 2018 AHA/ACC: Treatment Benefit Groups

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td><strong>1</strong></td>
<td>Patients ≥ 21 years of age with <strong>ASCVD</strong>, reduce LDL-C with high-intensity statin therapy or maximally tolerated dose</td>
<td></td>
</tr>
<tr>
<td><strong>2</strong></td>
<td>Patients ≥21 years of age with <strong>very high risk ASCVD</strong> use LDL-C threshold of 70 mg/dL to <strong>consider adding non-statin to statin therapy</strong></td>
<td></td>
</tr>
<tr>
<td><strong>3</strong></td>
<td>Patients ≥21 years of age with <strong>severe FH, baseline LDL-C ≥190 mg/dL</strong> without calculating 10-year ASCVD risk, begin high-intensity statin therapy</td>
<td></td>
</tr>
<tr>
<td><strong>4</strong></td>
<td>Patients ages 40–75 years of age with <strong>diabetes and LDL-C ≥ 70 mg/dL</strong> start moderate-intensity statin without calculating 10-year ASCVD risk</td>
<td></td>
</tr>
<tr>
<td><strong>5</strong></td>
<td>Patients 40–75 years of age with <strong>diabetes with LDL-C ≥ 70 mg/dL</strong> with a 10-year ASCVD risk of:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥7.5% discuss treatment options, start moderate-intensity statin, if favored</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;7.5% - 19.9% risk enhancing factors favor starting statin; If statin decision is uncertain measure coronary artery calcium (CAC)</td>
<td></td>
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</tbody>
</table>

2018 AHA/ACC: Factors to Consider

- Adherence and lifestyle
- Statin-associated side effects
- Control of other risk factors
- Clinician–patient discussion regarding potential benefits, potential harms, and patient preferences regarding addition of non-statin medications
- Percentage LDL-C reduction (may consider absolute LDL-C level achieved)
- Monitoring of response to therapy, adherence, and lifestyle

2018 ACC: Optional Interventions

- Referral to lipid specialist and registered dietitian or nutritionist
- Ezetimibe
- Bile acid sequestrants
- PCSK9 inhibitors
- Mipomersen, lomitapide, and/or LDL apheresis may be considered by a lipid specialist for patients with FH

Audience Question
Statin-Associated Side Effects

• What are some common causes of statin intolerance?

• Is it feasible and clinically appropriate to use statins in patients with statin intolerance?
Statin-Associated Side Effects

• Along with lifestyle changes, statins are the foundational drug class for treatment of hyperlipidemia
• Adverse effects, particularly myalgia, may limit the application of statins in some populations
• In other patients, statins may not achieve lipid reduction goals
• Alternative therapies may be required to achieve lipid reduction goals

Statin Intolerance Risk Factors

Potential Patient Factors

- Pre-existing neuromuscular condition, hepatic disease, renal disease, and/or untreated hypothyroidism
- Known history of myopathy or family history of myopathy syndrome
- Certain rare genetic polymorphisms regulating hepatic cytochrome enzyme pathways
- Drug–drug interactions that increase plasma levels of statins

2015 NLA Dyslipidemia Management Recommendations

• “Patient-centered”

• Key tenet: lifestyle therapies are central to prevention of ASCVD
  • Nutrition/diet (low in saturated fat)
  • Weight loss
  • Exercise/physical activity

2015 NLA Dyslipidemia Management Recommendations

- Lifestyle therapies
- Cholesterol-lowering drug therapies
  - First-line (unless contraindicated): moderate– or high-intensity statin
  - Combination therapies

# 2015 NLA: Treatment Goals and Criteria for Drug Therapy, Low and Moderate Risks

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Criteria</th>
<th>Treatment Goal</th>
<th>Consider Drug Therapy</th>
</tr>
</thead>
</table>
| Low | • 0 or 1 major ASCVD risk factors (RFs)  
• Consider other risk indicators, if known | <130  
<100 | ≥190  
≥160 |
| Moderate | • 2 major ASCVD RFs  
• Consider quantitative risk scoring  
• Consider other risk indicators (additional testing may be considered) | <130  
<100 | ≥160  
≥130 |

### 2015 NLA: Treatment Goals and Criteria for Drug Therapy, High-Risk

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Criteria</th>
<th>Treatment Goal</th>
<th>Consider Drug Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>• ≥3 major ASCVD RFs&lt;br&gt;• Diabetes (type 1 or 2)&lt;br&gt;• 0 or 1 other major ASCVD RF &lt;br&gt;&lt;em&gt;and&lt;/em&gt;&lt;br&gt;• No evidence of end-organ damage&lt;br&gt;• Chronic kidney disease (CKD) stage 3B or 4&lt;br&gt;• LDL-C of ≥190 mg/dL&lt;br&gt;• Quantitative risk score reaching the high-risk threshold</td>
<td>Non-HDL-C: &lt;130&lt;br&gt;LDL-C: &lt;100</td>
<td>Non-HDL-C: ≥130&lt;br&gt;LDL-C: ≥100</td>
</tr>
</tbody>
</table>

## 2015 NLA: Treatment Goals and Criteria for Drug Therapy, Very High-Risk

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Criteria</th>
<th>Treatment Goal</th>
<th>Consider Drug Therapy</th>
</tr>
</thead>
</table>
| Very high     | ▪ ASCVD  
▪ Diabetes (type 1 or 2)  
  ▪ ≥2 other major ASCVD RFs  
  ▪ Evidence of end-organ damage* | Non–HDL-C, mg/mL  
LDL-C, mg/mL <100  
<70 | Non–HDL-C, mg/mL  
LDL-C, mg/mL ≥100  
≥70 |

*End-organ damage indicated by increased albumin-to-creatinine ratio (≥30 mg/g), CKD (eGFR, 60 mL/min/1.73 m²), or retinopathy. eGFR, estimated glomerular filtration rate

Non-statins Therapies

Classes of Drugs
1. Bile acid binding resins (eg, cholestyramine, colesvelam)
2. Cholesterol absorption inhibitor (ezetimibe)
3. PCSK9 inhibitors (alirocumab, evolocumab)

Additional Drugs for HoFH
1. Mipomersen: antisense oligonucleotide inhibitor of apolipoprotein B
2. Lomitapide: small molecule inhibitor of microsomal triglyceride transfer protein

LDL Apheresis
Bile Acid Binding Resins

Medications in this class include:
1. Colestipol (Colestid)
2. Cholestyramine (Questran, Questran Light, Cholybar, Olestyr)
3. Colesevelam (Welchol)

- **Mechanism of Action (MOA)**
  - Bind bile acids in the GI tract → LDL-C lowering ≈10%-27%
- **Advantages**
  - No systemic absorption
- **Disadvantages**
  - Recent FDA labeling change to remove CV indications
  - Little in the way of convincing outcomes trials for CVD end points
- **Adverse events**
  - Constipation, bloating, nausea, gas

CVD, cardiovascular disease; GI, gastrointestinal
Cholesterol Absorption Inhibitor

- Ezetimibe (Zetia) is the only currently available drug in this class
  - Also available in a combination product with simvastatin
- MOA
  - Inhibition of GI tract cholesterol absorption via Niemann-Pick C1-Like 1 (NPC1L1) transmembrane protein receptor → ≈20% ↓LDL
- May improve CV outcomes in certain patient populations (IMPROVE-IT trial)
- Common adverse events include diarrhea, upper respiratory infection, arthralgia, pain in extremity

Comparison of MOAs: Statins

Comparison of MOAs: Ezetimibe

Comparison of MOAs: Bile Acid Sequestrants

Comparison of MOAs: PCSK9 Inhibitors

Non-Statin Therapies (con’t)  
REDUCE-IT Trial  
Cardiovascular Risk Reduction with Icosapent Ethyl in High Risk Patients on Statin Therapy

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Inclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Multicenter, randomized, double-blind placebo-controlled</td>
<td>• Age ≥45 with established CVD (Secondary Prevention Cohort) or ≥50 years with diabetes with ≥1 additional risk factor for CVD (Primary Prevention Cohort)</td>
</tr>
<tr>
<td>• High dose icosapent ethyl (a highly purified ethyl ester of eicosapentaenoic acid (EPA); 2 g BID, 4 g/day vs. placebo</td>
<td>• Fasting triglyceride ≥150 mg/dL and &lt;500 mg/dL</td>
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<tr>
<td>• 8179 patients</td>
<td>• LDL-C ≥40 mg/dL and ≤100 mg/dL and on stable statin therapy for ≥4 weeks prior to qualifying measurements for randomization</td>
</tr>
<tr>
<td>• Duration: 7 years (2011-2018)</td>
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<tr>
<td>• Primary Endpoint: Composite of CV death, nonfatal myoccardial infarction, nonfatal stroke, coronary revascularization, or unstable angina</td>
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### Results

- **Primary endpoint event occurrences:**
  
  Icosapent ethyl: **17.2%**  
  Placebo: **22.0%**  
  
  Hazard ratio, 0.75; 95% confidence interval, 0.68 to 0.83;  
  \( P<0.001 \)

- **Effects on Lipids:**
  
  - Median change in triglycerides from baseline to 1 year, \( \downarrow 18.3\% \) in icosapent ethyl group vs \( \uparrow 2.2\% \) in placebo.
  
  - Median reduction from baseline was 19.7% higher in the icosapent ethyl group than placebo.
  
  - Median change in LDL-C from baseline was an \( \uparrow 3.1\% \) in the icosapent ethyl group vs \( \uparrow 10.2\% \) in placebo.

### Conclusions

- Compared with placebo, icosapent ethyl 4g/day significantly reduced CV events by 25%, including:
  
  - 20% reduction in death due to CV causes
  
  - 31% reduction in MI
  
  - 28% reduction in stroke

- Low rate of adverse effects, including:
  
  - Small but significant increase in atrial fibrillation/flutter
  
  - Non-statistically significant increase in serious bleeding

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Case Study

- 54-year-old man with FH
  - BMI: 31.7
  - LDL-C: ≈220 mg/dL
  - Smoking: 1 pack/day
  - High-fat diet
  - Exercise: walking ≈30 minutes, 1 or 2 days/week
  - Meds: atorvastatin 80 mg qd, lisinopril 20 mg qd

What recommendations for the patient?
Audience Discussion Question 2

What medication changes, if any, would you recommend for the patient?

A. Ezetimibe
B. Change statin
C. Fibrate
D. PCSK9i
E. No change
PCSK9 Inhibitors

- A class of lipid-lowering drugs first approved in 2015
  - Alirocumab (Praluent), evolocumab (Repatha)
- Current members of this class are monoclonal antibodies (mAbs), a type of biological drug, that require a subcutaneous (SC) route of administration
  - Alirocumab is a human mAb of the immunoglobulin G₁ (IgG₁) isotype
  - Evolocumab is a human mAb of the immunoglobulin G₂ (IgG₂) isotype

PCSK9 Inhibitors (MOA): Inactive

Hepatocytes

Magnified Hepatocyte

Blood Vessel

LDL
LDL Receptor
PCSK9
PCSK9 mab

Degraded LDL

Adapted image courtesy of Louis Kuritzky, MD.

PCSK9 Inhibitors (MOA): Active PCSK9

Hepatocytes

Magnified Hepatocyte

Degraded LDL

Degraded LDL Receptor

Degraded LDL

Blood Vessel

Adapted image courtesy of Louis Kuritzky, MD.

PCSK9 Inhibitors (MOA): Inhibited PCSK9

Blood Vessel

Hepatocytes

Magnified Hepatocyte

Degraded LDL

Degraded LDL Receptor

Degraded LDL

Adapted image courtesy of Louis Kuritzky, MD.

FDA-Approved Indications

**Alirocumab**
- Adjunct to diet and maximally tolerated statin therapy for the treatment of adults with HeFH or clinical ASCVD who require additional lowering of LDL-C

**Evolocumab**
- To reduce the risk of myocardial infarction, stroke, and coronary revascularization in adults with established CVD
- Adjunct to diet, alone, or in combination with other lipid-lowering therapies (eg, statins, ezetimibe) for treatment of adults with primary hyperlipidemia (including HeFH) to reduce LDL-C
- Adjunct to diet and other LDL-lowering therapies (eg, statins, ezetimibe, LDL apheresis) in patients with HoFH who require additional lowering of LDL-C

New and Updated Indications! Effective December 1, 2017

Summary of Indication Differences

• **Alirocumab**
  - Just as combination therapy with maximally tolerated statin for patients with HeFH or clinical ASCVD
  - *Not approved for HoFH*

• **Evolocumab**
  - New, broader indication:
    - *To reduce the risk of myocardial infarction, stroke, and coronary revascularization in adults with established CVD*
  - Monotherapy or combination therapy with other lipid-lowering drugs
  - Approved for HeFH as well as HoFH

Alirocumab: Dosing and Administration

- Recommended starting dose: 75 mg SC biweekly (2x/month) or 300 mg q4 weeks
- Maximum dose: 150 mg SC biweekly
- Available in the following forms:
  - Prefilled, single-dose, disposable pens
  - Syringes in 2 doses/concentrations:
    - 75 mg or 150 mg alirocumab in 1 mL solution
Evolocumab: Dosing and Administration

• For patients with HoFH, the recommended dose is 420 mg SC once per month
• For other patients, including those with HeFH, the recommended dose is either 140 mg biweekly (2x/month) or 420 mg monthly
• Available in the following forms:
  • Single-use prefilled autoinjector (SureClick) containing 140 mg of evolocumab in 1 mL solution
  • Single-use on-body infusor (Pushtronex) for monthly injection with prefilled cartridges containing 420 mg evolocumab in 3.5 mL of solution

Cardiac Outcomes Studies and Lipid-Lowering Drugs

**IMPROVE–IT**
- Ezetimibe in combination with simvastatin in patients with recent acute coronary syndrome (ACS)

**FOURIER**
- Evolocumab in patients with established CVD on statin therapy

**ODYSSEY OUTCOMES**
- Alirocumab in patients 1–12 months out from an ACS event
IMPROVE-IT Trial Results

• Goal: study the safety and efficacy of ezetimibe in combination with simvastatin compared with simvastatin alone in reducing CV events in patients at high risk

• Multicenter, randomized, double-blind, active-control trial

• Patients randomized to receive ezetimibe 10 mg/simvastatin 40 mg (n=9067) or placebo/simvastatin 40 mg (n=9077)
  • Patients were followed for 6 years

IMPROVE-IT Trial Results

- Ezetimibe/simvastatin reduced LDL-C compared with placebo/simvastatin, 53.7 mg/dL versus 69.5 mg/dL ($P<0.001$)

- Ezetimibe/simvastatin compared with placebo/simvastatin significantly reduced the risk of:
  - Primary end point (CV death/MI/unstable angina (UA)/coronary revascularization/stroke/moderate or severe bleeding): 32.7% versus 34.7% (HR, 0.94; 95% CI, 0.89-0.99; $P=0.016$)
    - MI: 13.1% versus 14.8% ($P=0.002$)
    - Stroke: 4.2% versus 4.8% ($P=0.05$)
    - CVD/MI/stroke: 20.4% versus 22.2% ($P=0.003$)

FOURIER Trial Results

• Goal: evaluate the efficacy and safety of evolocumab, a PCSK9 inhibitor, among subjects with elevated CV risk on statin therapy
• Randomized, parallel, double-blind, placebo-controlled trial
• Patients assigned to evolocumab 140 mg SC q2 weeks or 420 mg monthly (n=13,784) versus placebo q2 weeks (n=13,780)

FOURIER Trial Results

• Evolocumab reduced LDL-C by up to 59% compared with placebo ($P<0.001$)
• Evolocumab, compared with placebo, significantly reduced the risk of:
  • Primary end point (composite of CV death, MI, stroke, hospitalization for UA, or coronary revascularization)
    • 9.8% versus 11.3% (HR, 0.85; 95% CI, 0.79-0.92; $P<0.001$)
  • Key secondary end point (composite of CV death, MI, or stroke)
    • 5.9% versus 7.4% (HR, 0.80; 95% CI, 0.73-0.88; $P<0.001$)

FOURIER Trial: Prior MI Subset

- In the FOURIER Trial, 22,351 patients had prior MI
  - MI within 2 years prior: 8402 patients (38%)
  - Multiple MIs (≥2): 5285 patients (24%)
  - Residual, multivessel CAD: 5618 patients (25%)
- Evolocumab lowered LDL-C and reduced the risk of CV death, MI, stroke, hospitalization for UA, or coronary revascularization in high-risk patients


CAD, coronary artery disease
## FOURIER Trial: Prior MI Subset

<table>
<thead>
<tr>
<th>Patient Subset (number of patients)</th>
<th>Relative Risk Reduction, Primary Endpoint</th>
<th>Hazard Ratio (range)</th>
<th>Absolute Risk Reduction at 3 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI within 2 years prior (8402)</td>
<td>20%</td>
<td>0.80 (0.71-0.91)</td>
<td>3.4%</td>
</tr>
<tr>
<td>≥2 MIs (5285)</td>
<td>18%</td>
<td>0.82 (0.72-0.93)</td>
<td>3.7%</td>
</tr>
<tr>
<td>Residual, multivessel CAD (5618)</td>
<td>21%</td>
<td>0.79 (0.69-0.91)</td>
<td>3.6%</td>
</tr>
</tbody>
</table>

Preliminary ODYSSEY Outcomes Topline Results

• Data presented at the American College of Cardiology 2018 Meeting
• Random, placebo-controlled trial with nearly 19,000 patients
• No safety signal with alirocumab other than injection-site reactions (with treatment extending >3 years in some patients)

Preliminary ODYSSEY Outcomes
Topline Results

- Preliminary, primary outcome (major adverse cardiac events):
  - Alirocumab (9.5%) versus placebo (11.1%) (HR, 0.85; 95% CI, 0.78-0.93; \( P = 0.0003 \))
    - Coronary heart disease death: 2.2% versus 2.3% (\( P = 0.38 \))
    - MI: 6.6% versus 7.6% (\( P = 0.006 \))
    - Ischemic stroke: 1.2% versus 1.6% (\( P = 0.01 \))
    - UA: 0.4% versus 0.6% (\( P = 0.02 \))

American College of Cardiology. ODYSSEY Outcomes: results suggest use of PCSK9 inhibitor reduces CV events, LDL-C in ACS patients.
PCSK9 Inhibitors: Adverse Events

- Both alirocumab and evolocumab are generally well tolerated.
- Adverse events are typically limited to nasopharyngitis, injection-site reactions, arthralgia, myalgia, and headache.
- Concerns about the impact of lowering LDL-C levels have been mitigated based on subanalysis of FOURIER trial results.
  - LDL-C levels were reduced to <7.7 mg/dL in some patients.
  - No safety concerns observed over the ≥2-year study period.

Therapy Recommendations

• Several professional organizations and associations have updated existing guidelines and recommendations based on the efficacy and safety of PCSK9 inhibitors
  • National Lipid Association
  • American College of Cardiology
  • American Association of Clinical Endocrinologists/American College of Endocrinology

2017 NLA Expert Panel
Recommendations on PCSK9 Inhibitors

Recommendations for 3 patient populations:

1. ASCVD
2. LDL-C ≥190 mg/dL (including polygenic hypercholesterolemia, HeFH, and HoFH phenotype)
3. Very high-risk/statin intolerance

<table>
<thead>
<tr>
<th>Disorder</th>
<th>LDL-C/Non–HDL-C (mg/dL) Threshold</th>
<th>Strength/Quality of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASCVD + additional RFs</td>
<td>≥70 / ≥100</td>
<td>A/High</td>
</tr>
<tr>
<td>Progressive ASCVD</td>
<td>≥70 / ≥100</td>
<td>B/Moderate</td>
</tr>
<tr>
<td>LDL-C ≥190, age 40-79 years, No uncontrolled RFs or key additional risk markers</td>
<td>≥100 / ≥130</td>
<td>B/Moderate</td>
</tr>
<tr>
<td>LDL-C ≥190, age 40-79 years, Uncontrolled RFs or key additional risk markers</td>
<td>≥70 / ≥100</td>
<td>B/Moderate</td>
</tr>
<tr>
<td>LDL-C ≥190, age 18-39 years, Uncontrolled RFs, key additional risk markers, or FH causing mutation</td>
<td>≥100 / ≥130</td>
<td>E/Low</td>
</tr>
<tr>
<td>HoFH phenotype</td>
<td>≥70 / ≥100</td>
<td>B/Moderate</td>
</tr>
<tr>
<td>ASCVD + statin intolerance</td>
<td>Clinical judgment</td>
<td>C/Low</td>
</tr>
</tbody>
</table>

Potential Barriers to PCSK9 Inhibitor Access

• NLA survey reported initial denial rates of >85%

• Approval rates were higher for patients with heart failure (43%) compared with ASCVD (36%)

• Documentation reported to be the most critical factor in facilitating approvals

(N.B.—study was conducted prior to new indication for evolocumab)

Approximately one-third of PCSK9 inhibitor prescriptions were dispensed.

Less than half of all prescribed PCSK9 inhibitors were approved by payers.

Rx abandonment most associated with higher co-pay costs.

Higher rates of approval when dispensed at a mail-order or specialty pharmacy.

Additional Potential Barriers to Access

• Approaches used by payers to manage access to costly medications
  • Prior authorization
  • Step therapy
    • Also referred to as “fail first” therapy
• Burdensome appeals process
• Formulary restrictions

Prior Authorization Template

- 3 sections
  - Prescriber information
  - Patient history
  - Current therapy

Prior Authorization Template

## PCSK9 Inhibitor Prior Authorization Form

To be completed by Prescriber

<table>
<thead>
<tr>
<th>Prescriber Information</th>
<th>Patient Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prescriber’s NPI:</td>
<td>Patient’s Medical ID #</td>
</tr>
<tr>
<td>Prescriber Name:</td>
<td>Patient Name:</td>
</tr>
<tr>
<td>Phone #:</td>
<td>Patient DOB:</td>
</tr>
<tr>
<td>Fax #:</td>
<td>Primary ICD Diagnosis code:</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prescription Information</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug Requested:</td>
<td>Frequency of Dosing:</td>
</tr>
<tr>
<td>☐ New therapy ☐ Continuation</td>
<td>Quantity Requested:</td>
</tr>
</tbody>
</table>

Prior Authorization Template

<table>
<thead>
<tr>
<th>Clinical Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 18 years or older</td>
</tr>
<tr>
<td>Patient pregnant</td>
</tr>
<tr>
<td>Is there a diagnosis of clinical ASCVD, heterozygous familial hypercholesterolemia (HeFH), or homozygous hypercholesterolemia (HoFH)?</td>
</tr>
<tr>
<td>Is taking his/her maximally tolerated statin dose. *</td>
</tr>
<tr>
<td><em>Maximally tolerated statin therapy is defined as the highest tolerated intensity and frequency of a statin, even if the dose is zero.</em> This is preferably the guideline-recommended intensity of statin, but may of necessity be a lower intensity dose or reduced frequency of statin dosing, or even no statin at all. Statin intolerance can be defined as unacceptable adverse effects that resolve with discontinuation of therapy and recur with re-challenge of 2 to 3 statins, preferably ones that use different metabolic pathways with 1 of which being prescribed at the lowest approved dose.</td>
</tr>
<tr>
<td>Has HeFH. *</td>
</tr>
<tr>
<td><em>HeFH is defined as untreated LDL-C ≥160 mg/dL for children and ≥190 mg/dL for adults and with 1 first-degree relative similarly affected or with premature coronary artery disease or with positive genetic testing for an LDL-C-raising gene defect (LDL-R, Apo-B, or PCSK9).</em></td>
</tr>
<tr>
<td>Has HoFH. *</td>
</tr>
<tr>
<td><em>HoFH is defined as LDL-C ≥400 mg/dL and ≥1 parent with clinically diagnosed FH, positive genetic testing for two LDL-C-raising gene defects (LDL-R, apoB, or PCSK9), or autosomal-recessive FH.</em></td>
</tr>
<tr>
<td>Has Clinical ASCVD. *</td>
</tr>
<tr>
<td>*Clinical ASCVD includes acute coronary syndromes, history of MI, stable or unstable angina, coronary or other arterial revascularization, stroke, TIA, or peripheral arterial disease presumed to be of atherosclerotic origin, as well as other forms of atherosclerotic vascular disease including significant atherosclerosis of the coronary, carotid, iliofemoral, circumflex, and the aorta. Documentation of ASCVD requiring additional lipid lowering.” (check all that apply)</td>
</tr>
<tr>
<td>□ Acute Coronary Syndrome □ History of MI</td>
</tr>
<tr>
<td>□ Stable or Unstable Angina □ Coronary revascularization</td>
</tr>
<tr>
<td>□ Other arterial revascularization □ Stroke □ TIA</td>
</tr>
<tr>
<td>□ PAD</td>
</tr>
<tr>
<td>Extensive Subclinical atherosclerosis:</td>
</tr>
</tbody>
</table>
  - □ Coronary Circulation |
  - □ Carotid Circulation |
  - □ Iliofemoral Circulation |
  - □ Atherosclerosis of the aorta |

Prior Authorization Template

### Requires additional LDL lowering

*Patients with clinical ASCVD, HeFH, or HoFH who may require additional lowering of LDL-C include those with less than expected percent reduction in LDL-C or residual absolute levels of LDL-C, non-HDL-C, or apoB that exceed goals for atherogenic lipoproteins as specifically defined in any of the current guidelines for these very high-risk and “extreme risk” populations.*

<table>
<thead>
<tr>
<th>Baseline LDL:</th>
<th>Current LDL:</th>
</tr>
</thead>
</table>

### Current Lipid Lowering Medication and Amount

- **Statin**: Dose: 
- **Other LLM’s**: Dose: 
- **Ezetimibe**: Dose:  
- **LDL Apheresis**: Yes or No

### In my professional opinion, this patient requires the medication prescribed. The information provided supports this opinion.

Prescriber Signature: ____________________________ Date: ____________________________

Which Non-statin to Use?

- Primary goal: LDL reduction for patients at the highest risk
- Use recommendations from guidelines as applicable for patient
- Patient status, particularly if there are risks for ASCVD
- Emphasize adherence to lifestyle recommendations and to prescribed therapy
  - Coordinate with other health care professionals
- Discuss economic issues with patients
  - If cost is a major factor, it will affect compliance/adherence
  - When available, use manufacturer financial assistance programs
Case Study

• 54-year-old man with FH
  • BMI: 31.7
  • New LDL-C: ≈195 mg/dL
  • Smoking down to 0.5 pack/day
  • Diet modifications made
  • Exercise: walking ≈30 minutes, 3 or 4 days/week
  • Meds: atorvastatin 80 mg qd, lisinopril 20 mg qd, ezetimibe

What recommendations for the patient?
Summary

• Statin therapy is not feasible for every patient
• Clinical guidelines provide direction on the use of non-statins, including ezetimibe and PCSK9 inhibitors
• Obtaining payer approval for a PCSK9 inhibitor will require coordination of the health care team and clear documentation for payer processes
• Preliminary clinical trial data for alirocumab may result in updated indications
Additional Resources

• National Lipid Association (www.lipid.org)
  • Resources for patients and clinicians
• The FH Foundation (thefhfoundation.org)
  • Resources for patients and clinicians

  • Includes template forms for prior authorization and appeal letter
The National Lipid Association (NLA) published recommendations for patient-centered management of dyslipidemia in 2015. Those recommendations propose treatment goals for non–HDL-C and LDL-C based on 4 risk categories: Low, Moderate, High, and Very High. Treatment goals for the Low, Moderate, and High risk categories are the same. Which of the following represents the NLA treatment goals for LDL-C?

A. Low, Moderate, High: <70 mg/mL; Very High: <70 mg/mL
B. Low, Moderate, High: <70 mg/mL; Very High: <100 mg/mL
C. Low, Moderate, High: <100 mg/mL; Very High: <100 mg/mL
D. Low, Moderate, High: <100 mg/mL; Very High: <70 mg/mL
Statin and nonstatin combination therapy may improve lipid-lowering efficacy and may improve cardiovascular outcomes. Which of the following combination therapies was studied in the IMPROVE-IT trial and demonstrated reductions in cardiovascular outcomes?

A. Colestipol and simvastatin
B. Ezetimibe and simvastatin
C. Evolocumab and simvastatin
D. Lomitapide and simvastatin
Post-test Question 3

Which of the following is TRUE regarding indications for PCSK9 inhibitors?

A. Alirocumab is approved for either monotherapy or combination therapy for patients with heterozygous familial hypercholesterolemia (HeFH), homozygous familial hypercholesterolemia (HoFH), or clinical atherosclerotic cardiovascular disease (ASCVD).

B. Alirocumab is approved for combination therapy with a maximally tolerated statin for patients with HeFH, HoFH, or clinical ASCVD.

C. Evolocumab is indicated to reduce the risk of myocardial infarction, stroke, and coronary revascularization in adults with established CVD.

D. Evolocumab is just approved for combination therapy for patients with HeFH or clinical ASCVD.
BN is a 27-year-old woman diagnosed at age 13 years with HoFH. Current lipid medications are lovastatin, colesevelam, and ezetimibe. BN adheres to a healthy lifestyle with a low-fat diet and regular exercise. However, BN’s LDL-C levels remain high with the most recent level of 213 mg/dL. With the HoFH diagnosis, her family history of cardiovascular disease, and the recent increase in LDL-C despite high-dose lipid-lowering drugs, BN asks her physician about the new PCSK9 inhibitors. Which of the following would be an appropriate treatment option for BN?

A. Alirocumab 75 mg subcutaneously biweekly (2x/month)
B. Alirocumab 300 mg subcutaneously q4 weeks
C. Evolocumab 300 mg subcutaneously q4 weeks
D. Evolocumab 420 mg subcutaneously q4 weeks
Thank you for your attention and participation!