The Role of Non-Statin Therapies for Management of ASCVD Risk

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Learning Objectives

- Review the latest guidelines and recommendations on cholesterol management
- Identify potential cholesterol-lowering therapies beyond statins and know when to utilize
- Recognize the indications for PCSK9 inhibitor therapy
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Case Study

- John, 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 US
  - 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: *APOB*, *LDLR*, or *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

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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

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### 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


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### 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

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2018 AHA/ACC Cholesterol Treatment Guidelines

Statin and Non-statin Benefit Groups

Factors to Consider

Optional Interventions to Consider


Patients ≥ 21 years of age with ASCVD, reduce LDL-C with high-intensity statin therapy or maximally tolerated dose

Patients ≥21 years of age with very high risk ASCVD use LDL-C threshold of 70 mg/dL to consider adding non-statin to statin therapy

Patients ≥21 years of age with severe FH, baseline LDL-C ≥190 mg/dL without calculating 10-year ASCVD risk, begin high-intensity statin therapy

Patients ≥ 21 years of age with diabetes and LDL-C ≥ 70 mg/dL start moderate-intensity statin without calculating 10-year ASCVD risk

Patients 40–75 years of age without diabetes with LDL-C ≥ 70 mg/dL with a 10-year ASCVD risk of:

≥7.5% discuss treatment options, start moderate-intensity statin, if favored

>7.5% - 19.9% risk enhancing factors favor starting statin; if statin decision is uncertain measure coronary artery calcium (CAC)

Patients 40–75 years of age with diabetes with LDL-C ≥ 70 mg/dL with a 10-year ASCVD risk of:

≥7.5% discuss treatment options, start moderate-intensity statin, if favored

>7.5% - 19.9% risk enhancing factors favor starting statin; if statin decision is uncertain measure coronary artery calcium (CAC)

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

## 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

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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 Non–HDL-C, mg/mL</th>
<th>Consider Drug Therapy Non–HDL-C, mg/mL</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</td>
<td>LDL-C, mg/mL</td>
<td>Non-HDL-C, mg/mL</td>
</tr>
<tr>
<td></td>
<td>Diabetes (type 1 or 2)</td>
<td></td>
<td>&lt;130</td>
</tr>
<tr>
<td></td>
<td>0 or 1 other major ASCVD RF and</td>
<td></td>
<td>&lt;100</td>
</tr>
<tr>
<td></td>
<td>No evidence of end-organ damage</td>
<td></td>
<td>≥130</td>
</tr>
<tr>
<td></td>
<td>Chronic kidney disease (CKD) stage 3B or 4</td>
<td></td>
<td>≥100</td>
</tr>
<tr>
<td></td>
<td>LDL-C of ≥190 mg/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Quantitative risk score reaching the high-risk threshold</td>
<td></td>
<td></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>
<tbody>
<tr>
<td>Very high</td>
<td>ASCVD</td>
<td>LDL-C, mg/mL</td>
<td>Non-HDL-C, mg/mL</td>
</tr>
<tr>
<td></td>
<td>Diabetes (type 1 or 2)</td>
<td></td>
<td>&lt;100</td>
</tr>
<tr>
<td></td>
<td>≥2 other major ASCVD RFs or</td>
<td></td>
<td>&lt;70</td>
</tr>
<tr>
<td></td>
<td>Evidence of end-organ damage*</td>
<td></td>
<td>≥100</td>
</tr>
</tbody>
</table>

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

ejGFR, estimated glomerular filtration rate

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Non-statin Therapies

Classes of Drugs

1. Bile acid binding resins (eg, cholestyramine, colesevelam)
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
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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

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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>
</tr>
<tr>
<td>8,179 patients</td>
<td>LDL-C ≥40 mg/dL and ≤100 mg/dL and on stable statin therapy for ≥24 weeks prior to qualifying measurements for randomization</td>
</tr>
<tr>
<td>Duration: 7 years (2011-2018)</td>
<td></td>
</tr>
<tr>
<td>Primary Endpoint: Composite of CV death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina</td>
<td></td>
</tr>
</tbody>
</table>

Non-Statin Therapies (con’t) REDUCE-IT Trial

<table>
<thead>
<tr>
<th>Results</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ Primary endpoint event occurrences: Icosapent ethyl: <strong>17.2%</strong> Placebo: <strong>22.0%</strong> Hazard ratio, 0.75; 95% confidence interval, 0.68 to 0.83; P&lt;0.001</td>
<td>▪ 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</td>
</tr>
<tr>
<td>▪ Effects on Lipids: ▪ Median change in triglycerides from baseline to 1 year, ↓18.3% in icosapent ethyl group vs ↑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 ↑3.1% in the icosapent ethyl group vs ↑10.2% in placebo</td>
<td>▪ Low rate of adverse effects, including: ▪ Small but significant increase in atrial fibrillation/flutter ▪ Non-statistically significant increase in serious bleeding</td>
</tr>
</tbody>
</table>


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?
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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


Adapted image courtesy of Louis Kuritzky, MD.

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**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**

- Hepatocytes
- Magnified Hepatocyte
- Degraded LDL
- Degraded LDL Receptor
- Degraded LDL
- Blood Vessel

Adapted image courtesy of Louis Kuritzky, MD.

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**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

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**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 ($\geq2$): 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)

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**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)


**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

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
The Role of Non-Statin Therapies for Management of ASCVD Risk

2017 NLA Recommendations on PCSK9 Inhibitors

<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)

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

Summary

- Statin therapy is not feasible for every patient
- Clinical guidelines provide direction on the use of non-statin, 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