Reducing Cardiovascular Risk Through Non-Statins

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Joseph Saseen, PharmD
Target Audience: Pharmacists
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Disclosures

Dr. Saseen and Dr. Birtcher have no conflicts of interest to disclose.

The American Pharmacists Association is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.
Learning Objectives

1. Discuss the evidence evaluating the efficacy and safety of non-statin therapies in patients with dyslipidemia, including the impact on long-term cardiovascular outcomes.

2. Describe appropriate use of non-statin therapies based on recommendations from authoritative national organizations.

3. Identify patients who may be appropriate for treatment with non-statin therapies.

4. Develop monitoring strategies to assess the efficacy and toxicity of PCSK9 inhibitors.
1. Assessment Question

Which two non-statin medications have been shown to reduce the risk of CV events when added to statin therapy in two different large-scale, long-term clinical trials?

A. Colesevelam and Alirocumab
B. Colesevelam and Evolocumab
C. Ezetimibe and Alirocumab
D. Ezetimibe and Evolocumab
2. Assessment Question

Which of the following is the threshold for adding a nonstatin medication to a statin, according to the 2017 American College of Cardiology Expert Consensus Decision Pathway in a 30 year-old patient with a baseline LDL-C of 230 mg/dL and no other relevant medical history?

A. LDL-C ≥ 70 mg/dL
B. LDL-C ≥ 100 mg/dL
C. Non-HDL-C ≥ 100 mg/dL
D. LDL-C reduction of 40% after 4 weeks of starting a moderate intensity statin
3. Assessment Question

According to the 2017 American College of Cardiology Expert Consensus Decision Pathway, which of the following is recommended in a 60-year-old primary prevention patient with diabetes, hypertension, who smokes, and has a LDL-C of 120 mg/dL while treated with ezetimibe and rosuvastatin 5 mg daily (maximally tolerated dose)?

A. Alirocumab  
B. Colesevelam  
C. Evolocumab  
D. No additional therapy is recommended
4. Assessment Question

According to the 2017 American College of Cardiology Expert Consensus Decision Pathway, which of the following is an appropriate efficacy measure for the addition of evolocumab to maximally tolerated statin therapy?

A. Assess for changes in cognitive function
B. Assess for injection site reactions and rash
C. Assess LDL-C in 1-3 months after initiating the PCSK9 inhibitor
D. Assess LDL-C in 3-12 months after initiating the PCSK9 inhibitor
Hypercholesterolemia
Treatment and the Evidence for
Non-Statin Therapy

Joseph Saseen, PharmD, BCPS, BCACP, CLS
Professor and Vice Chair
University of Colorado Skaggs School of Pharmacy
Expert Recommendations

- 2013: ACC-AHA Guidelines
- 2014: NLA Recommendations
- 2016: ACC Expert Consensus Decision Pathway
- 2017: NLA PCSK9 inhibitor recommendations
- 2017: ACC Expert Consensus Decision Pathway
- 2018: Updated ACC-AHA Guidelines

ACC-AHA = American College of Cardiology/American Heart Association
NLA = National Lipid Association
PCSK9 = Proprotein Convertase Subtilisin/Kexin Type 9
Clinical ASCVD

LDL-C ≥190 mg/dL

Diabetes
Type 1 or 2
Aged 40-75 yrs

≥7.5% estimated 10-yr ASCVD risk
and aged 40-75 yrs

2013 ACC-AHA Guidelines: Statin Benefit Groups

- High-intensity statin if aged ≤75 yrs
- Moderate-intensity statin if aged >75 yrs or not candidate for high-intensity

High-intensity statin

Moderate-intensity statin

High-intensity statin if 10-year ASCVD risk ≥7.5%

Moderate-to-high intensity statin

### 2013 ACC-AHA Guideline: Statin Intensity

<table>
<thead>
<tr>
<th>High-Intensity</th>
<th>Moderate-Intensity</th>
<th>Low-Intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily dose lowers LDL-C on average by ~ ≥50%</td>
<td>Daily dose lowers LDL-C on average by ~30% to &lt;50%</td>
<td>Daily dose lowers LDL-C on average by &lt;30%</td>
</tr>
</tbody>
</table>

- **Atorvastatin (40)–80 mg**
- **Rosuvastatin 20 (40) mg**

- **Atorvastatin 10 (20) mg**
- **Rosuvastatin (5) 10 mg**
- **Simvastatin 20–40 mg**
- **Pravastatin 40 (80) mg**
- **Lovastatin 40 mg**
- **Fluvastatin XL 80 mg**
- **Fluvastatin 40 mg bid**
- **Pitavastatin 2–4 mg**

- **Simvastatin 10 mg**
- **Pravastatin 10–20 mg**
- **Lovastatin 20 mg**
- **Fluvastatin 20–40 mg**
- **Pitavastatin 1 mg**

Specific statins and doses are noted in **bold** that were evaluated in randomized controlled trials (RCTs). Statins and doses that are approved by the U.S. FDA but were not tested in the RCTs reviewed are listed in **italics**.

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<table>
<thead>
<tr>
<th>Drugs Affecting Lipoprotein Metabolism</th>
<th>LDL-C</th>
<th>HDL-C</th>
<th>TG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statins</td>
<td>↓18-55%</td>
<td>↑5-15%</td>
<td>↓7-30%</td>
</tr>
<tr>
<td>Bile acid sequestrants</td>
<td>↓15-30%</td>
<td>↑3-5%</td>
<td>↑0-10%</td>
</tr>
<tr>
<td>Nicotinic acid</td>
<td>↓5-25%</td>
<td>↑15-35%</td>
<td>↓20-50%</td>
</tr>
<tr>
<td>Fibric acids</td>
<td>↓5-↑20%</td>
<td>↑10-20%</td>
<td>↓20-50%</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>↓13-20%</td>
<td>↑3-5%</td>
<td>↓5-11%</td>
</tr>
<tr>
<td>Omega-3 fatty acids</td>
<td>↓6-↑25%</td>
<td>↓5-↑7%</td>
<td>↓19-44%</td>
</tr>
<tr>
<td>PCSK9 inhibitors</td>
<td>↓40-72%</td>
<td>↑0-10%</td>
<td>↓0-17%</td>
</tr>
</tbody>
</table>

→ Primarily for LDL-C lowering

Ezetimibe – Mechanism of Action

Liver Biosynthesis → Extrahepatic Tissues

Intestinal Absorption → Dietary Cholesterol

Enterohepatic Circulation

Intestinal Lumen

Excretion

Ezetimibe

IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT)

- Double-blind trial in 18,144 patients with acute coronary syndrome, age \geq 50\ yr with a high CV risk feature, LDL-C 50-125\ mg/dL (50-100\ if on therapy)
- Randomized to simvastatin 40\ mg or ezetimibe/simvastatin 10/40\ mg for 4.9\ yr
- Primary endpoint: CV death, MI, hospitalization for unstable angina, coronary revascularization, stroke
- Mean LDL-C values
  - Simvastatin alone 69.9\ mg/dL
  - Ezetimibe/simvastatin 53.2\ mg/dL

IMPROVE-IT: Primary Endpoint

- 7-yr event rates,
  - Simvastatin alone   34.7%
  - Ezetimibe /simvastatin  32.7%

5.4% RRR
HR 0.936 (95% CI, 0.89-0.99)
P=0.016

### IMPROVE-IT: Safety

<table>
<thead>
<tr>
<th>Adverse Effects (%)*</th>
<th>Simvastatin (N=9077)</th>
<th>Simvastatin/Ezetimibe (N=9067)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT, AST, or both ≥3 × ULN</td>
<td>2.3</td>
<td>2.5</td>
</tr>
<tr>
<td>Cholecystectomy</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Gallbladder-related adverse events</td>
<td>3.5</td>
<td>3.1</td>
</tr>
<tr>
<td>Rhabdomyolysis</td>
<td>0.2</td>
<td>0.1</td>
</tr>
<tr>
<td>Myopathy</td>
<td>0.1</td>
<td>0.2</td>
</tr>
<tr>
<td>Rhabdomyolysis or myopathy</td>
<td>0.3</td>
<td>0.3</td>
</tr>
<tr>
<td>Rhabdomyolysis, myopathy, myalgia with creatine kinase elevation ≥5 × ULN</td>
<td>0.6</td>
<td>0.6</td>
</tr>
<tr>
<td>Cancer</td>
<td>10.2</td>
<td>10.2</td>
</tr>
<tr>
<td>Death from Cancer</td>
<td>3.6</td>
<td>3.8</td>
</tr>
</tbody>
</table>

*all p=ns between groups*
Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitors

PCSK9 Inhibitors: Role in Therapy

- Alirocumab and Evolocumab FDA approval:
  - Fully human monoclonal antibodies
  - Adjunct to diet and maximally tolerated statin therapy for adults with heterozygous familial hypercholesterolemia (FH) or clinical ASCVD, who require additional lowering of LDL-C
  - Evolocumab also approved for homozygous FH, to prevent CV events in ASCVD, and for primary hyperlipidemia as monotherapy

<table>
<thead>
<tr>
<th></th>
<th><strong>Dosing</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alirocumab</strong></td>
<td>75 mg subcutaneous every 2 weeks increase to 150 mg if needed, or 300 mg once monthly</td>
</tr>
<tr>
<td><strong>Evolocumab</strong></td>
<td>140 subcutaneous every 2 weeks or 420 mg once monthly</td>
</tr>
</tbody>
</table>
Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER)

- Double-blind trial in 27,564 patients with ASCVD
- Age 40-85 yr, and LDL-C ≥70 mg/dL or non-HDL-C ≥100 mg/dL
- On optimal (high-intensity preferred, minimum atorvastatin 20 mg daily or equivalent) therapy
- Randomized to placebo or evolocumab for 2.2 yr
- Primary endpoint:
  - CV death, MI, stroke, hospitalization for unstable angina, or coronary revascularization

## FOURIER – Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Evolocumab N=13,784</th>
<th>Placebo N=13,780</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus (%)</td>
<td>36.7</td>
<td>36.5</td>
</tr>
<tr>
<td>Statin use (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• High intensity</td>
<td>69.5</td>
<td>69.1</td>
</tr>
<tr>
<td>• Moderate intensity</td>
<td>30.2</td>
<td>30.7</td>
</tr>
<tr>
<td>• Low intensity/unknown</td>
<td>0.3</td>
<td>0.2</td>
</tr>
<tr>
<td>Ezetimibe (%)</td>
<td>5.3</td>
<td>5.2</td>
</tr>
<tr>
<td>Other cardiovascular medications (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Antiplatelet medication</td>
<td>92.7</td>
<td>92.0</td>
</tr>
<tr>
<td>• Beta-blocker</td>
<td>75.8</td>
<td>75.4</td>
</tr>
<tr>
<td>• ACEi or ARB, aldosterone antagonist, or both</td>
<td>78.4</td>
<td>77.9</td>
</tr>
<tr>
<td>Baseline LDL-C (mg/dL)</td>
<td>92</td>
<td>92</td>
</tr>
<tr>
<td>Mean LDL-C at 48 weeks (mg/dL)</td>
<td>30</td>
<td>89</td>
</tr>
</tbody>
</table>

FOURIER: Results

**15% RRR**

HR 0.85 (95% CI, 0.79-0.92)

P<0.0001

**Patients with Primary Endpoint (%)**

<table>
<thead>
<tr>
<th>Month</th>
<th>Placebo</th>
<th>Evolocumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>12.6%</td>
<td>14.6%</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>36</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FOURIER: Landmark Analysis

16% RRR
HR 0.84 (95% CI, 0.74-0.96)
P=0.008

25% RRR
HR 0.75 (95% CI, 0.66-0.85)
P<0.00001

FOURIER: Lower LDL-C was better quartile of baseline LDL-C and treatment arm

![Graph showing the relationship between achieved LDL-C and patients with primary endpoint. The graph indicates a positive correlation, with a p-value of <0.0001. The data points for Placebo and Evolocumab are shown, with Placebo in blue and Evolocumab in red. The graph also shows the quartile markers and the trend line.]
FOURIER: Safety

<table>
<thead>
<tr>
<th>Adverse events (%)</th>
<th>Evolocumab (N=13,769)</th>
<th>Placebo (N=13,756)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Any</td>
<td>77.4</td>
<td>77.4</td>
</tr>
<tr>
<td>• Serious</td>
<td>24.8</td>
<td>24.7</td>
</tr>
<tr>
<td>• Injection-site reaction*</td>
<td>2.1</td>
<td>1.6</td>
</tr>
<tr>
<td>• Treatment-related leading to stopping study drug</td>
<td>1.6</td>
<td>1.5</td>
</tr>
<tr>
<td>• Muscle related</td>
<td>5.0</td>
<td>4.8</td>
</tr>
<tr>
<td>• Cataract</td>
<td>1.7</td>
<td>1.8</td>
</tr>
<tr>
<td>• New onset diabetes</td>
<td>8.1</td>
<td>7.7</td>
</tr>
<tr>
<td>• Neurocognitive</td>
<td>1.6</td>
<td>1.5</td>
</tr>
<tr>
<td>Laboratory Abnormality (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Aminotransferase &gt;3 x upper limit of normal</td>
<td>1.8</td>
<td>1.8</td>
</tr>
<tr>
<td>• Creatine kinase &gt;5 x upper limit of normal</td>
<td>0.7</td>
<td>0.7</td>
</tr>
<tr>
<td>Binding/Neutralizing antibody production (%)</td>
<td>0.3/none</td>
<td>n/a</td>
</tr>
</tbody>
</table>

*P<0.001

Cognitive Function in FOURIER: EBBIGINGHAUS

- Prospective subgroup study in 1204 patients from FOURIER (median of 19 months)
- Cognitive function assessed using the Cambridge Neuropsychological Test Automated Battery at baseline, week 24, yearly, and at the end of the trial
- Results:
  - No significant differences in cognitive function
  - No associations between LDL-C levels and cognitive changes, even when LDL-C < 25 mg/dL

Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab (ODYSSEY Outcomes)

- Double-blind trial in 18,000 patients with recent acute coronary syndrome (ACS)
- Age ≥ 40 y, and LDL-C ≥70 mg/dL, non-HDL-C ≥100 mg/dL, or ApoB ≥80 mg/dL, on optimal therapy (high-intensity statin, or maximally tolerated dose)
- Randomized to placebo or alirocumab for at least 2 y (endpoint driven duration until 1613 primary endpoints)
- Primary endpoint: coronary heart disease death, myocardial infarction, ischemic stroke, or hospitalization for unstable angina
- Expected completion: January 2018

## 2017 NLA Expert Panel PCSK9 Inhibitor Recommendations

<table>
<thead>
<tr>
<th>Disorder</th>
<th>LDL-C/Non-HDL-C Threshold (mg/dL)</th>
<th>Strength of Evidence</th>
<th>Quality of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASCVD + additional risk factors (RF)</td>
<td>≥ 70 / ≥ 100</td>
<td>A</td>
<td>High</td>
</tr>
<tr>
<td>Progressive ASCVD</td>
<td>≥ 70 / ≥ 100</td>
<td>B</td>
<td>Moderate</td>
</tr>
<tr>
<td>LDL-C ≥190 mg/dL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Age 40-79; no uncontrolled RF or key additional risk markers</td>
<td>≥ 100 / ≥ 130</td>
<td>B</td>
<td>Moderate</td>
</tr>
<tr>
<td>• Age 40-79; uncontrolled RF or key additional risk markers</td>
<td>≥ 70 / ≥ 100</td>
<td>B</td>
<td>Moderate</td>
</tr>
<tr>
<td>• Age 18-39; uncontrolled RF or key additional risk markers or FH mutation</td>
<td>≥ 100 / ≥ 130</td>
<td>E</td>
<td>Low</td>
</tr>
<tr>
<td>Homozygous FH phenotype</td>
<td>≥ 70 / ≥ 100</td>
<td>B</td>
<td>Moderate</td>
</tr>
<tr>
<td>ASCVD + Statin intolerance</td>
<td>Clinical judgement</td>
<td>C</td>
<td>Low</td>
</tr>
</tbody>
</table>

EXPERT CONSENSUS DECISION PATHWAY

2017 Focused Update of the 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

A Report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways Endorsed by the National Lipid Association

2017 ACC ECDP: ≥ 21 years, clinical ASCVD with Comorbidities

≥50% LDL-C reduction (may consider LDL-C <70 mg/dL or non-HDL-C <100 mg/dL) on maximally tolerated statin

CLINICIAN-PATIENT DISCUSSION REGARDING TREATMENT FACTORS

Decision for no additional medication

Optional non-statin medications to consider

Consider either ezetimibe or PCSK9 inhibitor as initial non-statin agent, and addition of other agent as second if needed

≥50% LDL-C reduction (may consider LDL-C <70 mg/dL or non-HDL-C <100 mg/dL) on maximally tolerated statin

Continue to monitor adherence with treatment and LDL-C response

2017 ACC ECDP: Comorbidities

- Diabetes
- Recent (<3 mo) ASCVD event
- ASCVD event while already taking statin therapy
- Poorly controlled other major ASCVD risk factors
  - HDL-C <40 mg/dL men, <50 mg/dL women
  - Current smoking
- hs-CRP >2 mg/L
- Elevated Lp(a)
- Residual coronary artery disease with ≥40% stenosis in ≥2 large vessels
- Age ≥ 65 years
- CKD
- Symptomatic heart failure*
- Maintenance hemodialysis*
- Prior MI or non-hemorrhagic stroke
- Symptomatic PAD
- History of non-MI-related coronary revascularization


*require individualized care
### 2017 ACC ECDP: Other Recommendations

<table>
<thead>
<tr>
<th>Statin Benefit Group</th>
<th>LDL-C Threshold: %Reduction or LDL-C value (mg/dL)</th>
<th>Nonstatin Add-On Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical ASCVD</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No comorbidities</td>
<td>≥50% or &lt;70</td>
<td>Ezetimibe first, PCSK9i second</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>≥50% or &lt;70</td>
<td>Ezetimibe or PCSK9i</td>
</tr>
<tr>
<td><strong>LDL-C ≥190 mg/dL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No clinical ASCVD</td>
<td>≥50% or &lt;100</td>
<td>Ezetimibe or PCSK9i</td>
</tr>
<tr>
<td>Clinical ASCVD</td>
<td>≥50% or &lt;70</td>
<td>Ezetimibe or PCSK9i</td>
</tr>
<tr>
<td><strong>Diabetes Type 1 or 2</strong></td>
<td>10-yr ASCVD risk &lt;7.5% and no high risk markers</td>
<td>Ezetimibe†</td>
</tr>
<tr>
<td>Aged 40-75 yrs</td>
<td>≥30-49% or &lt;100</td>
<td>Ezetimibe†</td>
</tr>
<tr>
<td>Most patients</td>
<td>≥50% or &lt;100</td>
<td>Ezetimibe†</td>
</tr>
<tr>
<td><strong>≥7.5% estimated 10-yr ASCVD risk and aged 40-75 yrs</strong></td>
<td>30-49% or &lt;100</td>
<td>Ezetimibe†</td>
</tr>
<tr>
<td>No high risk markers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High risk markers</td>
<td>≥50% or &lt;100</td>
<td>Ezetimibe†</td>
</tr>
</tbody>
</table>

†May consider a bile acid sequestrant as optional alternative agent if ezetimibe intolerant and triglycerides <300 mg/dL

2017 ACC ECDP: High Risk Markers

- 10-yr ASCVD risk ≥20%
- Baseline LDL-C ≥160 mg/dL
- Poorly controlled other major risk factor
- Family history of premature ASCVD
- Subclinical atherosclerosis (e.g., coronary artery calcification)
- Elevated hs-CRP
- Other risk modifying condition (CKD, HIV, chronic inflammatory disorders)

Monitoring for Lipid-Lowering Therapy

- To assess therapeutic response and determine if at LDL-C threshold:
  - Measure LDL-C (using a fasting lipid panel) 4-12 weeks after starting or modifying therapy
- To assess ongoing adherence with therapy in patients on stable medication doses/regimens:
  - Measure LDL-C every 3-12 months
## Select Monitoring Parameters

<table>
<thead>
<tr>
<th>Class</th>
<th>Baseline Monitoring Parameters</th>
<th>Toxicity Monitoring Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statin</td>
<td>Fasting lipid panel; fasting glucose/A1C, LFTs; creatine kinase</td>
<td>Fasting glucose/A1C, LFTs (only if clinically indicated); creatine kinase (only if muscle complaints)</td>
</tr>
<tr>
<td>Bile Acid Sequestrant</td>
<td>Fasting lipid panel</td>
<td>GI symptoms</td>
</tr>
<tr>
<td>Cholesterol Absorption Inhibitor</td>
<td>Fasting lipid panel</td>
<td>LFTs (only if used with a statin)</td>
</tr>
<tr>
<td>PCSK9 Inhibitor</td>
<td>Fasting lipid panel</td>
<td>Allergic/injection site reactions</td>
</tr>
</tbody>
</table>
Navigating the Prior Authorization Process
Clinical Pearls

- Know the FDA approved indications
- Prescribe *ONLY* according to FDA indications
- Know the definitions of the disease states in the FDA indications
- Document, document, document
  - Disease state
  - Previous medications tried
  - Description of intolerances
  - Response to drug discontinuation
  - Response to drug re-challenge
Navigating the Prior Authorization Process

Manufacturer Website Resources

- Links to insurance coverage (by state, plan) – can determine formulary agent
- ICD-10 guide
- Sample letters and forms
  - Prior authorization cover letter
  - Medical necessity letter
  - Appeals letter
  - Specialist consult referral form
  - Medicare Part D coverage determination form
Navigating the Prior Authorization Process

Consolidate Efforts

- Designate someone to fill out the prior authorization forms
  - Allows expertise to develop
  - May save time
  - May increase approval rate

- Pharmacy-led intervention (n=47) compared to “usual care” (n=77)
  - Average PA process time: 0.53 ± 0.8 days versus 7.2 days ± 12.8 days (p=0.0001)
  - Average approval rate: 93% versus 68%

J Manag Care Spec Pharm 2016;22(10):1167-71
Navigating the Prior Authorization Process
Include the Patient

- Manage patient expectations, particularly with newer, more expensive medications
  - Time to navigate approval process
  - Potential for denial
  - Appeal process
  - Potential for higher co-pays even if approved

- Teach the patient to support the process
  - Statin + nonstatin adherence
  - Lab monitoring
  - Ordering process for refilling prescription for specialty meds
Specialty Pharmacies: PCSK9 inhibitor Access

- Stock biologic medications with restricted use, are high cost (e.g., PCSK9 inhibitors), or have safety concerns

- Typically specialty pharmacy services:
  - Home delivery or select in-store pickup for patients
  - Help with prior authorizations and appeals
  - Electronic prior authorization programs, such as www.covermymeds.com
  - Train patients to self-inject drugs
  - Send patient reminders
  - Call regarding refills
  - Enroll patients in patient assistance programs
Specialty Pharmacies: PCSK9 inhibitor Access

- Stock biologic medications with restricted use, are high cost (e.g., PCSK9 inhibitors), or have safety concerns

- Typically specialty pharmacy services:
  - Home delivery or select in-store pickup for patients
  - Help with prior authorizations and appeals
  - Electronic prior authorization programs, such as www.covermymeds.com
  - Train patients to self-inject drugs
  - Send patient reminders
  - Call regarding refills
  - Enroll patients in patient assistance programs
A Case-Based Approach to Define the Role of Non-Statin Therapy

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Putting It All Together

- Ask ...
  - Which statin treatment group applies to my patient?
    - Clinical ASCVD
    - Baseline LDL-C > 190 mg/dL (no ASCVD)
    - 40-75 yr (no ASCVD) + diabetes + LDL-C 70 – 189 mg/dL
    - 40-75 yr (no ASCVD or diabetes) + LDL-C 70 – 189 mg/dL + estimated 10-yr risk ≥ 7.5%
  - Which 2017 ECDP algorithm applies to my patient?

http://dx.doi.org/10.1016/j.jacc.2017.07.745
Putting It All Together

- Factors to consider
  - Adherence and lifestyle
  - Response to therapy (percentage LDL-C reduction)
    - May consider absolute LDL-C or non-HDL-C
  - Statin intolerance
  - Other risk factors
  - Clinician-patient discussion regarding potential benefits/harms, patient preferences regarding addition of non-statin

http://dx.doi.org/10.1016/j.jacc.2017.07.745
Putting It All Together

• Optional interventions to consider
  • Referral to lipid specialist or dietitian
  • Ezetimibe
    • Bile acid sequestrants if ezetimibe-intolerant + triglycerides < 300 mg/dL
  • PCSK9 inhibitors
  • Lipid specialist may consider mipomersen, lomitapide, LDL apheresis for patients with familial hypercholesterolemia

http://dx.doi.org/10.1016/j.jacc.2017.07.745
Case 1

- 48-year old man presents for follow-up in the clinic
- PMH: hyperlipidemia, chronic stable angina
- Meds: atorvastatin 20 mg/day, aspirin, metoprolol
- States adherence to medications + lifestyle modifications
- BP 128/81 mm Hg, heart rate 58 beats/min
- BMI 32 kg/m² (stable x 3 yrs)
- Lipids (mg/dL): TC 181, HDL-C 42, TG 120, LDL-C 115
- LDL-C ↓ 42% from baseline
Putting It All Together

- Ask ...
  - Which statin treatment group applies to my patient?
  - Which 2017 ECDP algorithm applies to my patient?
- Consider
  - Adherence and lifestyle
  - Response to therapy (percentage LDL-C reduction)
    - May consider absolute LDL-C or non-HDL-C
  - Statin intolerance, other risk factors
  - Clinician-patient discussion regarding potential benefits/harms, patient preferences regarding addition of non-statin
- Optional interventions?

http://dx.doi.org/10.1016/j.jacc.2017.07.745
According to the 2017 ACC ECDP, at which threshold may you consider adding nonstatin therapy for this patient?

A. LDL-C reduction of \( \leq 40\% \) from baseline
B. LDL-C \( \geq 70 \text{ mg/dL} \)
C. LDL-C \( \geq 100 \text{ mg/dL} \)
D. Non-HDL-C \( \geq 130 \text{ mg/dL} \)
E. I do not know.
According to the 2017 ACC ECDP, which of the following do you recommend?

A. The patient is intolerant to statin therapy. Stop atorvastatin.

B. The patient had less-than-anticipated response to moderate-intensity statin. Start ezetimibe.

C. Change the current statin to high-intensity statin therapy prior to considering a non-statin.

D. The clinician and patient should consider potential net ASCVD risk-reduction benefit of adding non-statin and patient preferences.

E. I do not know.
**2017 ACC ECDP: Stable ASCVD without comorbidities**

**Comorbidities:**
- Diabetes
- Recent (<3 mo) ASCVD event
- ASCVD event while already taking statin therapy
- Poorly controlled other major ASCVD risk factors
- HDL-C <40 mg/dL men, <50 mg/dL women
- Current smoking
- hs-CRP >2 mg/L
- Elevated Lp(a)
- Residual CAD + ≥40% stenosis in ≥2 large vessels
- History of non-MI-related coronary revascularization
- Age ≥ 65 years
- Prior MI or non-hemorrhagic stroke
- CKD
- Symptomatic heart failure*
- Maintenance hemodialysis*
- Symptomatic PAD

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**Diagram Details:**

- **Patients with stable clinical ASCVD without comorbidities,* on statin for secondary prevention**
- **Patient has ≥50% LDL-C reduction (may consider LDL-C <70 mg/dL or non-HDL-C <100 mg/dL) on maximally tolerated statin therapy†**
  - YES
  - NO
  - 1. Address statin adherence.
  - 2. Intensify lifestyle (may consider phytosterols).
  - 3. Increase to high-intensity statin if not already taking.
  - 4. Evaluate for statin intolerance if unable to tolerate moderate-intensity statin. Consider referral to lipid specialist if statin intolerant.
  - 5. Control other risk factors.

- **Patient has ≥50% LDL-C reduction (may consider LDL-C <70 mg/dL or non-HDL-C <100 mg/dL) on maximally tolerated statin therapy†**
  - YES
  - NO

- **CLINICIAN-PATIENT DISCUSSION FACTORS TO CONSIDER**
  - Potential for additional ASCVD risk reduction from addition of non-statin therapy to lower LDL-C (see Table 5)
  - Potential for adverse events or drug-drug interactions from addition of non-statin therapy (see Table 4)
  - Patient preferences (see Table 3)

- **Decision for no additional medication**

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**Optional non-statin medications to consider**

- Consider ezetimibe first§
- Consider adding or replacing with PCSK9 inhibitor second †

- Patient has ≥50% LDL-C reduction (may consider LDL-C <70 mg/dL or non-HDL-C <100 mg/dL) on maximally tolerated statin/other medications†
  - YES
  - NO

- **Continue to monitor adherence to medications and lifestyle, and LDL-C response to therapy.**

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2017 ACC ECDP: Stable ASCVD without comorbidities

- Same initial clinical steps across most algorithms
  - assess adherence
  - intensify lifestyle
  - increase to high-intensity statin if not already taking
  - Evaluate for statin intolerance if cannot take moderate-intensity statin
  - control other risk factors

- Ask ... Has the patient
  - achieved ≥ 50% LDL-C reduction on maximum statin?
  - achieved LDL-C < 70 mg/dL or non-HDL-C < 100 mg/dL?

- If no, consider
  - adding ezetimibe 1\textsuperscript{st}
  - adding or replacing with PCSK9 inhibitor 2nd
Case 1 – Speaker Remarks

- 48-year old man presents for follow-up in the clinic
- PMH: hyperlipidemia, chronic stable angina
- Meds: atorvastatin 20 mg/day, aspirin, metoprolol
- States adherence to medications + lifestyle modifications
- BP 128/81 mm Hg, heart rate 58 beats/min
- BMI 32 kg/m² (stable x 3 yrs)
- Lipids (mg/dL): TC 181, HDL-C 42, TG 120, LDL-C 115
- LDL-C ↓ 42% from baseline
Case 1 Tweak

- 48-year old man admitted for acute MI
- PMH: hyperlipidemia, non-STEMI (2 years ago)
- Meds: rosvuastatin 40 mg/day, aspirin, metoprolol, lisinopril
- States adherence to medications + lifestyle modifications
- BP 128/81 mm Hg, heart rate 58 beats/min
- BMI 32 kg/m² (stable x 3 yrs)
- Lipids (mg/dL): TC 181, HDL-C 42, TG 120, LDL-C 115
- LDL-C ↓ 42% from baseline
Putting It All Together

- Ask ...
  - Which statin treatment group applies to my patient?
  - Which 2017 ECDP algorithm applies to my patient?

- Consider
  - Adherence and lifestyle
  - Response to therapy (percentage LDL-C reduction)
    - May consider absolute LDL-C or non-HDL-C
  - Statin intolerance, other risk factors
  - Clinician-patient discussion regarding potential benefits/harms, patient preferences regarding addition of non-statin

- Optional interventions?

http://dx.doi.org/10.1016/j.jacc.2017.07.745
According to the 2017 ACC ECDP, which of the following do you recommend?

A. The patient has achieved the expected LDL-C reduction. No modifications to therapy are needed.

B. The patient had less-than-anticipated response to his moderate-intensity statin. Start ezetimibe.

C. Discontinue rosuvastatin. Start atorvastatin 20 mg daily + ezetimibe 10 mg daily.

D. The clinician and patient should consider potential net ASCVD risk-reduction benefit of adding non-statin and patient preferences.

E. I do not know.
Comorbidities:
- Diabetes
- Recent (<3 mo) ASCVD event
- ASCVD event while already taking statin therapy
- Poorly controlled other major ASCVD risk factors
- HDL-C <40 mg/dL men, <50 mg/dL women
- Current smoking
- hs-CRP >2 mg/L
- Elevated Lp(a)
- Residual CAD + ≥40% stenosis in ≥2 large vessels
- Age ≥ 65 years
- CKD
- Symptomatic heart failure*
- Maintenance hemodialysis*
- Prior MI or non-hemorrhagic stroke
- Symptomatic PAD
- History of non-MI-related coronary revascularization
2017 ACC ECDP: ASCVD with comorbidities

- Same initial clinical steps across most algorithms
  - assess adherence
  - intensify lifestyle
  - increase to high-intensity statin if not already taking
  - Evaluate for statin intolerance if cannot take moderate-intensity statin
  - control other risk factors
- Ask ... Has the patient
  - achieved $\geq 50\%$ LDL-C reduction on maximum statin?
  - achieved LDL-C < 70 mg/dL or non-HDL-C < 100 mg/dL?
- If no, consider
  - adding ezetimibe or PCSK9 inhibitor as initial therapy
  - adding other agent second if needed
Case 1 Tweak – Speaker Remarks

- 48-year old man admitted for acute MI
- PMH: hyperlipidemia, non-STEMI (2 years ago)
- Meds: rosvuvastatin 40 mg/day, aspirin, metoprolol, lisinopril
- States adherence to medications + lifestyle modifications
- BP 128/81 mm Hg, heart rate 58 beats/min
- BMI 32 kg/m² (stable x 3 yrs)
- Lipids (mg/dL): TC 181, HDL-C 42, TG 120, LDL-C 115
- LDL-C ↓ 42% from baseline
Case 2

- 32-year old man presents for follow-up in the clinic
- PMH: hyperlipidemia
- Med: rosuvastatin 40 mg/day
- States adherence to medications + lifestyle modifications
- Lost 10 pounds with lifestyle modifications
- LDL-C (mg/dL): baseline 284
- Lipids (mg/dL): TC 209, HDL-C 42, TG 130, LDL-C 141
Putting It All Together

- Ask ...
  - Which statin treatment group applies to my patient?
  - Which 2017 ECDP algorithm applies to my patient?

- Consider
  - Adherence and lifestyle
  - Response to therapy (percentage LDL-C reduction)
    - May consider absolute LDL-C or non-HDL-C
  - Statin intolerance, other risk factors
  - Clinician-patient discussion regarding potential benefits/harms, patient preferences regarding addition of non-statin

- Optional interventions?

http://dx.doi.org/10.1016/j.jacc.2017.07.745
According to the 2017 ACC ECDP, which of the following do you recommend?

A. Add colesevelam
B. Add ezetimibe or a PCSK9 inhibitor
C. Add lomitapide
D. Nonstatin therapy should not be considered at this time.
E. I do not know.
2017 ACC ECDP: Baseline LDL-C $\geq$ 190 mg/dL (no ASCVD)

Patients without clinical ASCVD and with baseline LDL-C $\geq$ 190 mg/dL, not due to secondary causes,* on statin for primary prevention

Patient has $\geq$50% LDL-C reduction (may consider LDL-C <100 mg/dL or non-HDL-C <130 mg/dL) on maximally tolerated statin therapy†

YES

1. Address statin adherence.
2. Intensify lifestyle (may consider phytosteresols).
3. Increase to high-intensity statin if not already taking.
4. Evaluate for statin intolerance if unable to tolerate moderate-intensity statin.‡
   Referral to lipid specialist recommended if statin intolerant.
5. Control other risk factors.
6. Consider referral to lipid specialist and RDN for all patients.§

NO

Patient has $\geq$50% LDL-C reduction (may consider LDL-C <100 mg/dL or non-HDL-C <130 mg/dL) on maximally tolerated statin therapy†

YES

CLINICIAN-PATIENT DISCUSSION FACTORS TO CONSIDER
1. Potential for additional ASCVD risk reduction from addition of non-statin therapy to lower LDL-C (see Table 5)
2. Potential for adverse events or drug-drug interactions from addition of non-statin therapy (see Table 4)
3. Patient preferences (see Table 5)

Decision for no additional medication

Optional non-statin medications to consider
- Consider either ezetimibe or PCSK9 inhibitor as initial non-statin agent, and addition of other agent second if needed¶#

Patient has $\geq$50% LDL-C reduction (may consider LDL-C <100 mg/dL or non-HDL-C <130 mg/dL) on maximally tolerated statin/other medications†

YES

1. Repeat clinician-patient discussion.
2. Add other non-statin medication(s) above.
3. Consider referral to lipid specialist and RDN.

NO

Patient has $\geq$50% LDL-C reduction (may consider LDL-C <100 mg/dL or non-HDL-C <130 mg/dL) on maximally tolerated statin/other medications†

YES

Continue to monitor adherence to medications and lifestyle, and LDL-C response to therapy.

NO

Referral to lipid specialist recommended

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http://dx.doi.org/10.1016/j.jacc.2017.07.745
2017 ACC ECDP: Baseline LDL-C $\geq 190$ mg/dL (no ASCVD)

- Same initial clinical steps across most algorithms
  - assess adherence
  - intensify lifestyle
  - increase to high-intensity statin if not already taking
  - Evaluate for statin intolerance if cannot take moderate-intensity statin
  - control other risk factors
- Ask ... Has the patient
  - achieved $\geq 50\%$ LDL-C reduction on maximum statin?
  - achieved LDL-C $< 100$ mg/dL or non-HDL-C $< 130$ mg/dL?
- If no, consider
  - adding ezetimibe or PCSK9 inhibitor as initial therapy
  - adding other agent second if needed
Case 2 – Speaker Remarks

- 32-year old man presents for follow-up in the clinic
- PMH: hyperlipidemia
- Med: rosvastatin 40 mg/day
- States adherence to medications + lifestyle modifications
- States lost 10 pounds with lifestyle modifications
- LDL-C (mg/dL): baseline 284
- Lipids (mg/dL): TC 209, HDL-C 42, TG 130, LDL-C 141
Case 3

- 62-year old man presents for follow-up in the clinic
- PMH: diabetes, HTN
- Meds: aspirin, lisinopril, atorvastatin 80 mg/day
- States adherence to medications + lifestyle modifications
- LDL-C (mg/dL): baseline 174
- Lipids (mg/dL): TC 213, HDL-C 40, TG 325, LDL-C 108
- eGFR > 60 mL/min/1.73m²
- 10-yr ASCVD risk 11.4%
Putting It All Together

- Ask ...
  - Which statin treatment group applies to my patient?
  - Which 2017 ECDP algorithm applies to my patient?

- Consider
  - Adherence and lifestyle
  - Response to therapy (percentage LDL-C reduction)
    - May consider absolute LDL-C or non-HDL-C
  - Statin intolerance, other risk factors
  - Clinician-patient discussion regarding potential benefits/harms, patient preferences regarding addition of non-statin

- Optional interventions?

http://dx.doi.org/10.1016/j.jacc.2017.07.745
According to the 2017 ACC ECDP, which of the following do you recommend?

A. Add colesevelam
B. Add ezetimibe
C. Add ezetimibe or a PCSK9 inhibitor
D. Non-statin therapy should not be considered at this time
E. I do not know
Algorithm did not change regarding the use of ezetimibe and not using PCSK9 inhibitors when 10-yr ASCVD risk ≥ 7.5% or presence of high-risk features

Clarified statements within the text of manuscript to distinguish patients with or without high risk features

- retinopathy
- CKD [eGFR <60 mL/min/1.73 m²]
- albuminuria [urinary albumin/creatinine ratio >30 mg/g]
- elevated Lp(a) [>30 mg/dL]
- hs-CRP [>2 mg/dL], or
- presence of subclinical atherosclerosis
2017 ACC ECDP: 40-75 yr (no ASCVD) + Diabetes + Baseline LDL-C 70-189 mg/dL

FIGURE 4 | Patients Aged 40-75 years without Clinical ASCVD and with Diabetes and Baseline LDL-C 70-189 mg/dL, on Statin for Primary Prevention

- Patients aged 40-75 years without clinical ASCVD and with diabetes and baseline LDL-C 70-189 mg/dL, on statin for primary prevention

1. Address statin adherence.
2. Initiate lifestyle (may consider phytosterols).
3. Evaluate for statin intolerance. If unable to tolerate moderate-intensity statin, consider referral to lipid specialist if statin intolerant.
4. Control other risk factors.

Patient has ≥50% LDL-C reduction (may consider LDL-C <100 mg/dL, or may consider non-HDL-C <130 mg/dL in patients with diabetes) on maximally tolerated statin?

- YES
  - 1. Potential for additional ASCVD risk reduction from addition of a statin therapy to lower LDL-C (see Table 5)
  - 2. Potential for adverse events or drug-drug interactions from addition of non-statin therapy (see Table 4)
  - 3. Patient preferences (see Table 5)

- NO

Optional non-statin medications to consider

For the small proportion of patients in this group with 10-year ASCVD risk <7.5% and no other high-risk features, starting with moderate-intensity statin to achieve 30-40% LDL-C reduction (may consider LDL-C <100 mg/dL, or non-HDL-C <130 mg/dL) is acceptable. If this level of LDL-C reduction is not achieved, consider increasing to high-intensity statin.

- Decision for no additional medication

- Consider statin therapy

- Continue to monitor adherence to medications and lifestyle, and LDL-C response to therapy.

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http://dx.doi.org/10.1016/j.jacc.2017.07.745
2017 ACC ECDP: 40-75 yr (no ASCVD) + Diabetes + Baseline LDL-C 70-189 mg/dL

10-yr ASCVD <7.5% without high risk features

• Acceptable to start with moderate-intensity statin to achieve 30-49% LDL-C reduction (may consider LDL-C <100 mg/dL or non-HDL-C <130 mg/dL)
• May increase to high-intensity statin, if LDL-C reduction is not achieved

For the small proportion of patients in this group with 10-year ASCVD risk <7.5% and no other high-risk features, starting with moderate-intensity statin to achieve 30-49% LDL-C reduction (may consider LDL-C <100 mg/dL or non-HDL-C <130 mg/dL) is acceptable. If this level of LDL-C reduction is not achieved, consider increasing to high-intensity statin.

Continue to monitor adherence to medications and lifestyle, and LDL-C response to therapy.

high risk features = retinopathy; CKD [eGFR <60 mL/min/1.73 m²]; albuminuria [urinary albumin/creatinine ratio >30 mg/g]; elevated Lp(a) [>30 mg/dL]; hs-CRP [>2 mg/dL], or presence of subclinical atherosclerosis

2017 ACC ECDP: 40-75 yr (no ASCVD) + Diabetes + Baseline LDL-C 70-189 mg/dL

10-yr ASCVD ≥7.5% or with high risk features

- May add non-statin medication (ezetimibe)

high risk features = retinopathy; CKD [eGFR <60 mL/min/1.73 m²]; albuminuria [urinary albumin/creatinine ratio >30 mg/g]; elevated Lp(a) >30 mg/dL; hs-CRP >2 mg/dL, or presence of subclinical atherosclerosis

2017 ACC ECDP: 40-75 yr (no ASCVD) + Diabetes + Baseline LDL-C 70-189 mg/dL

Summary

- Algorithm did not change regarding the use of ezetimibe and not using PCSK9 inhibitors
- Text continues to emphasize need to identify patients with 10-yr ASCVD risk >7.5% or with high risk features
  - May consider addition of ezetimibe for some patients
- Encourage
  - Estimation of 10-yr ASCVD risk
  - Screening for high risk features

high risk features = retinopathy; CKD [eGFR <60 mL/min/1.73 m²]; albuminuria [urinary albumin/creatinine ratio >30 mg/g]; elevated Lp(a) [>30 mg/dL]; hs-CRP [>2 mg/dL], or presence of subclinical atherosclerosis

http://dx.doi.org/10.1016/j.jacc.2017.07.745
Case 3 – Speaker Remarks

- 62-year old man presents for follow-up in the clinic
- PMH: diabetes, HTN
- Meds: aspirin, lisinopril, atorvastatin 80 mg/day
- States adherence to medications + lifestyle modifications
- LDL-C (mg/dL): baseline 174
- Lipids (mg/dL): TC 213, HDL-C 40, TG 325, LDL-C 108
- eGFR > 60 mL/min/1.73m²
- 10-yr ASCVD risk 11.4%
Case 3 Tweak– Speaker Remarks

- 62-year old man presents for follow-up in the clinic
- PMH: diabetes, HTN
- Meds: aspirin, lisinopril, atorvastatin 80 mg/day
- States adherence to medications + lifestyle modifications
- LDL-C (mg/dL): baseline 174
- Lipids (mg/dL): TC 213, HDL-C 40, TG 325, LDL-C 108
- eGFR 40 mL/min/1.73m²
- 10-yr ASCVD risk 5.8%
1. Assessment Question

Which two non-statin medications have been shown to reduce the risk of CV events when added to statin therapy in two different large-scale, long-term clinical trials?

A. Colesevelam and Alirocumab
B. Colesevelam and Evolocumab
C. Ezetimibe and Alirocumab
D. Ezetimibe and Evolocumab
2. Assessment Question

Which of the following is the threshold for adding a nonstatin medication to a statin, according to the 2017 American College of Cardiology Expert Consensus Decision Pathway in a 30 year-old patient with a baseline LDL-C of 230 mg/dL and no other relevant medical history?

A. LDL-C > 70 mg/dL
B. LDL-C > 100 mg/dL
C. Non-HDL-C > 100 mg/dL
D. LDL-C reduction of 40% after 4 weeks of starting a moderate intensity statin
3. Assessment Question

According to the 2017 American College of Cardiology Expert Consensus Decision Pathway, which of the following is recommended in a 60-year-old primary prevention patient with diabetes, hypertension, who smokes, and has a LDL-C of 120 mg/dL while treated with ezetimibe and rosvastatin 5 mg daily (maximally tolerated dose)?

A. Alirocumab
B. Colesevelam
C. Evolocumab
D. No additional therapy is recommended
4. Assessment Question

According to the 2017 American College of Cardiology Expert Consensus Decision Pathway, which of the following is an appropriate efficacy measure for the addition of evolocumab to maximally tolerated statin therapy?

A. Assess for injection site reactions and rash
B. Assess for changes in cognitive function
C. Assess LDL-C in 1-3 months after initiating the PCSK9 inhibitor
D. Assess LDL-C in 3-12 months after initiating the PCSK9 inhibitor