Your Annual Cholesterol Management Update: Reducing ASCVD Risk

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Janelle Ruisinger, PharmD
Disclosures

• Dr. Saseen and Dr. Ruisinger report no conflicts
CPE Information

• Target Audience: Pharmacists
• ACPE#: 0202-0000-19-083-L01-P
• Activity Type: Application-based
Pharmacist Learning Objectives

At the completion of this application-based activity, participants will be able to:

1. Discuss recent evidence-based updates in atherosclerotic cardiovascular disease (ASCVD) risk reduction and cholesterol management.


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

4. Describe recommendations for appropriate use of nonstatin therapies based on recommendations from authoritative national organizations.


6. Formulate patient-centered treatment plans for patients with hyperlipidemia, beyond statin therapy.
1. A 50-year-old South Asian primary prevention man has the following fasting lipid panel:
   • Total Cholesterol 245 mg/dL, LDL-C 165 mg/dL, HDL-C 30 mg/dL, TG 250 mg/dL

   Results are similar to previous values. His 10-year ASCVD risk score is 12% and he is a smoker. According to the 2018 American College of Cardiology-American Heart Association (ACC-AHA) cholesterol guidelines, which regimen is recommended?

   A. Lifestyle modifications alone
   B. Lifestyle modifications with a moderate-intensity statin
   C. Lifestyle modifications with a high-intensity statin
   D. Lifestyle modifications with a high-intensity statin and ezetimibe
2. A 70-year-old woman with a recent ischemic stroke is complaining of generalized muscle aches for the last 4 weeks. She was started on Atorvastatin 40 mg PO daily approximately 6 weeks ago. According to the ACC-AHA cholesterol guidelines, what is recommended?

A. Discontinue the Atorvastatin and start Niacin immediate release (IR) 500 mg PO BID
B. Discontinue the Atorvastatin and start Rosuvastatin 20 mg PO daily
C. Discontinue Atorvastatin as lipid lowering therapy is not indicated for this patient
D. Continue Atorvastatin 40 mg PO daily and initiate CoQ10 PO daily
Assessment Questions

3. KC is a 45-year-old man, primary prevention, heterozygous familial hypercholesterolemia (HeFH) confirmed with genetic testing, taking rosvastatin 40 mg PO daily and ezetimibe 10 mg PO daily; his LDL level today is 137 mg/dL. According to the ACC-AHA cholesterol guidelines, what is recommended?

A. Continue current lipid lowering regimen with no additions or changes
B. Initiate lifestyle modifications for 6 months then re-assess
C. Initiate 4 grams of omega-3 fatty acids PO daily
D. Initiate alirocumab 75 mg subq every 2 weeks
4. Which patient would be a good candidate for the apoC-III antisense drug?

A. A 23-year-old man, primary prevention; LDL-C 435 mg/dL, TG 75 mg/dL, Lp(a) 75 mg/dL
B. A 45-year-old woman, history of ischemic stroke; LDL-C 119 mg/dL, TG 135 mg/dL and Lp(a) 147 mg/dL
C. A 60-year-old man, primary prevention; LDL-C 127 mg/dL, TG 75 mg/dL and Lp(a) 19 mg/dL taking rosuvastatin 40 mg daily and evolocumab 140 mg SQ every 14 days
D. A 55-year-old woman, history of MI; LDL-C 64 mg/dL, TG 625 mg/dL, Lp(a) 9 mg/dL
Hypercholesterolemia: Overview of Guidelines

Joseph Saseen, PharmD
Professor and Vice Chair
University of Colorado
**Clinical ASCVD**

- LDL-C ≥190 mg/dL
- Diabetes Aged 40-75 yrs
- ≥7.5% 10-yr ASCVD risk Aged 40-75 yrs

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

**ACC-AHA 2013 Blood Cholesterol Guideline**

Evolution of Guidelines and Landmark Trials

- **NCEP ATP I** (1988)
- **NCEP ATP II** (1993)
- **NCEP ATP III** (2001)
- **NCEP ATP III** (2004)
- **ACC/AHA, 2013**
- **ACC/AHA, 2018**

**Expanded/Modified Treatment Recommendations**

- Framingham
- MRFIT
- LRC-CPPT
- Helsinki Heart Coronary Drug Project
- CLAS
- FATS, POSCH, SCORE, STARTS, Ornish, MARS, Meta-analyses (Holmes Rossouw)
- VA-HIT
- 4S
- WOSCOPS
- CARE
- LIPID
- AFCAPS/TexCAPS
- HPS
- PROVE-IT
- ASCOT-LLA
- PROSPER
- ALLHAT-LLT
- TNT
- IDEAL
- ACCORD
- JUPITER
- CTT Meta-analyses
- ENHANCE
- SHARP
- AURORA
- CORONA
- AIM HIGH
- HPS2-Thrive
- HOPE-3
- IMPROVE-IT
- FOURIER
- ODYSSEY

**Abbreviations**

NCEP ATP = National Cholesterol Education Panel Adult Treatment Panel

AHA = American Heart Association

ACC = American College of Cardiology
## ACC-AHA Evidence-Based Recommendations

### Class (Strength) of Recommendation

<table>
<thead>
<tr>
<th>Class</th>
<th>Benefit vs Risk</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Class I (Strong)</strong></td>
<td>Benefit &gt;&gt;&gt; Risk</td>
<td>Is recommended, is indicated, should be performed</td>
</tr>
<tr>
<td><strong>Class IIa (Moderate)</strong></td>
<td>Benefit &gt;&gt; Risk</td>
<td>Is reasonable, can be useful</td>
</tr>
<tr>
<td><strong>Class IIb (Weak)</strong></td>
<td>Benefit ≥ Risk</td>
<td>May/might be reasonable/considered, effectiveness unknown</td>
</tr>
<tr>
<td><strong>Class III: No Benefit (Moderate)</strong></td>
<td>Benefit = Risk</td>
<td>Is not recommended, is not useful</td>
</tr>
<tr>
<td><strong>Class III: Harm (Strong)</strong></td>
<td>Benefit &lt; Risk</td>
<td>Potentially harmful, causes harm</td>
</tr>
</tbody>
</table>

### Level (Quality) of Evidence

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Level A</strong></td>
<td>High-quality evidence from &gt; one randomized clinical trial (RCT)</td>
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<tr>
<td></td>
<td>Meta-analyses of high-quality RCTs</td>
</tr>
<tr>
<td><strong>Level B-R</strong></td>
<td>Moderate-quality evidence from &gt; one RCT</td>
</tr>
<tr>
<td></td>
<td>Meta-analyses of moderate-quality RCTs</td>
</tr>
<tr>
<td><strong>Level B-NR</strong></td>
<td>Moderate-quality from nonrandomized studies, observational, registry</td>
</tr>
<tr>
<td><strong>Level C-LD</strong></td>
<td>Limited Data</td>
</tr>
<tr>
<td><strong>Level C-EO</strong></td>
<td>Expert Opinion</td>
</tr>
</tbody>
</table>

Prevailing Concept: Lower LDL-C is Better

- **Cholesterol Treatment Trialists’ Collaboration**
  - Meta-analysis of 26 statin trials (n=169,138)
  - 1 mmol/L LDL-C reduction reduced major vascular events 22%

- **Cooper Center Longitudinal Study**
  - 36,375 low risk (10-yr ASCVD score <7.5%) patients followed for 27 yrs
  - Lower LDL-C associated with lower ASCVD events and death

The DEVIL is in the DETAILS...
Clarifying Terminology

Goals…
for LDL-C lowering in response to therapy are defined by percentage responses

Threshold…
a specific value for LDL-C (or non-HDL-C) at or above which clinicians should consider starting or intensifying therapy

**Clinical ASCVD**

**Secondary Prevention (age ≥18 yr)**

- History of multiple ASCVD events or 1 major ASCVD event plus multiple high-risk conditions
  - **Yes**: Very High Risk ASCVD
    - High-Intensity/Maximal Statin
  - **No**: Stable ASCVD
    - High- or Moderate-Intensity Statin

**Primary Prevention (age 40-75 yr)**

- LDL-C ≥190 mg/dL
  - **Yes**: Diabetes
    - 10-yr ASCVD risk
      - ≥20% (High)
      - ≥7.5 to 19.9% (Intermediate)
      - 5 to 7.4% (Borderline)
      - <5% (Low)
      - Evaluate Risk Enhancers and CAC score if uncertain
      - Risk Discussion for statin benefit; consider Risk Enhancers
    - Lifestyle; Selective Moderate-Intensity Statin
  - **No**: LDL-C 70-189 mg/dL
    - **Yes**: 10-yr ASCVD risk
      - ≥20% (High)
      - ≥7.5 to 19.9% (Intermediate)
      - 5 to 7.4% (Borderline)
      - <5% (Low)
      - Evaluate Risk Enhancers and CAC score if uncertain
      - Risk Discussion for statin benefit; consider Risk Enhancers
    - **No**: LDL-C <70 mg/dL
      - Assess Lifetime Risk
      - Lifestyle and risk discussion

**ASCVD** = atherosclerotic cardiovascular disease; **CAC** = coronary artery calcium

Secondary Prevention of ASCVD

Clinical ASCVD

Healthy Lifestyle

Very High-Risk

Age ≤75 yr

High-intensity statin (Goal ↓LDL-C 50%) [Class I]

If high-intensity not tolerated use moderate-intensity statin [Class I]

If on maximal statin and LDL-C ≥70 mg/dL adding ezetimibe may be reasonable [Class IIb]

Age >75 yr

Moderate or high-intensity statin is reasonable [Class IIa]

Continuing high-intensity statin is reasonable [Class IIa]

High-intensity/maximal statin [Class I]

If on clinically judged-maximal LDL-C lowering medication and LDL-C ≥70 mg/dL (or non-HDL-C ≥100 mg/dL adding a PCSK9i is reasonable [Class IIa]

If on maximal statin and LDL-C ≥70 mg/dL adding ezetimibe is reasonable [Class IIa]

If PCSK9i is considered, add ezetimibe to maximal statin first [Class I]

Randomized controlled study support, but less cost effective

Very High ASCVD

### Major ASCVD Events
- Recent acute coronary syndrome (ACS) (past 12 mo)
- Prior myocardial infarction (other than recent ACS event listed above)
- Prior ischemic stroke
- Symptomatic peripheral arterial disease

### High-Risk Conditions
- Age ≥65 yr
- Heterozygous familial hypercholesterolemia
- Prior coronary revascularization outside of the major ASCVD event(s)
- Diabetes mellitus
- Hypertension
- Chronic kidney disease (eGFR 15-59 mL/min/1.73 m²)
- Current smoking
- LDL-C ≥100 mg/dL despite maximally tolerated statin and ezetimibe
- History of congestive heart failure

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### Statin Intensity

<table>
<thead>
<tr>
<th>LDL-C* Lowering</th>
<th>High Intensity</th>
<th>Moderate Intensity</th>
<th>Low Intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≥50%</td>
<td>30 to 49%</td>
<td>&lt;30%</td>
</tr>
<tr>
<td>Atorvastatin (40 mg) 80 mg Rosuvastatin 20 mg (40 mg)</td>
<td>Atorvastatin 10 mg (20 mg) Rosuvastatin (5 mg) 10 mg Simvastatin 20-40 mg</td>
<td>Simvastatin 10 mg</td>
<td></td>
</tr>
<tr>
<td>Pravastatin 40 mg (80 mg) Lovastatin 40 mg (80 mg) Fluvastatin XL 80 mg Fluvastatin 40 mg twice daily Pitavastatin 1-4 mg</td>
<td>Pravastatin 10-20 mg Lovastatin 20 mg Fluvastatin 20-40 mg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Reductions with the primary statin medications (atorvastatin, rosuvastatin, simvastatin) estimated using median reduction from the VOYAGER database; for other statin medications (fluvastatin, lovastatin, pitavastatin, pravastatin) identified according to FDA-approved product labeling in adults with hyperlipidemia, primary hypercholesterolemia, and mixed dyslipidemia.

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

- Randomized, double-blind trial
- 18,144 patients with ACS; age ≥50 yr with a high CV risk feature, LDL-C 50-125 mg/dL
- Randomized to simvastatin 40 mg or ezetimibe/simvastatin 10/40 mg for 4.9 yr
- Primary endpoint:
  - Cardiovascular (CV) death, myocardial infarction (MI), hospitalization for unstable angina, coronary revascularization, stroke

Mean LDL-C values (mg/dL)
- Simvastatin 69.9
- Ezetimibe/simvastatin 53.2

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

6% RRR
HR 0.94 (95% CI, 0.89-0.99)
P=0.016

Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER)

- Randomized, double-blind trial
- 27,564 patients with ASCVD; age 40-85 yr, and LDL-C ≥70 mg/dL or non-HDL-C ≥100 mg/dL
- On maximal statin therapy
- Randomized to placebo or evolocumab for 2.2 yr
- Primary endpoint:
  - CV death, MI, stroke, hospitalization for unstable angina, or coronary revascularization

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

- Randomized, double-blind trial
- 18,924 patients with recent ACS; age ≥40 yr, and LDL-C ≥70 mg/dL, non-HDL-C ≥100 mg/dL, or ApoB ≥80 mg/dL
- On maximal statin therapy
- Randomized to placebo or alirocumab (titrated) for ≥2 yr
- Primary endpoint:
  - Major Adverse Cardiovascular Events (MACE): coronary heart disease (CHD) death, non-fatal MI, fatal/non-fatal ischemic stroke, or hospitalization for unstable angina

### Other Recommendations: Secondary Prevention

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Value Statement:</strong> Low Value (LOE: B-NR)</td>
<td>At mid-2018 list prices, PCSK9i have a low cost value (&gt;$150,000 per quality-adjusted life years (QALY)) compared to good cost value (&lt;$50,000 per QALY)</td>
</tr>
<tr>
<td>IIb</td>
<td>B-R</td>
<td>Heart failure with reduced ejection fraction (HFrEF) from ischemic heart disease with reasonable life expectancy (3 to 5 yr) consider initiation of moderate-intensity statin therapy if not on statin</td>
</tr>
</tbody>
</table>

Getting LDL-C to <70 mg/dL

• Cohort of 631,855 patients with ASCVD, age 40-85 yr from the VA system meeting FOURIER study criteria
  • 49.9% were on high-intensity statins, 47.5% were on moderate-intensity statins, and 2.6% were on a statin/ezetimibe combination

<table>
<thead>
<tr>
<th>Predicted percent with LDL-C &lt;70 mg/dL with treatment intensification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Titration to high-intensity statin therapy alone</td>
</tr>
<tr>
<td>Addition of ezetimibe therapy alone</td>
</tr>
<tr>
<td>Titration to high-intensity statin therapy plus ezetimibe use</td>
</tr>
</tbody>
</table>

Clinical ASCVD

Secondary Prevention (age ≥18 yr)

- History of multiple ASCVD events or 1 major ASCVD event plus multiple high-risk conditions
  - Yes: Very High Risk ASCVD
    - High-Intensity/Maximal Statin
  - No: Stable ASCVD
    - High-or Moderate-Intensity Statin

Primary Prevention (age 40-75 yr)

- LDL-C ≥190 mg/dL
  - Yes: Diabetes
    - 10-yr ASCVD risk
      - Yes: ≥20% (High)
        - Evaluate Risk Enhancers and CAC score if uncertain
      - No: ≥7.5 to 19.9% (Intermediate)
        - Risk Discussion for statin benefit; consider Risk Enhancers
      - No: 5 to 7.4% (Borderline)
        - Lifestyle; Selective Moderate-Intensity Statin
      - No: <5% (Low)
        - Lifestyle and risk discussion
  - No: LDL-C 70-189 mg/dL
    - Yes: Assess Lifetime Risk
    - No: LDL-C <70 mg/dL

ASCVD = atherosclerotic cardiovascular disease; CAC = coronary artery calcium
Primary Prevention

Assess ASCVD risk and emphasize adherence to healthy lifestyle

- **Age <20 yr**
  - Lifestyle to prevent or reduce ASCVD risk; Statin if diagnosis of familial hypercholesterolemia

- **Age 20 to 39 yr**
  - Estimate lifetime risk to encourage lifestyle to reduce ASCVD risk; consider statin if family history of premature ASCVD and LDL-C 160-189 mg/dL

- **Age 40-75 yr and LDL-C 70-189 mg/dL without diabetes**
  - 10-yr ASCVD risk begins discussion

- **LDL-C ≥190 mg/dL, risk assessment not needed**: High-intensity statin [Class I]

- **Diabetes, age 40-75 yrs**: Moderate-intensity statin [Class I]

- **Diabetes, age 40-75 yrs**: Risk assessment to consider high-intensity statin [Class IIa]

- **Age >75 yr**: Clinical assessment, risk discussion

- **<5% Low Risk**
  - Emphasize lifestyle [Class I]

- **5 to 7.4% Borderline Risk**
  - If Risk Enhancers, risk discussion regarding moderate-intensity statin [Class IIb]

- **7.5 to 19.9% Intermediate Risk**
  - If risk estimate and enhancers favor treatment, moderate-intensity statin to reduce LDL-C 30-49% [Class I]

- **≥20% High Risk**
  - Statin to reduce LDL-C ≥50% [Class I]

- If risk decision is uncertain: Consider measuring coronary artery calcium

Primary Prevention:
Assess ASCVD risk and emphasize adherence to healthy lifestyle

**Age <20 yr**
Lifestyle to prevent or reduce ASCVD risk; Statin if diagnosis of familial hypercholesterolemia

**Age 20 to 39 yr**
Estimate lifetime risk to encourage lifestyle to reduce ASCVD risk; consider statin if family history of premature ASCVD and LDL-C 160-189 mg/dL

**Age 40-75 yr and LDL-C 70-189 mg/dL without diabetes**
10-yr ASCVD risk begins discussion

- LDL-C ≥190 mg/dL, risk assessment not needed: High-intensity statin [Class I]
- Diabetes, age 40-75 yrs: Moderate-intensity statin [Class I]
- Diabetes, age 40-75 yrs: Risk assessment to consider high-intensity statin [Class IIa]

**Age >75 yr:**
Clinical assessment, risk discussion

- <5% Low Risk
  - Emphasize lifestyle [Class I]
- 5 to 7.4% Borderline Risk
  - If Risk Enhancers, risk discussion regarding moderate-intensity statin [Class IIb]

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- ≥20% High Risk
  - Statin to reduce LDL-C ≥50% [Class I]

If risk decision is uncertain: Consider measuring coronary artery calcium

When to use High-Intensity Statin therapy in Primary Prevention Patients with Diabetes?

“In patients with diabetes mellitus at higher risk, especially those with multiple risk factors or those 50 to 75 years of age”

“Adults with diabetes mellitus who have multiple ASCVD risk factors”

“among men >50 years of age and women >60 years of age”

“in patients with diabetes mellitus as they age or develop risk modifiers”

Other Recommendations: Primary Prevention and Diabetes

<table>
<thead>
<tr>
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<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIa</td>
<td>B-NR</td>
<td>&gt;75 yr with diabetes and already on statin therapy, reasonable to continue</td>
</tr>
<tr>
<td>IIb</td>
<td>C-LD</td>
<td>&gt;75 years with diabetes, reasonable to initiate statin therapy after benefit/risk discussion</td>
</tr>
</tbody>
</table>
| IIb | C-LD | 20 to 39 yr with diabetes reasonable to initiate statin therapy if diabetes-specific risk enhancer present:  
  • long duration (≥10 yr for type 2, ≥20 yr for type 1)  
  • albuminuria (≥30 mcg of albumin/mg creatinine)  
  • eGFR < 60 mL/min/1.73 m²  
  • retinopathy  
  • neuropathy  
  • ankle-brachial index <0.9 |

**Primary Prevention**

Assess ASCVD risk and emphasize adherence to healthy lifestyle

- **Age <20 yr**
  - Lifestyle to prevent or reduce ASCVD risk;
  - Statin if diagnosis of familial hypercholesterolemia

- **Age 20 to 39 yr**
  - Estimate lifetime risk to encourage lifestyle to reduce ASCVD risk;
  - Consider statin if family history of premature ASCVD and LDL-C 160-189 mg/dL

- **Age 40-75 yr and LDL-C 70-189 mg/dL without diabetes**
  - 10-yr ASCVD risk begins discussion

- **LDL-C ≥190 mg/dL, risk assessment not needed:**
  - High-intensity statin [Class I]

- **Diabetes, age 40-75 yrs:**
  - Moderate-intensity statin [Class I]

- **Diabetes, age 40-75 yrs:**
  - Risk assessment to consider high-intensity statin [Class IIa]

- **Age >75 yr:**
  - Clinical assessment, risk discussion

#### Risk Classification

- **<5% Low Risk**
  - Emphasize lifestyle [Class I]

- **5 to 7.4% Borderline Risk**
  - If Risk Enhancers, risk discussion regarding moderate-intensity statin [Class IIb]

- **7.5 to 19.9% Intermediate Risk**
  - If risk estimate and enhancers favor treatment, moderate-intensity statin to reduce LDL-C 30-49% [Class I]

- **≥20% High Risk**
  - Statin to reduce LDL-C ≥50% [Class I]

- If risk decision is uncertain: Consider measuring coronary artery calcium

Risk Enhancing Factors

- Family history of premature ASCVD
- LDL-C 160–189 mg/dL or non–HDL-C 190–219 mg/dL
- Metabolic syndrome
- Chronic kidney disease (CKD)
  - eGFR 15–59 mL/min/1.73 m2 with or without albuminuria
  - not dialysis or kidney transplantation
- Chronic inflammatory conditions (e.g., rheumatoid arthritis, HIV)
- Premature menopause (before age 40 y) and pregnancy-associated conditions that increase later ASCVD risk (e.g., preeclampsia)
- High-risk race/ethnicities (e.g., South Asian ancestry)

Risk Enhancing Factors, cont.

- **Lipid/biomarkers:**
  - Persistently elevated, primary hypertriglyceridemia ($\geq 175$ mg/dL)
- **In select individuals, If measured:**
  - High-sensitivity C-reactive protein $\geq 2.0$ mg/L
  - Lp(a) $\geq 50$ mg/dL
  - apoB $\geq 130$ mg/dL
  - Ankle brachial index $< 0.9$

**Other Recommendations:**
**Primary Prevention, without Diabetes, LDL-C 70-189 mg/dL**

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</thead>
<tbody>
<tr>
<td>Ila</td>
<td>B-NR</td>
<td><strong>Intermediate-risk or selected borderline-risk in whom a coronary artery calcium (CAC) score is measured:</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Zero: reasonable to withhold statin therapy and reassess in 5 to 10 years, as long as higher risk conditions are absent (diabetes, family history of premature CHD, cigarette smoking)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 1 to 99: reasonable to initiate statin therapy for patients ≥55 years of age</td>
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<tr>
<td></td>
<td></td>
<td>• ≥100*: reasonable to initiate statin therapy</td>
</tr>
</tbody>
</table>

*or ≥ 75th percentile

Coronary Artery Calcium Measurement

Patients Who Might Benefit from Knowing Their CAC Score Is Zero

• Reluctant to initiate statin therapy and wish to understand their risk/benefit more precisely
• Concerned about need to reinstitute statin after stopping for SAMS
• Older patients (men, 55-80 yr; women, 60-80 yr) with low burden of risk factors who are uncertain
• Middle-aged patients (40-55 yr) with 10-yr ASCVD risk 5 to 7.4% with other factors that increase ASCVD risk

Other Recommendations:  
Primary Prevention, without Diabetes, LDL-C 70-189 mg/dL

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<td>IIb</td>
<td>B-R</td>
<td>&gt;75 yr, moderate-intensity statin may be reasonable</td>
</tr>
<tr>
<td>IIb</td>
<td>B-R</td>
<td>&gt;75 yr, reasonable to stop statin therapy when functional decline (physical or cognitive), multimorbidity, frailty, or reduced life-expectancy limits the potential benefits of statin therapy</td>
</tr>
<tr>
<td>IIb</td>
<td>B-R</td>
<td>76 to 80 yr, reasonable to measure CAC to reclassify those with a CAC score of zero to avoid statin therapy</td>
</tr>
</tbody>
</table>

## Statin-Associated Side Effects: Statin-Associated Muscle Symptoms (SAMS)

<table>
<thead>
<tr>
<th>Type</th>
<th>Frequency</th>
<th>Predisposing Factors</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Myalgias</strong></td>
<td></td>
<td>Age, female sex, low body mass index, high-risk medications (CYP3A4 inhibitors, OATP1B1 inhibitors), comorbidities (HIV, renal, liver, thyroid, preexisting myopathy), Asian ancestry, excess alcohol, high levels of physical activity, and trauma</td>
<td>RCTs, cohorts/observational</td>
</tr>
<tr>
<td>Creatine kinase (CK) is normal</td>
<td>Infrequent (1% to 5%) in randomized controlled trials (RCT)</td>
<td>• Infrequent (1% to 5%) in randomized controlled trials (RCT) • Frequent (5% to 10%) in observational studies and clinical setting</td>
<td></td>
</tr>
<tr>
<td><strong>Myositis/myopathy</strong></td>
<td>Rare</td>
<td>CK &gt; upper limit of normal (ULN) with concerning symptoms or objective weakness</td>
<td>RCTs, cohorts/observational</td>
</tr>
<tr>
<td>CK &gt; upper limit of normal (ULN)</td>
<td></td>
<td>Rhabdomyolysis (CK &gt;10× ULN + renal injury)</td>
<td>RCTs, cohorts/observational</td>
</tr>
<tr>
<td><strong>Statin-associated autoimmune myopathy</strong></td>
<td>Rare</td>
<td>Statin-associated autoimmune myopathy</td>
<td>Case Reports</td>
</tr>
</tbody>
</table>
### Statin-Associated Side Effects: Other

<table>
<thead>
<tr>
<th>Type</th>
<th>Frequency</th>
<th>Predisposing Factors</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>New-Onset Diabetes Mellitus</strong></td>
<td>Depends on population; more frequent if diabetes mellitus risk factors are present, such as body mass index ≥30, fasting blood sugar ≥100 mg/dL; metabolic syndrome, or A1c ≥6%</td>
<td>Diabetes mellitus risk factors/metabolic syndrome, High-dose statin therapy</td>
<td>RCTs/meta-analyses</td>
</tr>
<tr>
<td><strong>Transaminase Elevation (&gt;3 x ULN)</strong></td>
<td>Infrequent</td>
<td></td>
<td>RCTs, cohorts/observational, case reports</td>
</tr>
<tr>
<td><strong>Hepatic Failure</strong></td>
<td>Rare</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Statin-Associated Side Effects: Myths

<table>
<thead>
<tr>
<th>Type</th>
<th>Frequency</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Memory/cognition</td>
<td>Rare/unclear</td>
<td>Case reports; no increase in 3 large RCTs</td>
</tr>
<tr>
<td>Cancer</td>
<td>No definite association</td>
<td>RCTs/meta-analyses</td>
</tr>
<tr>
<td>Renal Dysfunction, Tendon Rupture, Interstitial lung disease, Low testosterone</td>
<td>Unclear/Unfounded</td>
<td></td>
</tr>
<tr>
<td>Cataracts, Hemorrhagic stroke</td>
<td>Unclear</td>
<td></td>
</tr>
</tbody>
</table>

Noteworthy Additional Elements

• In patients treated with dialysis, it is reasonable to continue statin therapy, but do not initiate statin therapy

• In patients with heart failure with reduced ejection fraction attributable to ischemic heart disease who have a reasonable life expectancy (3 to 5 years) and are not already on a statin because of ASCVD, clinicians may consider initiation of moderate-intensity statin therapy to reduce the occurrence of ASCVD events

• Recommendations for certain populations:
  • Women, children and adolescents, racial/ethnic groups, CKD, chronic inflammatory diseases

• Supplemental tables regarding medications

Top 10 Messages

1. Emphasize a heart-healthy lifestyle across the life course

2. In clinical ASCVD, reduce LDL-C with high-intensity statin therapy or maximally tolerated statin therapy

3. In very high-risk ASCVD, use a LDL-C threshold of 70 mg/dL to consider addition of nonstatins to statin therapy

4. In severe primary hypercholesterolemia (LDL-C $\geq$ 190 mg/dL) without calculating 10-year ASCVD risk, begin high-intensity statin therapy

5. 40 to 75 years of age with diabetes mellitus and LDL-C $\geq$ 70 mg/dL, start moderate-intensity statin therapy without calculating 10-year ASCVD risk

6. 40 to 75 years of age primary ASCVD prevention, have a clinician–patient risk discussion before starting statin therapy

7. 40 to 75 years of age without diabetes and LDL-C $\geq$ 70 mg/dL, at a 10-year ASCVD risk of $\geq$ 7.5%, start a moderate-intensity statin if a discussion of treatment options favors statin therapy

8. 40 to 75 years of age without diabetes and 10-year risk of 7.5-19.9% (intermediate risk), risk-enhancing factors favor statin therapy

9. 40 to 75 years of age without diabetes and LDL-C 70-189 mg/dL, at a 10-year ASCVD risk of 7.5-19.9%, if a decision about statin therapy is uncertain, consider measuring coronary artery calcium

10. Assess adherence and % LDL-C–lowering response with repeat lipid measurement 4 to 12 weeks after statin initiation or dose adjustment, repeated every 3 to 12 months as needed

Hypercholesterolemia: A Case-Based Approach to Treating Patients

Janelle Ruisinger, PharmD
Professor
University of Kansas

Joseph Saseen, PharmD
Professor and Vice Chair
University of Colorado
Case 1
Case 1

- HB is a 50-year-old African American woman who has a history of hypertension and hypercholesterolemia. Her only medications are olmesartan 40 mg po daily and amlodipine 10 mg po daily. She weighs 188 lbs, and is 65" tall (body mass index (BMI) is 31.3 kg/m²).

- While measuring her BP (136/82, 138/82 mm Hg), she tells you that her mother also had hypertension and suddenly died of a heart attack when she was 55-years-old.

- She smokes cigarettes (1-packs/day x 40 years) and drinks alcohol rarely.

- Other than hypertension and hypercholesterolemia, she is relatively healthy and is post-menopausal (menopause at age 35 yr).
Case 1 continued...

• Over the past year, she has lost 10 pounds by exercising three times a week (aerobic) and eating better after working with a dietitian. However, she feels like her efforts have plateaued.

• Recent laboratory values are:
  • Fasting Lipid Panel:
    • Total cholesterol 225 mg/dL
    • HDL-C 40 mg/dL
    • LDL-C 135 mg/dL
    • Triglycerides 200 mg/dL
  • A1C 6%
  • Serum chemistries and liver function tests are normal

10-yr ASCVD Risk
8.4%
Case 1 continued...

How would you treat this patient’s hypercholesterolemia?
Primary Prevention:
Assess ASCVD risk and emphasize adherence to healthy lifestyle

Age <20 yr
Lifestyle to prevent or reduce ASCVD risk; Statin if diagnosis of familial hypercholesterolemia

Age 20 to 39 yr
Estimate lifetime risk to encourage lifestyle to reduce ASCVD risk; consider statin if family history of premature ASCVD and LDL-C 160-189 mg/dL

Age 40-75 yr and LDL-C 70-189 mg/dL without diabetes
10-yr ASCVD risk begins discussion

<5%
Low Risk
Emphasize lifestyle [Class I]

5 to 7.4%
Borderline Risk
If Risk Enhancers, risk discussion regarding moderate-intensity statin [Class IIb]

7.5 to 19.9%
Intermediate Risk
If risk estimate and enhancers favor treatment, moderate-intensity statin to reduce LDL-C 30-49% [Class I]

≥20%
High Risk
Statin to reduce LDL-C ≥50% [Class I]

Age >75 yr:
Clinical assessment, risk discussion

LDL-C ≥190 mg/dL, risk assessment not needed:
High-intensity statin [Class I]

Diabetes, age 40-75 yrs:
Moderate-intensity statin [Class I]

Diabetes, age 40-75 yrs: Risk assessment to consider high-intensity statin [Class IIa]

Risk Enhancing Factors

- Family history of premature ASCVD
- LDL-C 160–189 mg/dL or non–HDL-C 190–219 mg/dL
- Metabolic syndrome
- CKD
  - eGFR 15–59 mL/min/1.73 m2 with or without albuminuria
  - not dialysis or kidney transplantation
- Chronic inflammatory conditions (e.g., rheumatoid arthritis, HIV)
- Premature menopause (before age 40 y) and pregnancy-associated conditions that increase later ASCVD risk (e.g., preeclampsia)
- High-risk race/ethnicities (e.g., South Asian ancestry)

## Statin Intensity

<table>
<thead>
<tr>
<th></th>
<th>High Intensity</th>
<th>Moderate Intensity</th>
<th>Low Intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C* Lowering</td>
<td>≥50%</td>
<td>30 to 49%</td>
<td>&lt;30%</td>
</tr>
<tr>
<td>Atorvastatin (40 mg) 80 mg</td>
<td>Atorvastatin 10 mg (20 mg)</td>
<td>Pravastatin 10-20 mg</td>
<td></td>
</tr>
<tr>
<td>Rosuvastatin 20 mg (40 mg)</td>
<td>Rosuvastatin (5 mg) 10 mg</td>
<td>Lovastatin 40 mg (80 mg)</td>
<td></td>
</tr>
<tr>
<td>Simvastatin 20-40 mg</td>
<td>Simvastatin 10 mg</td>
<td>Fluvastatin XL 80 mg</td>
<td></td>
</tr>
<tr>
<td>Pravastatin 40 mg (80 mg)</td>
<td>Pravastatin 10-20 mg</td>
<td>Fluvastatin 20-40 mg</td>
<td></td>
</tr>
<tr>
<td>Lovastatin 40 mg (80 mg)</td>
<td>Lovastatin 20 mg</td>
<td>Fluvastatin 40 mg twice daily</td>
<td></td>
</tr>
<tr>
<td>Fluvastatin 20-40 mg</td>
<td>Fluvastatin 40 mg</td>
<td>Pitavastatin 1-4 mg</td>
<td></td>
</tr>
</tbody>
</table>

*Reductions with the primary statin medications (atorvastatin, rosuvastatin, simvastatin) estimated using median reduction from the VOYAGER database; for other statin medications (fluvastatin, lovastatin, pitavastatin, pravastatin) identified according to FDA-approved product labeling in adults with hyperlipidemia, primary hypercholesterolemia, and mixed dyslipidemia.

How would your treatment be different if this patient had diabetes?

How would your treatment be different if this patient were Secondary Prevention?
Checklist for Clinician-Patient Shared Decision Making for Initiating Therapy

- ASCVD Risk Assessment
- Lifestyle Modifications
- Potential Net-Clinical Benefit from Pharmacotherapy
- Cost Considerations
- Shared Decision Making
  - Have patient verbalize what was heard, ask questions, express preferences
  - Refer patient to trustworthy materials to aid understanding
  - Collaborate with the patient to determine ultimate plan

1. A 50-year-old South Asian primary prevention man has the following fasting lipid panel:
   • Total Cholesterol 245 mg/dL, LDL-C 165 mg/dL, HDL-C 30 mg/dL, TG 250 mg/dL

Results are similar to previous values. His 10-year ASCVD risk score is 12% and he is a smoker. According to the 2018 ACC-AHA cholesterol guidelines, which regimen is recommended?

A. Lifestyle modifications alone
B. Lifestyle modifications with a moderate-intensity statin
C. Lifestyle modifications with a high-intensity statin
D. Lifestyle modifications with a high-intensity statin and ezetimibe
Case 2
Case 2

• SJ is a 57-year-old Hispanic man presenting to clinic with complaints of muscle pain and weakness in both legs; he is frustrated because now he can hardly carry his tools up ladders and staircases when he works because of the pain and weakness.

• Pt is an electrician

• Medical History: Type 2 DM, hypertension, mixed dyslipidemia

• Social History: 10-12 drinks per week; no tobacco

• Medications:
  • Metformin 1000 mg PO BID x 8 years,
  • Chlorthalidone 25 mg PO daily x 5 years
  • Lisinopril 10 mg PO daily X 5 years
  • Atorvastatin 80 mg PO daily x 2 years
Case 2 continued

• BP: 130/84  Pulse: 82  Height: 70”  Weight: 205 lbs  BMI: 29.4
• Current laboratory values:
  Lipids:
    TC = 140 mg/dL
    LDL-C = 62 mg/dL
    HDL-C = 43 mg/dL
    TG = 175 mg/dL
    LFTs, CPK, and other labs = WNL

• How should we address SJ’s complaints?
### 2018 ACC-AHA Cholesterol Guideline: Statin Safety Recommendations

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>A</td>
<td>A clinician–patient risk discussion is recommended before initiation of statin therapy to review net clinical benefit, weighing the potential for ASCVD risk reduction against the potential for statin-associated side effects, statin–drug interactions, and safety, while emphasizing that side effects can be addressed successfully.</td>
</tr>
<tr>
<td>I</td>
<td>A</td>
<td>In patients with statin-associated muscle symptoms (SAMS), a thorough assessment of symptoms is recommended, in addition to an evaluation for nonstatin causes and predisposing factors.</td>
</tr>
</tbody>
</table>

# 2018 ACC-AHA Cholesterol Guideline: Statin Safety Recommendations

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
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</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>B-R</td>
<td>In patients with indication for statin therapy, identification of potential predisposing factors for statin-associated side effects, including new onset diabetes mellitus and SAMS, is recommended before initiation of treatment.</td>
</tr>
<tr>
<td>I</td>
<td>B-R</td>
<td>In patients with statin-associated side effects that are not severe, it is recommended to reassess and to rechallenge to achieve a maximal LDL-C lowering by modified dosing regimen, an alternate statin or in combination with nonstatin therapy.</td>
</tr>
<tr>
<td>I</td>
<td>B-R</td>
<td>In patients with increased diabetes mellitus risk or new-onset diabetes mellitus, it is recommended to continue statin therapy, with added emphasis on adherence, net clinical benefit, and the core principles of regular moderate-intensity physical activity, maintaining a healthy dietary pattern, and sustaining modest weight loss.</td>
</tr>
</tbody>
</table>

2018 ACC-AHA Cholesterol Guideline: Statin Safety Recommendations

<table>
<thead>
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</tr>
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<tbody>
<tr>
<td>I</td>
<td>C-LD</td>
<td>In patients treated with statins, it is recommended to measure creatine kinase levels in individuals with severe statin-associated muscle symptoms, objective muscle weakness, and to measure liver transaminases (AST/ALT) as well as total bilirubin and alkaline phosphatase (hepatic panel) if symptoms suggesting hepatotoxicity.</td>
</tr>
<tr>
<td>I</td>
<td>B-R</td>
<td>In patients at increased ASCVD risk with chronic, stable liver disease (including non-alcoholic fatty liver disease) when appropriately indicated, it is reasonable to use statins after obtaining baseline measurements and determining a schedule of monitoring and safety checks.</td>
</tr>
<tr>
<td>IIa</td>
<td>B-R</td>
<td>In patients at increased ASCVD risk with severe statin-associated muscle symptoms or recurrent statin-associated muscle symptoms despite appropriate statin rechallenge, it is reasonable to use RCT proven nonstatin therapy that is likely to provide net clinical benefit.</td>
</tr>
</tbody>
</table>

2018 ACC-AHA Cholesterol Guideline: Statin Safety Recommendations

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>III: No Benefit</td>
<td>B-R</td>
<td>Coenzyme Q10 is not recommended for routine use in patients treated with statins or for the treatment of SAMS</td>
</tr>
<tr>
<td>III: No Benefit</td>
<td>C-LD</td>
<td>In patients treated with statins, routine measurements of creatine kinase and transaminase levels are not useful</td>
</tr>
</tbody>
</table>
AHA Scientific Statement: Recommendations for Management of Clinically Significant Drug-Drug Interactions With Statins

• Specific recommendations for statins with common cardiovascular medications:
  • Other lipid-lowering agents, calcium channel blockers, antiarrhythmics, antianginals, anticoagulants, antiplatelets, vasopressin receptor antagonists, calcineurin inhibitors, heart failure medications

• Examples:
  • Doses of lovastatin or simvastatin >20 mg daily when co-administered with amlodipine are not recommended

2. A 70-year-old woman with a recent ischemic stroke is complaining of generalized muscle aches for the last 4 weeks. She was started on Atorvastatin 40 mg PO daily approximately 6 weeks ago. According to the ACC-AHA cholesterol guidelines, what is recommended?

A. Discontinue the Atorvastatin and start Niacin IR 500 mg PO BID
B. Discontinue the Atorvastatin and start Rosuvastatin 20 mg PO daily
C. Discontinue Atorvastatin as lipid lowering therapy is not indicated for this patient
D. Continue Atorvastatin 40 mg PO daily and initiate CoQ10 PO daily
Case 3
Case 3

• PM 22-year-old white man who is presenting to the appointment because his parents told him he needed to get his cholesterol checked. He is in his 3rd year at the local university.
• Current medications: none
• Medical History: Paternal grandmother MI age 60 years, Father coronary artery bypass graft (CABG) age 55 years
• Social History: ~14 beers per week; no tobacco products
• Exercise: 60 minute workout 6 days per week (cardio + strength)
• Diet: “typical college diet” per patient
Case 3 continued

- BP: 119/82  Pulse: 71  Height: 73”  Weight: 180 lbs  BMI: 23.7
- Recent laboratory results
  - Fasting Lipid Panel:
    - TC: 285 mg/dL
    - LDL-C: 213 mg/dL
    - HDL-C: 44 mg/dL
    - TG: 140 mg/dL
  - A1c, CK, LFTs, and other labs = within normal limits
- How should we treat PM?
Primary Prevention

Assess ASCVD risk and emphasize adherence to healthy lifestyle

Age <20 yr
Lifestyle to prevent or reduce ASCVD risk; Statin if diagnosis of familial hypercholesterolemia

Age 20 to 39 yr
Estimate lifetime risk to encourage lifestyle to reduce ASCVD risk; consider statin if family history of premature ASCVD and LDL-C 160-189 mg/dL

Age 40-75 yr and LDL-C 70-189 mg/dL without diabetes
10-yr ASCVD risk begins discussion

<5%
Low Risk
Emphasize lifestyle [Class I]

5 to 7.4%
Borderline Risk
If Risk Enhancers, risk discussion regarding moderate-intensity statin [Class IIb]

7.5 to 19.9%
Intermediate Risk
If risk estimate and enhancers favor treatment, moderate-intensity statin to reduce LDL-C 30-49% [Class I]

≥20%
High Risk
Statin to reduce LDL-C ≥50% [Class I]

If risk decision is uncertain: Consider measuring coronary artery calcium

LDL-C ≥190 mg/dL, risk assessment not needed: High-intensity statin [Class I]

Diabetes, age 40-75 yrs: Moderate-intensity statin [Class I]

Diabetes, age 40-75 yrs: Risk assessment to consider high-intensity statin [Class IIa]

Age >75 yr:
Clinical assessment, risk discussion

Case 3 continued

• 4 months later, PM returns to clinic
• Current medications: Rosuvastatin 40 mg daily
  • Tolerating well
• Recent laboratory results:
  • Fasting Lipid Panel:
    TC       195 mg/dL
    LDL-C    126 mg/dL
    HDL-C    44 mg/dL
    TG       140 mg/dL
• Next step(s) for this patient?
## 2018 ACC-AHA Cholesterol Guideline: Severe Hypercholesterolemia (LDL-C ≥190 mg/dL)

<table>
<thead>
<tr>
<th>COR</th>
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<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIA</td>
<td>B-R</td>
<td>20 to 75 yr, &lt;50% LDL-C reduction with maximally tolerated statin and/or LDL-C level of ≥100 mg/dL, ezetimibe is reasonable</td>
</tr>
<tr>
<td>IIB</td>
<td>B-R</td>
<td>20 to 75 yr, &lt;50% LDL-C reduction and fasting triglycerides ≤300 mg/dL with maximally tolerated statin and ezetimibe, consider bile acid sequestrant</td>
</tr>
<tr>
<td>IIB</td>
<td>B-R</td>
<td>30 to 75 yr, heterozygous familial hypercholesterolemia (FH) and LDL-C ≥100 mg/dL with maximally tolerated statin and ezetimibe therapy, consider PCSK9 inhibitor</td>
</tr>
<tr>
<td>IIB</td>
<td>C-LD</td>
<td>40 to 75 yr, baseline LDL-C ≥220 mg/dL and LDL-C ≥130 mg/dL with maximally tolerated statin and ezetimibe, consider a PCSK9 inhibitor</td>
</tr>
</tbody>
</table>

**Value Statement:**
**Uncertain Value (B-NR)**
FH without clinical ASCVD, with maximally tolerated statin and ezetimibe therapy, PCSK9 inhibitors provide uncertain value at 2018 U.S. list prices

3. KC is a 45-year-old man, primary prevention, HeFH confirmed with genetic testing, taking rosuvastatin 40 mg PO daily and ezetimibe 10 mg PO daily; his LDL level today is 137 mg/dL. According to the ACC-AHA cholesterol guidelines, what is recommended?

A. Continue current lipid lowering regimen with no additions or changes
B. Initiate lifestyle modifications for 6 months then re-assess
C. Initiate 4 grams of omega-3 fatty acids PO daily
D. Initiate alirocumab 75 mg subq every 2 weeks
Hypercholesterolemia: Implementation and Medications on the Horizon

Janelle Ruisinger, PharmD
Clinical Professor
University of Kansas School of Pharmacy
## Implementation

<table>
<thead>
<tr>
<th>COR</th>
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</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>A</td>
<td>Interventions focused on improving adherence to prescribed therapy are recommended for management of adults with elevated cholesterol levels, including telephone reminders, calendar reminders, integrated multidisciplinary educational activities, and pharmacist-led interventions, such as simplification of the drug regimen to once-daily dosing.</td>
</tr>
<tr>
<td>I</td>
<td>B-R</td>
<td>Clinicians, health systems, and health plans should identify patients who are not receiving guideline-directed medical therapy and should facilitate the initiation of appropriate guideline-directed medical therapy, using multifaceted strategies to improve guideline implementation.</td>
</tr>
<tr>
<td>I</td>
<td>B-R</td>
<td>Before therapy is prescribed, a patient-clinician discussion should take place to promote shared decision-making and should include the potential for ASCVD risk-reduction benefit, adverse effects, drug-drug interactions, and patient preferences.</td>
</tr>
</tbody>
</table>

### Strategies to Improve Guideline Implementation

<table>
<thead>
<tr>
<th><strong>Patient</strong></th>
<th><strong>Clinician</strong></th>
<th><strong>Health Plan</strong></th>
<th><strong>Retail Pharmacy</strong></th>
<th><strong>Office/Health System</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple medication regimens</td>
<td>Initiate patient-clinician discussions</td>
<td>Embed decision support tools into electronic health records</td>
<td>Reduce costs of guideline directed medical therapy/medications</td>
<td>Automated refill programs</td>
</tr>
<tr>
<td>Clear instructions</td>
<td>Brief/simple messages</td>
<td>Use technology to identify high risk patients not receiving appropriate therapy</td>
<td>Greater transparency regarding access to medications, costs and formulary preferences</td>
<td>90-day refills instead of 30-day refills</td>
</tr>
<tr>
<td>Use of tools that promote adherence</td>
<td>Assess adherence often</td>
<td>Collaborative team-based approaches</td>
<td>Packaging that promotes adherence</td>
<td>Packaging that promotes adherence</td>
</tr>
<tr>
<td>Family/peer support</td>
<td>Maintain contact</td>
<td>Standard treatment plans and pathways</td>
<td></td>
<td>Medication synchronization programs</td>
</tr>
<tr>
<td>Lower medication barriers</td>
<td>Shared decision making, other strategies</td>
<td>Peer-to-peer feedback</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appointment reminders</td>
<td>Discuss lifestyle often</td>
<td>Registries to improve care</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bring medications to visits</td>
<td>Prescriptions for both diet and medications</td>
<td>Academic detailing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Education, support, case management, telehealth</td>
<td>Teach other clinicians</td>
<td>Use audit and feedback with stakeholders</td>
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<td></td>
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<tr>
<td>Empowerment</td>
<td>Use apps</td>
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<tr>
<td>Clinician-Patient shared accountability for performance</td>
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</tbody>
</table>

**Office/Health System**
- Automated refill programs
- 90-day refills instead of 30-day refills
- Packaging that promotes adherence
- Medication synchronization programs

---

Checklist for Clinician-Patient Shared Decision Making for Initiating Therapy

✓ ASCVD Risk Assessment
✓ Lifestyle Modifications
✓ Potential Net-Clinical Benefit from Pharmacotherapy
✓ Cost Considerations
✓ Shared Decision Making
  • Have patient verbalize what was heard, ask questions, express preferences
  • Refer patient to trustworthy materials to aid understanding
  • Collaborate with the patient to determine ultimate plan

American College of Cardiology Cardiovascular Team and Prevention Councils
Role of the Clinical Pharmacist in the Care of Patients with CVD

• Team-based care, including clinical pharmacists, can efficiently deliver high-quality care

• Substantial effect in a wide variety of settings through:
  • Optimization of drug use
  • Avoidance of adverse drug events
  • Transition of care activities focusing on medication reconciliation and patient education

Pharmacists Impact in Managing Dyslipidemia

- Multiple studies have determined that pharmacist-driven dyslipidemia management results in reductions in LDL-C (often greater than usual care)
- RxAct study has demonstrated that pharmacist-driven dyslipidemia management resulted in a 3-fold increase in patients who achieved target LDL-C goals compared to the standard of care
- RxEACH study was the first large randomized trial of CVD risk reduction (hypertension, dyslipidemia, diabetes) by community pharmacists, demonstrating a significant reduction in risk for CVD events
- A cluster RCT of a pharmacist led collaborative intervention on statin prescribing demonstrated improved statin prescribing and cholesterol target attainment
  - Patients receiving statin outreach support by pharmacists were significantly more likely to have cholesterol at target (69.5% vs 63.5%; OR 1.11, CI 1.00–1.23; p = 0.043)
Models where Pharmacists Providing Direct Patient Care for Hypercholesterolemia

• Face-to-face disease state management and education
  • Ambulatory clinic
  • Community pharmacy

• Collaborative drug therapy management protocols that allow
  • Initiation and titration of medications
  • Laboratory monitoring
  • Adherence assessment

• Inpatient/outpatient interprofessional models of care

• Telephonic outreach and follow-up

• Prospective population health outreach
Medications on the Horizon
Bempedoic Acid (BA)

• Esperion
• Novel ATP-citrate lyase inhibitor
• Oral, once daily medication
• Uses
  • Primary and secondary prevention patients
  • Monotherapy
  • Combination with statins, ezetimibe and PCSK9 inhibitors
• Phase 2 and 3 trials
  • Overall LDL-C reduction
    • ~29% monotherapy
    • ~22% added to background statin
    • ~29% added to background ezetimibe

Cardiol Clin. 2018 May;36(2):257-264
Bempedoic Acid MOA
https://www.esperion.com/lipid-management/
Inclisiran

• The Medicines Company
• Synthetic small interfering RNA (siRNA)
  • Targets PCSK9 production in the liver
  • Long acting – 1 or 2 injections per year
  • Works within hepatocytes
• Phase II trial in patients with ASCVD and LDL > 70 mg/dL or no ASCVD and LDL > 100 mg/dL
  • LDL-C ↓~28-42% with single 300 mg dose and ~36-53% with two 300 mg doses
Evinacumab

• Angiopoietin-like 3 (ANGPTL3) antibody by Regeneron
  • Fully human monoclonal antibody
• ANGPTL3 is a protein in the liver that increases TG, LDL-C and HDL-C in the plasma
• ANGPTL3 inhibition lowers LDL-C regardless of LDL receptor activity
• FDA designated as breakthrough therapy for Homozygous FH (HoFH)
• Phase 2 trial in patients with HoFH
  • Mean baseline LDL-C = 376 mg/dL
  • ↓ LDL-C 49% when added to background lipid lowering medications

https://investor.regeneron.com/node/12686/pdf
AKCEA-APO(a)-LRx

- Akcea Therapeutics
- 3rd generation antisense oligonucleotide that lowers Lipoprotein (a) (Lp(a))
- Lp(a) is a LDL-like plasma lipoprotein attached to apoprotein(a)
  - Pro-thrombotic
  - Contributes to ASCVD
- Phase II study
  - Plasma Lp(a) ↓ up to 90%
- Current phase II study enrolling patients with ASCVD and Lp(a) ≥ 60 mg/dL

https://www.lipid.org/node/2287
AKCEA-APOCIII-LRx

• Akcea Therapeutics
• Antisense drug
  • Administered subcutaneously
• Decreases production of apolipoprotein C-III (apoC-III)
  • apoC-III correlated with elevated TG and cardiovascular disease (CVD)
• Intended for established CVD and elevated TG
• Phase 1/2a clinical trial for 6 weeks
  • ↓ TG 71%
  • ↓ apolipoprotein B 30%
  • ↑ HDL-C 100%

Assessment Questions

4. Which patient would be a good candidate for the apoC-III antisense drug?

A. A 23-year-old man, primary prevention; LDL-C 435 mg/dL, TG 75 mg/dL, Lp(a) 75 mg/dL
B. A 45-year-old woman, history of ischemic stroke; LDL-C 119 mg/dL, TG 135 mg/dL and Lp(a) 147 mg/dL
C. A 60-year-old man, primary prevention; LDL-C 127 mg/dL, TG 75 mg/dL and Lp(a) 19 mg/dL taking rosuvastatin 40 mg daily and evolocumab 140 mg SQ every 14 days
D. A 55-year-old woman, history of MI; LDL-C 64 mg/dL, TG 625 mg/dL, Lp(a) 9 mg/dL
Questions and Answers