WHEN AND HOW TO PRESCRIBE STATINS

Statins are a class of medications that inhibit production of cholesterol in the liver. Whereas previous cholesterol guidelines emphasized the use of statin therapy to treat to target cholesterol levels, the 2013 ACC/AHA guideline on treating blood cholesterol focuses instead on the use of statin therapy to address the broader goal of reducing ASCVD risk and events. For this reason, the guideline recommends the use of statin therapy as first-line treatment not only for high-cholesterol patients but also for certain patients with known ASCVD or those with elevated risk for ASCVD.

Before initiating statin treatment in any patient, it should be emphasized that lifestyle changes [i.e., following a heart-healthy diet, exercising regularly, quitting and avoiding tobacco use, and maintaining a healthy weight] are a critical component of ASCVD prevention as well as cholesterol management. These areas require a thorough discussion and implementation to the extent recommended by the patient’s risk assessment and dictated by the patient’s level of compliance. Statins are the next focus of cholesterol management and/or risk reduction.

The guideline identifies four major groups of individuals [≥21 years old] as potentially benefitting from statins. For these groups, ASCVD risk reduction clearly outweighs the risk of adverse effects based on a strong body of evidence.

Four Major Statin Benefit Groups

1. Individuals with clinical ASCVD [i.e. acute coronary syndrome, or a history of myocardial infarction, stable or unstable angina, coronary or other arterial revascularization, stroke, transient ischemic attack, or peripheral arterial disease presumed to be of atherosclerotic origin]

2. Individuals with primary elevations of LDL-C ≥190 mg/dL

3. Individuals 40–75 years of age with diabetes and LDL-C 70–189 mg/dL without clinical ASCVD

4. Individuals without clinical ASCVD or diabetes who are 40–75 years of age and have LDL-C 70–189 mg/dL and an estimated 10-year ASCVD risk of ≥7.5%. [Clinician-patient discussion recommended before initiation of statin therapy].
Statin Therapy Recommendations

Recommendations for statin therapy in the four major statin benefit groups are summarized here and in Table 2. The use of statins in the group with known ASCVD is considered secondary prevention; and the use of statins in the other groups without ASCVD is considered primary prevention. An algorithm for determining appropriate statin therapy for individuals in these groups is presented in Figure 5 (see page 14).

**Figure 1**

**STATIN MANAGEMENT**

**CLINICAL ASCVD**

Heart-healthy lifestyle habits are the foundation of ASCVD prevention

A candidate for statin therapy

Not currently on statin therapy. Initial evaluation prior to statin initiation

- H & P
- Fasting lipid panel*
- ALT
- Hemoglobin A1c (if diabetes status unknown)
- CK (if indicated)
- Consider evaluation for other secondary causes (Table 6) or conditions that may influence statin safety (Table 8, Rec 1).

Evaluate and Treat Laboratory Abnormalities

1. Triglycerides ≥500 mg/dL
2. LDL-C ≥190 mg/dL
   - Secondary causes (Table 6)
   - If primary, screen family for FH
3. Unexplained ALT ≥3 x ULN

Clinical –Patient Discussion

1. Potential for ASCVD risk-reduction benefits
2. Potential for adverse effects and drug-drug interactions
3. Heart-healthy lifestyle
4. Management of other risk factors
5. Patient preferences
6. If decision is unclear, consider primary LDL-C ≥160 mg/dL, family history of premature ASCVD, lifetime ASCVD risk, abnormal AC score or ABI or hs-CRP ≥2 mg/L.

Age ≤75 y

without contraindications, conditions or drug-drug interactions influencing statin safety, or a history of statin intolerance

Initiate high-intensity statin therapy
Counsel on healthy lifestyle habits

Age >75 y

with conditions or drug-drug interactions influencing statin safety, or a history of statin intolerance

Initiate moderate-intensity statin therapy
Counsel on healthy lifestyle habits

No to statin

Encourage adherence to lifestyle
Manage other risk factors
Monitor adherence

Yes to statin

Encourage adherence to lifestyle
Initiate statin as appropriate intensity
Manage other risk factors
Monitor adherence and statin therapy

* For those in whom a risk assessment is uncertain, consider factors such as primary LDL-C ≥160 mg/dL, or other evidence of genetic hyperlipidemia, family history of premature ASCVD with onset <55 years of age in a first-degree male relative or <65 years of age in a first-degree female relative, hs-CRP ≥2 mg/L, CAC score ≥300 Agatston units, or ≥75th percentile for age, sex, and ethnicity (for additional information, see http://www.mesa-nhlbi.org/CARIReference.aspx). ABI <0.9 or lifetime risk of ASCVD. Additional factors that may aid in individual risk assessment may be identified in the future.
Heart-healthy lifestyle habits are the foundation of ASCVD prevention

A candidate for statin therapy

Not currently on statin therapy
Initial evaluation prior to statin initiation
- H & P
- Fasting lipid panel*
- ALT
- Hemoglobin A1c (if diabetes status unknown)
- CK (if indicated)
- Consider evaluation for other secondary causes (Table 6) or conditions that may influence statin safety (Table 8, Rec 1).

LDL-C ≥190 mg/dL

No diabetes

No Clinical ASCVD

High-intensity statin (Moderate-intensity if not a candidate)

Evaluate and Treat Laboratory Abnormalities
1. Triglycerides ≥500 mg/dL
2. LDL-C ≥190 mg/dL
   - Secondary causes (Table 6)
   - If primary, screen family for FH
3. Unexplained ALT ≥3 x ULN

INDIVIDUALS ≥21 YEARS OF AGE WITH LDL-C ≥190 MG/DL
Figure 3

STATIN MANAGEMENT
INDIVIDUALS 40–75 YEARS OF AGE WITHOUT DIABETES AND WITH LDL-C 70–189 MG/DL

Heart-healthy lifestyle habits are the foundation of ASCVD prevention

A candidate for statin therapy

Not currently on statin therapy

Initial evaluation prior to statin initiation
- H & P
- Fasting lipid panel*
- ALT
- Hemoglobin A1c (if diabetes status unknown)
- CK (if indicated)
- Consider evaluation for other secondary causes (Table 6) or conditions that may influence statin safety (Table 8, Rec 1).

No to statin

Evaluate and Treat Laboratory Abnormalities
1. Triglycerides ≥500 mg/dL
2. LDL-C ≥190 mg/dL
   - Secondary causes (Table 6)
   - If primary, screen family for FH
3. Unexplained ALT ≥3 x ULN

No diabetes

No Clinical ASCVD

Estimate 10-y ASCVD risk every 4–6 y

≥7.5% 10-y ASCVD risk
(Moderate- or high-intensity statin)

5% to <7.5% 10-y ASCVD risk
(Moderate-intensity statin)

Clinical –Patient Discussion
1. Potential for ASCVD risk-reduction benefits
2. Potential for adverse effects and drug-drug interactions
3. Heart-healthy lifestyle
4. Management of other risk factors
5. Patient preferences
6. If decision is unclear, consider primary LDL-C ≥160 mg/dL, family history of premature ASCVD, lifetime ASCVD risk, abnormal AC score or ABI or hs-CRP ≥2 mg/L *

No to statin
- Encourage adherence to lifestyle
- Manage other risk factors
- Monitor adherence

Yes to statin
- Encourage adherence to lifestyle
- Initiate statin as appropriate intensity
- Manage other risk factors
- Monitor adherence and statin therapy

* For those in whom a risk assessment is uncertain, consider factors such as primary LDL-C ≥160 mg/dL or other evidence of genetic hyperlipidemia, family history of premature ASCVD with onset <55 years of age in a first-degree male relative or <65 years of age in a first-degree female relative, hs-CRP ≥2 mg/L, CAC score ≥300 Agatston units, or ≥75th percentile for age, sex, and ethnicity for additional information, see http://www.mesa-nhlbi.org/CACReference.aspx, ABI <0.9, or lifetime risk of ASCVD. Additional factors that may aid in individual risk assessment may be identified in the future.
Heart-healthy lifestyle habits are the foundation of ASCVD prevention

A candidate for statin therapy

Not currently on statin therapy

Initial evaluation prior to statin initiation

• H & P
• Fasting lipid panel*
• ALT
• Hemoglobin A1c (if diabetes status unknown)
• CK (if indicated)
• Consider evaluation for other secondary causes (Table 6) or conditions that may influence statin safety (Table 8, Rec 1).

Evaluate and Treat Laboratory Abnormalities

1. Triglycerides ≥500 mg/dL
2. LDL-C ≥190 mg/dL
   • Secondary causes (Table 6)
   • If primary, screen family for FH
3. Unexplained ALT ≥3 x ULN

Diabetes

No Clinical ASCVD

10 year ASCVD risk ≥7.5%

NO

Moderate-intensity statin

YES

High-intensity statin

*Fasting lipid panel includes total cholesterol, HDL cholesterol, and triglycerides.
Table 2: Summary of Key Recommendations for the Treatment of Blood Cholesterol to Reduce ASCVD Risk in Adults

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. Heart-healthy lifestyle habits should be encouraged for all individuals</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>B. The appropriate intensity of statin therapy should be initiated or continued:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Clinical ASCVD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a. Age ≤75 y and no safety concerns: High-intensity statin</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>b. Age &gt;75 y or safety concerns: Moderate-intensity statin</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>2. Primary prevention—Primary LDL-C ≥190 mg/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a. Rule out secondary causes of hyperlipidemia (Table 6)</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>b. Age ≥21 y: High-intensity statin</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>c. Achieve at least a 50% reduction in LDL-C</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>d. LDL-C lowering nonstatin therapy may be considered to further reduce LDL-C</td>
<td>IIb</td>
<td>C</td>
</tr>
<tr>
<td>3. Primary prevention—Diabetes 40–75 years of age and LDL-C 70–189 mg/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a. Moderate-intensity statin</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>b. Consider high-intensity statin when ≥7.5% 10-y ASCVD risk using the Pooled Cohort Equations †</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>4. Primary prevention—No diabetes 40–75 years of age and LDL-C 70–189 mg/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a. Estimate 10-y ASCVD risk using the Risk Calculator based on the Pooled Cohort Equations † in those NOT receiving a statin; estimate risk every 4–6 y</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>b. To determine whether to initiate a statin, engage in a clinician-patient discussion of the potential for ASCVD risk reduction, adverse effects, drug–drug interactions, and patient preferences</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>c. Re-emphasize heart-healthy lifestyle habits and address other risk factors</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>i. ≥7.5% 10-y ASCVD risk: Moderate- or high-intensity statin</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>ii. 5 to &lt;7.5% 10-y ASCVD risk: Consider moderate-intensity statin</td>
<td>IIb</td>
<td>C</td>
</tr>
<tr>
<td>iii. Other factors may be considered ‡: LDL-C ≥160 mg/dL, family history of premature ASCVD, hs-CRP ≥2.0 mg/L, CAC score ≥300 Agaston units, ABI &lt;0.9, or lifetime ASCVD risk</td>
<td>IIb</td>
<td>C</td>
</tr>
<tr>
<td>5. Primary prevention when LDL-C &lt;190 mg/dL and age &lt;40 or &gt;75 y, or &lt;5% 10-y ASCVD risk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a. Statin therapy may be considered in selected individuals ‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Statin therapy is not routinely recommended for individuals with NYHA class II-IV heart failure or who are receiving maintenance hemodialysis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Refer to page 35 for applying the Class of Recommendation and Level of Evidence.
### Recommendations

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>**C. Regularly monitor adherence to lifestyle and drug therapy with lipid and</td>
<td></td>
<td></td>
</tr>
<tr>
<td>safety assessments**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Assess adherence, response to therapy, and adverse effects within 4–12 wk</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>following statin initiation or change in therapy</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>a. Measure a fasting lipid panel</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>b. Do not routinely monitor ALT or CK unless symptomatic</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>c. Screen and treat type 2 diabetes according to current practice guidelines.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Heart-healthy lifestyle habits should be encouraged to prevent progression to</td>
<td></td>
<td></td>
</tr>
<tr>
<td>diabetes</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>d. Anticipated therapeutic response: approximately ≥50% reduction in LDL-C from</td>
<td></td>
<td></td>
</tr>
<tr>
<td>baseline for high-intensity statin and 30% to &lt;50% for moderate-intensity statin</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>i. Insufficient evidence for LDL-C or non-HDL-C treatment targets from RCTs</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>ii. For those with unknown baseline LDL-C, an LDL-C &lt;100 mg/dL was observed</td>
<td></td>
<td></td>
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<tr>
<td>in RCTs of high-intensity statin therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>e. Less than anticipated therapeutic response:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>i. Reinforce improved adherence to lifestyle and drug therapy</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>ii. Evaluate for secondary causes of hyperlipidemia if indicated (Table 6)</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>iii. Increase statin intensity, or if on maximally-tolerated statin intensity,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>consider additions of nonstatin therapy in selected high-risk individuals §</td>
<td>IIb</td>
<td>C</td>
</tr>
<tr>
<td>f. Regularly monitor adherence to lifestyle and drug therapy every 3–12 mo</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>once adherence has been established. Continue assessment of adherence for</td>
<td></td>
<td></td>
</tr>
<tr>
<td>optimal ASCVD risk reduction and safety</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>1. If there are muscle or other symptoms, establish that they are related to</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>the statin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. For specific recommendations on managing muscle symptoms (Table 8)</td>
<td>IIa</td>
<td>B</td>
</tr>
</tbody>
</table>

*Clinical ASCVD includes acute coronary syndromes, history of ML stable or unstable angina, coronary or other arterial revascularization, stroke, TIA, or peripheral arterial disease presumed to be of atherosclerotic origin.


‡These factors may include primary LDL-C ≥160 mg/dL or other evidence of genetic hyperlipidemias; family history of premature ASCVD with onset <55 years of age in a first-degree male relative or <65 years of age in a first-degree female relative; hs-CRP ≥2 mg/L; CAC score ≥300 Agaston units or ≥75th percentile for age, sex, and ethnicity (for additional information, see http://www.mesa-nhlbi.org/CACReference.aspx); ABI < 0.9; or lifetime risk of ASCVD. Additional factors that might aid in individual risk assessment could be identified in the future.

§High-risk individuals include those with clinical ASCVD, an untreated LDL-C ≥190 mg/dL suggesting genetic hypercholesterolemia, or individuals with diabetes 40 to 75 years of age and LDL-C 70 to 189 mg/dL.

ABI indicates ankle-brachial index; ACC, American College of Cardiology; AHA, American Heart Association; ALT, alanine aminotransferase, a test of hepatic function; ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium; CHD, coronary heart disease; CK, creatinine kinase, a test of muscle injury; COR, Class of Recommendation; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; LOE, Level of Evidence; NHLBI, National Heart, Lung, and Blood Institute; NYHA, New York Heart Association; RCTs, randomized controlled trials; and TIA, transient ischemic attack.
Heart-healthy lifestyle habits are the foundation of ASCVD prevention
(See 2013 AHA/ACC Lifestyle Management Guideline)

Age ≥21 y and a candidate for statin therapy

Clinical ASCVD

Yes

Age ≤75 y
High-intensity statin
(Moderate-intensity statin if not candidate for high-intensity statin)

No

Yes

Age >75 y OR if not candidate for high-intensity statin
Moderate-intensity statin

Definitions of High- and Moderate-Intensity Statin Therapy *
(See Table 5)

High
Daily dose lowers LDL-C by approx. ≥50%

Moderate
Daily dose lowers LDL-C by approx. 30% to <50%

Regularly monitor adherence to lifestyle and drug therapy with lipid and safety assessments
(See Fig. 5)

LDL-C ≥190 mg/dL

Yes

High-intensity statin
(Moderate-intensity statin if not candidate for high-intensity statin)

No

Diabetes
LDL-C 70-189 mg/dL
Age 40-75 y

Yes

Moderate-intensity statin

No

Estimated 10-y ASCVD risk 37.5% †
High-intensity statin

Primary prevention
(No diabetes, LDL-C 70 to 189 mg/dL, and not receiving statin therapy)

Estimate 10-y ASCVD risk every 406 u
using Pooled Cohort Equations †

≥7.5% 10-y ASCVD risk
(Moderate- or high-intensity statin)

5% to <7.5% 10-y ASCVD risk
(Moderate-intensity statin)

≤5% 10-y ASCVD risk ‡

DM age <40 or >75 y or LDL-C <70 mg/dL

In selected individuals, additional factors may be considered to inform treatment decision making §

Clinician-Patient Discussion
Prior to initiating statin therapy, discuss

1. Potential for ASCVD risk-reduction benefits
2. Potential for adverse effects and drug-drug interactions ¶
3. Heart-healthy lifestyle
4. Management of other risk factors
5. Patient preferences
6. If decision is unclear, consider primary LDL-C ≥160 mg/dL, family history of premature ASCVD, lifetime ASCVD risk or ABI, OR HS-CRP ≥2 MG/L §

Emphasize adherence to lifestyle
Manage other risk factors
Monitor adherence *

No to statin

Yes to statin

Encourage adherence to lifestyle
Initiate statin at appropriate intensity
Manage other risk factors
Monitor adherence * (See Fig. 5)
Intensity of Statin Therapy

Intensity of statin therapy is defined based on the average LDL-C response to a specific statin dose. High-intensity statin therapy reduces ASCVD events more than moderate-intensity therapy, but lower-intensity statin therapy has also been shown to reduce ASCVD events, although to a lesser degree. To ensure that patients receive the most benefit from statin therapy, patients should generally be treated with the maximum appropriate intensity of a statin that is tolerated, provided there are no contraindications or safety issues, such as drug-drug interactions.

Table 3 provides a summary of the medications that constitute high-, moderate-, and low-intensity statin therapy and their recommended dosages.

### Table 3. High-, Moderate-, and Low-Intensity Statin Therapy

<table>
<thead>
<tr>
<th>High-Intensity Statin Therapy</th>
<th>Moderate-Intensity Statin Therapy</th>
<th>Low-Intensity Statin Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily dose lowers LDL-C, on average, by approximately ≥50%</td>
<td>Daily dose lowers LDL-C, on average, by approximately 30% to &lt;50%</td>
<td>Daily dose lowers LDL-C, on average, by &lt;30%</td>
</tr>
<tr>
<td><strong>Atorvastatin (40†)–80 mg</strong></td>
<td><strong>Atorvastatin 10 (20) mg</strong></td>
<td><strong>Simvastatin 10 mg</strong></td>
</tr>
<tr>
<td><strong>Rosuvastatin 20 (40) mg</strong></td>
<td><strong>Rosuvastatin (5) 10 mg</strong></td>
<td><strong>Pravastatin 10–20 mg</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Simvastatin 20–40 mg‡</strong></td>
<td><strong>Lovastatin 20 mg</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Pravastatin 40 (80) mg</strong></td>
<td><strong>Fluvastatin 20–40 mg</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Pitavastatin 1 mg</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Lovastatin 40 mg</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Fluvastatin 40 mg BID</strong></td>
<td></td>
</tr>
</tbody>
</table>

**Boldface type** indicates specific statins and doses that were evaluated in RCTs included in CQ1, CQ2, and the Cholesterol Treatment Trialists 2010 meta-analysis included in CQ3. All these RCTs demonstrated a reduction in major cardiovascular events. **Italic type** indicates statins and doses that have been approved by the FDA but were not tested in the RCTs reviewed.

**BID** indicates twice daily; **CQ**, critical question; **FDA**, Food and Drug Administration; **LDL-C**, low-density lipoprotein cholesterol; and **RCTs**, randomized controlled trials.

*Individual responses to statin therapy varied in the RCTs and should be expected to vary in clinical practice. There might be a biological basis for a less-than-average response.

† Evidence from 1 RCT only: down-titration if unable to tolerate atorvastatin 80 mg in the IDEAL [Incremental Decrease through Aggressive Lipid Lowering] study.

‡ Although simvastatin 80 mg was evaluated in RCTs, initiation of simvastatin 80 mg or titration to 80 mg is not recommended by the FDA because of the increased risk of myopathy, including rhabdomyolysis.
Monitoring of Statin Therapy

Adherence to medication and lifestyle changes, therapeutic response to statin therapy, and adverse effects should be regularly assessed. This should also include a fasting lipid panel performed within 4–12 weeks after initiation or dose adjustment and every 3–12 months thereafter. Other safety measurements should be measured as clinically indicated. The algorithm in Figure 6 provides guidance for monitoring therapeutic response and adherence to statin therapy.

Figure 6. Statin Therapy: Monitoring Therapeutic Response and Adherence

- Assess medication and lifestyle adherence
  - Fasting lipid panel
- Anticipated therapeutic response?
  - Yes: Reinforce continued adherence
    - Follow-up 3-12 mo
  - No: Less-than-anticipated therapeutic response?
    - Yes: Intolerance to recommended dose of statin therapy?
      - Yes: Management of statin intolerance (Table 6, Rec 8)
      - No: Reinforce medication adherence
        - Reinforce adherence to intensive lifestyle changes
        - Exclude secondary causes of hypercholesterolemia (Table 6)
        - Follow-up 4-12 wk
    - No: Reinforce improved adherence
      - Increase statin intensity
      - OR
      - Consider addition of nonstatin drug therapy
      - Follow-up 4-12 wk & thereafter as indicated

- Indicators of anticipated therapeutic response and adherence to selected statin therapy:
  - High-intensity statin therapy reduces LDL-C approx. ≥50% from the untreated baseline.
  - Moderate-intensity statin therapy reduces LDL-C approx. 30% to <50% from the untreated baseline.

- Anticipated therapeutic response: High-intensity statin therapy reduces LDL-C approx. >50% from the untreated baseline. Moderate-intensity statin therapy reduces LDL-C approx. 30% to <50% from the untreated baseline.

- Follow-up 4-12 wk & thereafter as indicated

* Fasting lipid panel preferred. In a non-fasting individual, a non–HDL-C level ≥220 mg/dL may indicate genetic hypercholesterolemia that requires further evaluation or a secondary etiology. If non-fasting triglycerides are ≥500 mg/dL, a fasting lipid panel is required.

† The Pooled Cohort Equations can be used to estimate 10-year ASCVD risk in individuals with and without diabetes.

‡ These factors may include primary LDL-C >160 mg/dL or other evidence of genetic hyperlipidemias, family history of premature ASCVD with onset <55 years of age in a first degree male relative or <65 years of age in a first degree female relative, sensitivity-C-reactive protein >2 mg/L ≥300 Agatston units or ≥75 percentile for age, sex, and ethnicity (For additional information, see http://www.mesa-nhlbi.org/CACReference.aspx), ABI <0.9, or lifetime risk of ASCVD. Additional factors that may aid in individual risk assessment may be identified in the future.

§1] Potential ASCVD risk reduction benefits (e.g., absolute risk reduction from moderate- or high-intensity statin therapy can be approximated by using the estimated 10-year ASCVD risk and the relative risk reduction of ~30% for moderate-intensity statin or ~45% for high-intensity statin therapy. 2) Potential adverse effects. The excess risk of diabetes is the main consideration in -0.1 excess case per 100 individuals treated with a moderate-intensity statin for 1 year and -0.3 excess cases per 100 individuals treated with a high-intensity statin treated patients for 1 year. Note: A case of diabetes is not considered equivalent to a fatal or nonfatal MI or stroke. Both statin-treated and placebo-treated participants experienced the same rate of muscle symptoms. The actual rate of statin-related muscle symptoms in the clinical population is unclear. Muscle symptoms attributed to statin should be evaluated in Table 8, Safety Rec 8.
HDL-C indicates high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; RCTs, randomized clinical trials; ABI, ankle-brachial index; ALT, alanine transaminase; ASCVD indicates atherosclerotic cardiovascular disease; CK, creatine kinase; FH, familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; and ULN, upper limit of normal.

**Key Points to Monitoring Statin Effects and Side Effects include:**

- First review heart-healthy lifestyle habits
- Assess adherence
- Response to therapy
- Adverse effects within 4 to 12 weeks following statin initiation or change in therapy
- Measure fasting lipid levels
- Unless symptomatic, do not routinely monitor creatine kinase levels
- If ALT and/or AST are ≥3x ULN, decrease or stop statin and consider other causes of liver disease; otherwise when statin dose is optimized and ALT and AST are ≤3x ULN normal liver enzymes do not need to be repeated.
- Screen for and treat type 2 diabetes according to current guidelines
Safety Considerations for Statin Therapy

Side Effects

Although statins are generally well tolerated and highly effective, some patients do experience side effects. The most common are myalgias (muscle aches, pains, weakness, or cramps). These side effects are often treatable and reversible.

A detailed list of adverse effects that are associated with statins can be found here. Of the ones listed, hepatotoxicity, myositis, rhabdomylosis, are the most serious. Recent research linking statin use with new-onset diabetes mellitus is also of concern. To address these issues, the guideline makes specific recommendations to assess for possible side effects related to statins in here. It is reasonable to evaluate and treat muscle symptoms including pain, tenderness, stiffness, cramping, weakness, or fatigue, for example. Screening for certain problems that can occur while taking statins [e.g. new-onset diabetes mellitus] is also advised.

| Table 4. How to Manage Statin Intolerance |
| Make sure there is no reversible cause such as: |
| › Medication interaction |
| › Hypothyroidism |
| With mild symptoms, try reducing the dose of statin |
| With intolerable symptoms, stop the statin |
| When symptoms resolve, attempt rechallenge: |
| › Low dose of same or different statin |
| › Dose statin intermittently, for instance, 2–3 times a week |
| › Use an alternative statin [eg, fluvastatin or pravastatin] plus ezetimibe or bile acid sequestrant |
| If symptoms return, use non–statin-based cholesterol-lowering medication such as ezetimibe or bile acid sequestrant [cholestyramine or colesvelam] |
| Encourage a healthy lifestyle in any event in all patients such as smoking cessation, weight loss, diet low in saturated fat, increased physical activity |
Statin Intolerance and Resulting Noncompliance

Some patients develop statin intolerance, an inability to use a statin. Statin intolerance is a result of unacceptable side effects (real or perceived) experienced by the patients or due to evidence from lab tests (e.g. abnormal markers of liver or muscle function), which may indicate organ dysfunction related to the statin. Patients who present with side effects or problems that lead to statin intolerance may choose to stop the medication. When faced with this situation, providers need to engage in an active discussion with their patients to determine exactly what is occurring. True intolerance to statins, as opposed to dose-titration intolerance, is rare and may possibly be resolved by evaluating and treating underlying health problems contributing to statin intolerance. To facilitate resolving issues related to statin intolerance, the guideline advises a basic algorithm to follow: see recommendation no. 8, in Table 8 of the guideline.

If and when symptoms resolve after discontinuing the statin, it is reasonable to consider a statin rechallenge, if the patient is willing. In many cases this “drug holiday” followed by a rechallenge can result in successful treatment. Some ways to rechallenge can include:

- Prescribing a low dose of the same or different statin.
- Dosing the statin intermittently
- Using an alternative statin (e.g. fluvastatin or pravastatin) with exetimibe or bile acid sequestant.

If symptoms do return, use of a nonstatin-based cholesterol-lowering medication such as ezetimibe or bile acid sequestrant (cholestryramine or colesvelam) is recommended. See Table 4 for a list of additional alternatives. Additionally, reinforcing and encouraging a heart-healthy lifestyle as described on page 27 can also provide benefit to the patient.

Patient Discussions About Side Effects

Side effects and fear of side effects such as muscle aches, pains, weakness, or cramps, are one of the primary patient barriers to initiating medication and medication adherence. Start the discussion by clearly communicating the benefits of statins in reducing incidence and risk of major ASCVD events. Ensure that the patient understands measures that will be taken to screen for and anticipate side effects, such as measurement of transaminase [alanine transaminase; ALT] levels and regular diabetes screening. Then discuss possible
risks, potential side effects including the probabilities of their occurrence, and discuss an action plan for dealing with any side effects with the patient. Emphasize that

- **most side effects are harmless**
- **side effects happen to few patients taking the drugs**
- **side effects abate when the medication is stopped.**

The most serious side effect, muscle breakdown (rhabdomyolysis), is quite rare (~1/10,000) and typically begins with moderately severe muscle aching. Urge the patient to report this complaint immediately, which may be a signal to stop taking the medication. With progression, myoglobinuria and renal insufficiency may ensue and require hospitalization. There is no withdrawal effect from suddenly stopping these medications. Revisit the conversation about side effects regularly.

A discussion of the magnitude of these risks versus the loss of benefit from the statin is an integral part of the provider-patient relationship. Involving patients in the decision-making process to arrive at a solution may help increase their compliance with the treatment plan.

- **Muscle complaints**—Warn patients taking statins to report worsening muscle pain without delay. Reassure them that prompt attention to this symptom can minimize an otherwise serious side effect.
- **Liver complaints**—If ALT and/or AST are ≥3x ULN, decrease or stop statin and consider other causes of liver disease; otherwise when statin dose is optimized and ALT and AST are ≤3x ULN normal liver enzymes do not need to be repeated.
- **Diabetes**—Statin treatment slightly increases the risk of developing diabetes.

**Patient discussion tip:** Use open-ended questions to discuss the patient’s fears about statin therapy.

*What are your fears or concerns regarding statins?*
Long-Term Management

In the 2013 ACC/AHA cholesterol guideline, there was no evidence found to support the continued use of specific LDL-C or non-HDL-C treatment targets. Nor was there any evidence that titrated (dose-adjusted) statin therapy or combination drug therapy to achieve specific target levels or percent reductions improved ASCVD outcomes. In addition, there was no data to support the routine use of nonstatin drugs combined with statin therapy to further reduce ASCVD events. Moreover, no RCTs were found that assessed ASCVD outcomes in statin-intolerant patients.

However, providers treating high-risk patients who have any of the three responses listed below may consider the addition of a nonstatin cholesterol-lowering therapy.

- Patients with a less-than-anticipated response to statins
- Patients who are unable to tolerate a less-than-recommended intensity of a statin
- Patients who are completely statin intolerant

High-risk patients include those with ASCVD, LDL-C ≥190 mg/dL, or diabetes between 40–75 years of age. In these situations, this guideline recommends clinicians preferentially prescribe drugs that have been shown in RCTs to provide ASCVD risk reduction benefits that outweigh the potential for adverse effects and drug-drug interactions along with consideration of patient preferences.

Whatever decision results, emphasize the substantial and safe benefits of heart-healthy lifestyle changes. That is where the emphasis should remain.

DID YOU KNOW?

Two recent trials, IMPoved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE IT) and Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER) trial have both recently demonstrated incremental benefit when a nonstatin agent is added to statin therapy. IMPROVE IT is the first trial demonstrating a reduction in cardiovascular events when a nonstatin agent (ezetimibe) is added to statin therapy and FOURIER showed a reduction of cardiovascular events when Evolocumab was added to statin therapy in elevated risk patients

Patient discussion tip: “Treating to Risk, Not Numbers”

Using patient-friendly language, explain that you are not recommending getting LDL-C levels down to a specific target number but rather treating the risk of future heart attack and stroke.
**Non-Statin Pharmacotherapy**

A number of alternatives treatments to statin therapy have proven effective in both improving lipid profiles and reducing cardiovascular events. A list of these treatments along with, dosing, actions, side effects, contraindications and clinical trial result information can be found in the table below. Proprotein convertase subtilisin/kexin 9 (PCSK9) agents are the newest, most expensive, and most dramatic reducers of LDL-C. Each class of agents has its place in the lipid armamentarium. Your knowledgeable discussion of risks and benefits of each will guide your patients to the best regimen for their unique situation.

**Table 5. Drugs Affecting Lipid Metabolism**

<table>
<thead>
<tr>
<th>Lipid/Lipoprotein Effects</th>
<th>Side Effects</th>
<th>Contraindications</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bile acid sequestrants</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Cholestyramine (4–16 g) Questran®, generics</td>
<td>LDL-C ↓ 15%–30% LDL particle number ↓ 15%–30% HDL-C ↑ 3%–5% TG no change or increase</td>
<td>GI distress</td>
<td>Absolute: Dysbetalipoproteinemia</td>
</tr>
<tr>
<td>• Colestipol (5–20 g Colestid®, generics</td>
<td></td>
<td>Constipation</td>
<td>TG &gt;400 mg/dL</td>
</tr>
<tr>
<td>• Colesevelam (2.6–3.8 g Welchol®</td>
<td></td>
<td>Decreased absorption of other drugs</td>
<td>Relative: TG &gt;200 mg/dL</td>
</tr>
<tr>
<td>Nicotinic acid</td>
<td></td>
<td></td>
<td>Reduced major coronary events and CHD deaths</td>
</tr>
<tr>
<td>• Immediate-release crystalline nicotinic acid (1.5–3 g) Niacor®, Nicolar®</td>
<td>LDL-C ↓ 5%–25% LDL particle number ↓ 10%–25% HDL-C ↑ 15%–35% HDL-P no change TG ↓ 20%–45%</td>
<td>Flushing</td>
<td>Absolute: Unexplained hepatic dysfunction, active peptic ulcer, arterial bleeding</td>
</tr>
<tr>
<td>• Extended-release nicotinic acid (1–2 g) Niaspan®</td>
<td></td>
<td>Hyperglycemia</td>
<td>Relative: DM</td>
</tr>
<tr>
<td>• Sustained-release nicotinic acid (1–2 g) Slo-Niacin®</td>
<td></td>
<td>Hyperuricemia (or gout)</td>
<td>Hyperuricemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Upper GI distress</td>
<td>Peptic ulcer disease</td>
</tr>
<tr>
<td>Table 5. Drugs Affecting Lipid Metabolism</td>
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<td></td>
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<tr>
<td><strong>Lipid/Lipoprotein Effects</strong></td>
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<tr>
<td><strong>Fibric acids</strong></td>
<td>LDL-C ↓ 5%-20% [may be increased in patients with high TG]</td>
<td>Dyspepsia</td>
<td>Absolute: Severe renal dysfunction or dialysis</td>
</tr>
<tr>
<td>• Gemfibrozil (600 mg bid) Lopid®, generics</td>
<td>LDL particle number ↓ 5%-20%</td>
<td>Gallstones</td>
<td>Active liver disease &amp; unexplained aminase elevation</td>
</tr>
<tr>
<td>• Fenofibrate (various doses) Antara®, Fenoglide®, Lipanthyl®, Lipofen®, Lofibra®, Tricor®, Triglide®, generics</td>
<td>HDL-C ↑ 10%-20%</td>
<td>Myopathy</td>
<td>Gall bladder disease</td>
</tr>
<tr>
<td>• Clofibrate (1,000 mg bid) generics</td>
<td>HDL-P ↑ 10%</td>
<td>Unexplained non-CHD deaths in WHO study using clofibrate</td>
<td>Nursing mothers</td>
</tr>
<tr>
<td>• Fenofibric acid Trilipix® (35-135 mg), Fibrinor® (35-105 mg)</td>
<td>TG ↓ 20%-50%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ezetimibe</strong></td>
<td>LDL-C ↓ 15%-20%</td>
<td>Myalgia, rare</td>
<td>Previous sensitivity</td>
</tr>
<tr>
<td>• Zetia®</td>
<td>LDL particle number ↓ 15-25% HDL-C ↑ 1%-2%</td>
<td>LFT values increase</td>
<td>No outcome trials completed</td>
</tr>
<tr>
<td></td>
<td>TG ↓ 10%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Omega-3</strong></td>
<td>LDL-C neutral or increase LDL-P neutral to ↓ 3%-5% [not significant in multiple trials]</td>
<td>Fishy taste</td>
<td>Relative: Fish hypersensitivity</td>
</tr>
<tr>
<td>• Lovaza® [EPA + DHA] (4 g)</td>
<td>HDL-C neutral to ↑ 10% HDL-P ↓ 2%</td>
<td>↑ bleeding time which does not exceed normal limits</td>
<td>Reduced mortality and sudden death in patients with history of MI, as well as patients with congestive heart failure</td>
</tr>
<tr>
<td></td>
<td>TG ↓ 20%-45%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ApoB ↓ 4%-5%</td>
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<tr>
<td>Lipid/Lipoprotein Effects</td>
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</tr>
<tr>
<td>Vascepa™ [EPA] (4 g)</td>
<td>LDL-C not increased LDL particle number ↓ 4%–15% HDL-C neutral TG ↓ 20%–45% ApoB ↓ 8.5%</td>
<td>Fishy taste</td>
<td>Relative: Fish hypersensitivity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑ bleeding time which does not exceed normal limits</td>
<td>Reduced nonfatal MI in Japanese patients on low-dose statin treatment</td>
</tr>
<tr>
<td>Proprotein convertase subtilisin/kexin 9 [PCSK9]</td>
<td>LDL-C ↓ 61%</td>
<td>Rash, urticaria, hypersensitivity vasculitis, respiratory infection, injection site reactions</td>
<td>Lower incidence of major cardiovascular events</td>
</tr>
<tr>
<td>Alirocumab Praluent® (75 mg SC Q2W)</td>
<td></td>
<td>Relative: Fish hypersensitivity</td>
<td></td>
</tr>
<tr>
<td>Evolocumab Repatha® (140 mg Q2W or 420 mg QM)</td>
<td>LDL-C ↓ 61%</td>
<td>Rash, urticarial, respiratory infections, back pain, injection site reactions, neurocognitive vents</td>
<td>Not reported</td>
</tr>
</tbody>
</table>