2013 ACC/AHA Guidelines Cholesterol Rx to Reduce ASCVD Risk in Adults

Major recommendations for statin therapy for ASCVD prevention.

CLASS I: Benefit >> Risk
CLASS IIa: Benefit >> Risk
CLASS IIb: Benefit ≈ Risk
CLASS III: No Benefit or CLASS III: Harm

ASCVD prevention benefit of statin therapy may be less clear in other groups. In selected individuals, consider additional factors influencing ASCVD risk and potential ASCVD risk benefits and adverse effects, drug-drug interactions, and patient preferences for statin treatment.

*% ↓ in LDL-C can be used as indication of response & adherence to Rx, but is not a Rx goal.
‡Primary LDL 160 mg/dL or evidence of genetic hyperlipidemias, FH of premature ASCVD, onset <55 yrs in 1st degree male or <65 yrs in 1st degree female relative, hsCRP >2 mg/L, CAC score ≥ 300 Agatston units or ≥75 percentile for age, sex, & ethnicity, ABI <0.9, or ↑ ASCVD lifetime risk.
Statin Therapy: Monitoring therapeutic response and adherence

Reinforce continued adherence
Flush lipid panel* 3-12 mo

Anticipated therapeutic response?

Fasting lipids preferred. Nonfasting non-HDL >220 mg/dL may indicate genetic condition that requires evalu for secondary etiology. If nonfasting TG >500 mg/dL, FLP is required.

*In those already on a statin, whom baseline LDL is unknown, an LDL <100 mg/dL was observed in most individuals receiving high-intensity statin in RCTs.

Follow-up 6-12 wk & thereafter as indicated

Less-than-anticipated therapeutic response?

Indications of anticipated therapeutic response and adherence to selected statin intensity:
- 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?

Reinforce improved adherence
Increase statin intensity
OR
Reinforce medication adherence
Reinforce adherence to lifestyle changes
Exclude secondary causes of hypercholesterolemia

Follow-up 6-12 wk

Management of statin intolerance

Clinical ASCVD
Not currently on statin therapy
Initial evaluation prior to statin initiation
- Fasting lipid panel* ALT OK (if indicated)
- Consider evaluation for other secondary causes or conditions that may influence statin safety

Evaluate and Treat Laboratory Abnormalities
1. Triglycerides >500 mg/dL
2. LDL-C >190 mg/dL
3. Secondary causes
   - A primary, genetic, family, or metabolic
   - Unexplained ALT >3X ULN

Initiating statin therapy in individuals with clinical ASCVD

Aged <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

Aged >75 y or 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

Monitor statin therapy

*Fasting lipids preferred. Nonfasting non-HDL >220 mg/dL may indicate genetic condition that requires evalu for secondary etiology. If nonfasting TG >500 mg/dL, FLP is required.
†Reasonable to evaluate potential for ASCVD benefits, adverse effects & consider patient preference, in initiating/continuing mod or high-intensity statin for ASCVD if >75 yrs old.
Initiating statin therapy in individuals without clinical ASCVD

- Fasting lipids preferred. Nonfasting non-HDL > 220 mg/dL may indicate genetic condition that requires eval for secondary etiology. If nonfasting TG > 500 mg/dL, FLP is required.
- Pooled Cohort Equations can be used to estimate 10-yr ASCVD risk with and without DM.
- These factors may include primary LDL > 160 mg/dL or evidence of genetic dyslipidemia, FH of premature ASCVD with onset < 55 yrs in first degree male or < 65 yrs in first degree female relative, hsCRP > 2 mg/L, CAC score > 300 Agatston units or > 75 percentile for age, sex, & ethnicity, ABI < 0.9, or ASCVD lifetime risk.
- 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-yr ASCVD risk and the relative risk reduction of ~30% for moderate-intensity statin or ~45% for high-intensity statins. 2) Potential adverse effects: Excess risk of DM is the main consideration in ~0.1 excess case per 100 individuals treated with a mod-intensity statin for 1 yr; ~0.3 excess cases per 100 individuals treated with a high-intensity statin treated patients for 1 yr. Note: a case of DM is not considered equivalent to a fatal or nonfatal MI or stroke. Both statin-treated and placebo-treated participants had the same rate of muscle symptoms. Actual rate of statin-related muscle symptoms in the clinical population is unclear. Muscle symptoms attributed to statin should be evaluated.
### High- Moderate- and Low-Intensity Statin Therapy

<table>
<thead>
<tr>
<th>High-Intensity Statin</th>
<th>Moderate-Intensity Statin</th>
<th>Low-Intensity Statin</th>
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</thead>
<tbody>
<tr>
<td>Daily dose lowers LDL-C on average, by ~25%</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>
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<tr>
<td>Atorvastatin (40(1)–80 mg)</td>
<td>Rosuvastatin 10 (20) mg</td>
<td>Simvastatin 10 mg</td>
</tr>
<tr>
<td>Pravastatin 20 (40) mg</td>
<td>Simvastatin 20–40 mg</td>
<td>Pravastatin 10–20 mg</td>
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<tr>
<td>Lovastatin 40 mg</td>
<td>Fluvastatin XL 80 mg</td>
<td>Lovastatin 20 mg</td>
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<tr>
<td>Fluvastatin 40 mg bid</td>
<td>Fluvastatin 40 mg</td>
<td>Fluvastatin 20–40 mg</td>
</tr>
<tr>
<td>Pitavastatin 2–4 mg</td>
<td>Pitavastatin 1 mg</td>
<td>Pitavastatin 1 mg</td>
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Specific statins and doses are noted in bold that were evaluated in RCTs. All of these RCTs demonstrated reduction in major cardiovascular events. Statins and doses that are approved by the U.S. FDA but were not tested in the RCTs reviewed are listed in italics.

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

Evidence from 1 RCT only: down-titration if unable to tolerate atorvastatin 80 mg in IDEAL. Although simvastatin 80 mg was evaluated in RCTs, initiation at 80 mg or titration to 80 mg is not recommended by the FDA due to increased risk of myopathy and rhabdomyolysis.

### Secondary Causes of Hyperlipidemia Most Commonly Encountered in Clinical Practice

<table>
<thead>
<tr>
<th>Secondary Cause</th>
<th>Elevated LDL-C</th>
<th>Elevated Triglycerides</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet</td>
<td>Saturated or trans fats, weight gain, anorexia</td>
<td>Weight gain, very low-fat diets, high refined carbohydrates intake, excess alcohol intake</td>
</tr>
<tr>
<td>Drugs</td>
<td>Diuretics, cyclosporine, glucocorticoids, amiodarone</td>
<td>Oral estrogen, glucocorticoids, bile acid sequestrants, protease inhibitors, retinoid acid, anabolic steroids, sirolimus, raloxifene, tamoxifen, beta blockers (not carvedilol), thiazides</td>
</tr>
<tr>
<td>Diseases</td>
<td>Biliary obstruction, nephrotic syndrome</td>
<td>Nephrotic syndrome, chronic renal failure, lipodystrophies</td>
</tr>
<tr>
<td>Disorders and altered states of metabolism</td>
<td>Hypothyroidism, obesity, pregnancy*</td>
<td>Diabetes (poorly controlled), hypothyroidism, obesity, pregnancy*</td>
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</table>

*Cholesterol and triglycerides rise progressively throughout pregnancy; treatment with statins, niacin, and ezetimibe are contraindicated during pregnancy and lactation.

### Summary of Statin Safety Recommendations

1. To maximize safety of statins, selection of appropriate statin & dose in men & nonpregnant/nonnursing women is based on characteristics, level of ASCVD* risk, and potential for adverse effects.

   - Mod-intensity statins should be used if high-intensity is recommended but with characteristics predisposing to statin- adverse effects, such as:
     - Multiple or serious comorbidities, e.g. impaired renal or hepatic function.
     - History of previous statin intolerance or muscle disorders.
     - Unexplained ALT elevations >3 times ULN.
     - Patient characteristics or concomitant drugs affecting statin metabolism.
     - >75 years of age.
     - Additional characteristics may include, but are not limited to:
       - History of hemorrhagic stroke.
       - Asian ancestry.

   - I
   - B

2a. CK should not be routinely measured in individuals receiving statins.

   - III: C
   - A

2b. Baseline measurement of CK is reasonable for individuals believed to be at increased risk for adverse muscle events based on a personal or family history of statin intolerance or muscle disease, clinical presentation, or concomitant drug therapy that might increase risk for myopathy.

   - IIa: C
   - C

2c. During statin Rx, reasonable to measure CK with muscle symptoms, e.g. pain, tenderness, stiffness, cramping, weakness, or generalized fatigue.

   - IIa: C
   - C
<table>
<thead>
<tr>
<th>Text</th>
<th>Level</th>
<th>Grade</th>
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<tbody>
<tr>
<td>1a. Baseline measurement of ALT before initiating statins.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>1b. During statin Rx, reasonable to measure hepatic function if symptoms suggest hepatotoxicity (e.g., unusual fatigue, weakness, loss of appetite, abdominal pain, dark-colored urine or yellowing of the skin or sclera).</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>2. Statin dose may be considered if 2 consecutive LDLs are &lt;40 mg/dL.</td>
<td>IIb</td>
<td>C</td>
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<tr>
<td>5. May be harmful to start simvastatin 80 mg or 1 dose to 80 mg daily.</td>
<td>III</td>
<td>Harm A</td>
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<tr>
<td>6. Individuals receiving statins should be evaluated for new-onset DM according to current screening guidelines. Those who develop DM during statin Rx should be encouraged to adhere to heart healthy diet, engage in physical activity, achieve and maintain a healthy body weight, cease tobacco use, and continue statins to reduce their risk of ASCVD events.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>7. For individuals taking any dose of statins, reasonable to use caution in those &gt;75 yrs, as well as those taking concomitant medications that alter drug metabolism, taking multiple drugs, or drugs for conditions that require complex medication regimens (e.g., for solid organ transplantation or HIV (Rx). Review manufacturer's prescribing information before initiating drug.</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>8. Reasons to evaluate/treat muscle symptoms, including pain, tenderness, stiffness, cramping, weakness, or fatigue, in statin-treated patients according to the following algorithm: • To avoid unnecessary discontinuation, obtain history of prior or current muscle symptoms to establish a baseline before initiating statin. • If unexplained severe muscle symptoms or fatigue develop during statin Rx, promptly stop statin &amp; address possibility of rhabdomyolysis by evaluating CK, Cr, &amp; U/A for myoglobinuria. • If mild to mod muscle symptoms develop on statin: – D/C statin till symptoms can be evaluated. – Evaluate for hypothyroidism, reduced renal or hepatic function, rheumatologic disorders such as polymyalgia rheumatica, steroid myopathy, vitamin D deficiency, or primary muscle diseases. • If symptoms resolve, &amp; no contraindication, give original or lower dose of same statin to establish causal relation between symptoms &amp; statin. • If a causal relation exists, D/C original statin. Once muscle symptoms resolve, use a low dose of a different statin. – Once low dose of statin is tolerated, gradually ↑ dose as tolerated. – If, after 2 months without statin, muscle symptoms or ↑ CK do not resolve completely, consider other causes of muscle symptoms as above. – If persistent muscle symptoms are from a condition unrelated to statin, or if prednisone condition was treated, resume statin at original dose.</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>9. For individuals presenting with a confusion state or memory impairment while on statin, reasonable to evaluate for nonstatin causes, e.g., exposure to other drugs, systemic &amp; neuropsychiatric causes, and possibility of adverse effects associated with statin Rx.</td>
<td>IIb</td>
<td>C</td>
</tr>
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</table>

*Based on presence of clinical ASCVD, DM. LDL >190 mg/dL, or est. 10-year ASCVD risk.

**Individuals with elevated ALT (>1.5 to 2 X ULN) were excluded from RCTs. Unexplained ALT >3 X ULN is a contraindication to statins as listed in manufacturer’s prescribing information. Statins use is associated with a very modest excess risk of new onset DM in RCTs meta-analyses (0.1 excess case per 100 individuals treated for 1 yr with moderate-intensity statin & 0.3 excess cases per 100 individuals treated for 1 yr with high-intensity statin). Increased risk of new onset DM is confined to those with risk factors for DM. They are also at higher risk of ASCVD due to these risk factors. If a statin-treated individual develops DM, detected by current diabetes screening guidelines, they should be counseled to adhere to a heart healthy diet, engage in physical activity, achieve and maintain a healthy body weight, cease tobacco use, and continue statin to reduce their risk of ASCVD events.

**Summary of Nonstatin Safety Recommendations**

**Safety of Niacin**

1. Baseline hepatic transaminases, fasting blood glucose or A1c, and uric acid should be obtained before initiating niacin, and again during up-titration to a maintenance dose and every 6 months thereafter. | I | B |
| 2. Niacin should not be used if: • Hepatic transaminase elevations are > 2 to 3 X ULN. • Persistent severe cutaneous symptoms, hyperglycemia, acute gout or unexplained abdominal pain or gastrointestinal symptoms occur. • New-onset atrial fibrillation or weight loss occurs. | III | Harm B |
3. With adverse effects from niacin, potential for ASCVD benefits/potential for adverse effects should be reconsidered before reintiating niacin.

4. To reduce frequency/severity of adverse cutaneous symptoms:
   • Start niacin at a low dose, titrate to higher dose over weeks as tolerated.
   • Take niacin with food or premedicating with ASA 325 mg 30 min before niacin dosing to alleviate flushing symptoms.
   • If extended-release preparation is used, increase dose from 500 mg to max 2,000 mg/day over 4-8 wks., with the dose increasing not > weekly.
   • If immediate-release niacin is chosen, start at a dose of 100 mg 3x daily and up-titrated to 3 g/day, divided into 2 or 3 doses.

Safety of Bile Acid Sequestrants (BAS)

1. BAS should not be used in individuals with baseline fasting TGs ≥300 mg/dL or type II hyperlipoproteinemia, because severe TG elevations might occur. (A fasting lipid panel should be obtained before BAS is initiated, 3 months after initiation, and every 6 to 12 months thereafter.)

2. Reasonable to use BAS with caution if baseline TGs are 250 to 299 mg/dL, and evaluate a fasting lipid panel in 4 to 6 weeks after initiation. Discontinue BAS if TGs exceed 400 mg/dL.

Safety of Cholesterol-Absorption Inhibitors

1. Reasonable to obtain baseline hepatic transaminases before initiating ezetimibe. When ezetimibe is coadministered with statin, monitor transaminases as clinically indicated; D/C ezetimibe if persistent ALT elevations >3 X ULN occur.

Safety of Fibrates

1. Gemfibrozil should not be initiated in patients on statins because of an increased risk for muscle symptoms and rhabdomyolysis.

2. Fenofibrate may be considered concomitantly with low-mod intensity statin only if the benefits from ASCVD risk reduction or TG lowering when TGs are >500 mg/dL, are judged to outweigh potential risk.

3. Renal status should be evaluated before fenofibrate initiation, within 3 months after initiation, and every 6 months thereafter. Assess renal safety with both a serum creatinine level and an eGFR based on creatinine.
   • Fenofibrate should not be used if moderate or severe renal impairment, defined as eGFR <30 mL/min per 1.73 m2, is present.
   • If eGFR is between 30 and 59 mL/min per 1.73 m2, the dose of fenofibrate should not exceed 54 mg/day.
   • If, during follow-up, the eGFR decreases persistently to ≤30 mL/min per 1.73 m2, fenofibrate should be discontinued.

Safety of Omega-3 Fatty Acids

1. If EPA and/or DHA are used for managing severe hypertriglyceridemia, defined as TGs ≥500 mg/dL, reasonable to evaluate the patient for gastrointestinal disturbances, skin changes, and bleeding.

Lifestyle as the Foundation for ASCVD Risk Reduction Efforts

It must be emphasized that lifestyle modification (i.e., adhering to a heart healthy diet, regular exercise habits, avoidance of tobacco products, and maintenance of a healthy weight) remains a critical component of health promotion and ASCVD risk reduction, both prior to and in concert with the use of cholesterol-lowering drug therapies. Healthy diet or lifestyle modifications were recommended as background therapy for the RCTs of cholesterol-lowering drug therapy.

Heart Failure and Hemodialysis

No recommendation was made regarding initiation or continuation of statins in 2 groups:
1) individuals with NYHA class II–IV heart failure, or
2) individuals undergoing maintenance hemodialysis.

In the 4 RCTs reviewed that specifically addressed statin treatment in these groups, there were individuals with and without heart disease. Although statin therapy did not reduce ASCVD events in 2 RCTs for each condition, there was insufficient information on which to base recommendations for or against statin treatment. Future research may identify subgroups of patients with these conditions that may benefit from statin therapy. In individuals with these conditions, the potential for ASCVD risk reduction benefits, adverse effects, and drug-drug interactions along with other cautions and contraindications to statin therapy and choice of statin dose must also be considered by the treating clinician.