2013 ACC/AHA Cholesterol Guidelines

The 2013 American Heart Association (AHA)/American College of Cardiology (ACC) lipid guidelines represent a paradigm shift in the treatment of dyslipidemia. These guidelines focus on reducing cardiovascular risk using proven interventions. Per the new guidelines, patients receive high- or moderate-dose statin therapy, depending on which of four “statin benefit groups” they fit into. The guidelines introduce a new risk calculator for estimation of 10-year cardiovascular disease risk. This calculator can be used to determine if a high- or moderate-dose statin is appropriate for primary prevention. Unlike previous guidelines, the 2013 guidelines do not recommend titrating the statin dose to achieve a specific LDL target. This is because randomized controlled trials have demonstrated cardiovascular risk reduction using specific statin doses, not LDL targets. Treating to a given target may result in statin undertreatment if an evidence-based statin dose is not used, or overtreatment. The addition of a nonstatin has not been proven to further reduce cardiovascular risk; therefore, nonstatins are no longer routinely recommended. The table below provides a summary of these guidelines, with an emphasis on pharmacotherapy.

--Information in table is from reference 1 unless otherwise denoted.--

<table>
<thead>
<tr>
<th>Who should be assessed for cardiovascular risk, and how?</th>
<th>For patients without atherosclerotic cardiovascular disease:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Assess traditional risk factors (e.g., lipids, blood pressure, diabetes) every four to six years in patients 20 to 79 years of age.²³</td>
</tr>
<tr>
<td></td>
<td>• In patients 40 to 75 years of age not receiving cholesterol-lowering therapy, and with LDL 70 to 189 mg/dL (1.8 to 4.9 mmol/L), also estimate 10-year risk using the Pooled Cohort Equations Cardiovascular Risk Calculator, available at <a href="http://my.americanheart.org/cvriskcalculator">http://my.americanheart.org/cvriskcalculator</a>. Get an app from iTunes (for iPhone, iPad, and iPod), or Google Play (for Android).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>What lifestyle changes are recommended to reduce cardiovascular risk?</th>
<th>Adhere to a heart-healthy diet:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Eat vegetables, fruits, whole grain, low-fat dairy, poultry, fish, beans, nontropical vegetable oils, and nuts, but avoid red meat (i.e., Mediterranean-style diet, DASH [Dietary Approaches to Stop Hypertension] diet).²</td>
</tr>
<tr>
<td></td>
<td>• Limit sugary drinks and sweets.²</td>
</tr>
<tr>
<td></td>
<td>• Limit saturated and trans fat to 5% to 6% of calories.²</td>
</tr>
<tr>
<td></td>
<td>• Limit sodium intake to 2400 mg daily (about one teaspoon table salt [kosher/sea salt have less sodium per teaspoon]).²</td>
</tr>
<tr>
<td></td>
<td>• For adults who would benefit from blood pressure lowering, further reduction to 1500 mg daily is ideal. Combine sodium restriction with the DASH diet.²</td>
</tr>
</tbody>
</table>

Exercise regularly:
• Engage in moderate-to-vigorous aerobic activity for at least 40 minutes (on average) three to four times each week.²

Avoid tobacco.
Maintain a healthy weight.
Who should be treated with a statin?  

<table>
<thead>
<tr>
<th>Pharmacotherapy</th>
<th>Use for…</th>
</tr>
</thead>
</table>
| High-dose Statin (average LDL reduction about 50% or higher):  
  - Atorvastatin 80 mg once daily (40 mg if 80 mg not tolerated).  
  - Rosuvastatin 20 mg to 40 mg once daily.  
| Secondary prevention in adults 75 years of age and younger.  
  (Level A)  
  - Primary prevention in adults with LDL 190 mg/dL (5 mmol/L) or higher.  
  (Level A)  
  - Primary prevention in adults 40 to 75 years of age with LDL 70 to 189 mg/dL (1.8 to 4.9 mmol/L) and an estimated 10-year risk of atherosclerotic cardiovascular disease of 7.5% or higher (moderate-dose also an option).  
  (Level A)  
  - Primary prevention in diabetes patients 40 to 75 years of age with LDL 70 to 189 mg/dL (1.8 to 4.9 mmol/L) and an estimated 10-year risk of atherosclerotic cardiovascular disease of 7.5% or higher.  
  (Level C) |
<table>
<thead>
<tr>
<th>Pharmacologic treatment options, continued</th>
<th>Pharmacotherapy</th>
<th>Use for…</th>
</tr>
</thead>
</table>
| Moderate-dose Statin (average LDL reduction about 30 to <50%):<sup>a</sup> | • Atorvastatin 10 to 20 mg once daily.<sup>b</sup>  
• Fluvastatin 40 mg twice daily or 80 mg (XL) once daily.<sup>b</sup>  
• Lovastatin 40 mg once daily.  
• Pitavastatin 2 to 4 mg once daily.<sup>b</sup>  
• Pravastatin 40 to 80 mg once daily.<sup>b</sup>  
• Rosuvastatin 5 to 10 mg once daily.<sup>b</sup>  
• Simvastatin 20 to 40 mg once daily. | • Secondary prevention in adults older than 75 years. (Level A)  
• Patients who cannot tolerate a high-dose statin.  
• Primary prevention in adults 40 to 75 years of age with LDL 70 to 189 mg/dL (1.8 to 4.9 mmol/L) and an estimated 10-year risk of atherosclerotic cardiovascular disease of 7.5% or higher (high-dose also an option). (Level A)  
• Primary prevention in diabetes patients 40 to 75 years of age, with LDL 70 to 189 mg/dL (1.8 to 4.9 mmol/L) and an estimated 10-year risk of atherosclerotic cardiovascular disease of less than 7.5%. (Level A) |
| Low-dose Statin (average LDL reduction <30%):<sup>a</sup> | • Fluvastatin 20 to 40 mg once daily.<sup>b</sup>  
• Lovastatin 20 mg once daily.  
• Pitavastatin 1 mg once daily.<sup>b</sup>  
• Pravastatin 10 to 20 mg once daily.  
• Simvastatin 10 mg once daily.<sup>b</sup> | • For patients who cannot tolerate a high- or moderate-dose statin. |
| Nonstatin | • Reinforce statin adherence and lifestyle changes, and check for secondary causes before adding a nonstatin.  
• Do not add gemfibrozil to statin therapy.  
• No proof adding a nonstatin to a statin further reduces cardiovascular risk. | • Triglycerides 500 mg/dL or higher (use omega-3 fatty acids [e.g., fish oil], niacin, or fenofibrate).  
• Patients who cannot tolerate the recommended statin dose or do not achieve the expected statin response and are high-risk (i.e., patient with LDL 190 mg/dL [5 mmol/L] or higher at baseline, diabetes, or clinical atherosclerotic cardiovascular disease). |
| How is statin therapy monitored? | • Check ALT (alanine aminotransferase) at baseline. Repeat only if symptoms of hepatotoxicity occur.  
• Document any pre-existing muscle symptoms before starting a statin to establish a baseline.  
• Consider checking creatine kinase at baseline in patients at increased risk for myopathy (e.g., drug interactions, etc). Repeat only if symptomatic.  
• If severe muscle symptoms or fatigue of unknown cause develop, hold the statin and check creatinine and urinalysis to rule-out rhabdomyolysis. | Continue… |

<sup>a</sup> Drug monograph or patient’s document.<sup>b</sup> Refer to Dosing section for more detailed information.
Statin monitoring, continued

- Check fasting lipid panel four to 12 weeks after statin initiation, then every three to 12 months.
  - Check adherence to statin and lifestyle interventions if LDL drop less than expected.
  - Consider statin dose reduction if two consecutive LDL measurements are less than 40 mg/dL (1.03 mmol/L).
  - Monitor for new-onset diabetes per diabetes screening guidelines.

a. Doses listed are for patients with normal renal function not taking an interacting medication. See our PL Chart, Characteristics of the Various Statins, for renal dosing and select drug interactions. High-dose, moderate-dose, and low-dose statin designations are categorical only. Actual statin percent LDL-lowering may vary in practice.
b. Atorvastatin 20 mg, fluvastatin extended-release (XL) 80 mg, fluvastatin 20 to 40 mg, pitavastatin, pravastatin 80 mg, rosuvastatin 5 mg and 40 mg, and simvastatin 10 mg are FDA-approved but lack evidence from randomized-controlled trials for reduction in major cardiovascular events.

Users of this PL Detail-Document are cautioned to use their own professional judgment and consult any other necessary or appropriate sources prior to making clinical judgments based on the content of this document. Our editors have researched the information with input from experts, government agencies, and national organizations. Information and internet links in this article were current as of the date of publication.
**Levels of Evidence**

In accordance with the trend towards Evidence-Based Medicine, we are citing the LEVEL OF EVIDENCE for the statements we publish.

<table>
<thead>
<tr>
<th>Level</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>High-quality randomized controlled trial (RCT) High-quality meta-analysis (quantitative systematic review)</td>
</tr>
<tr>
<td>B</td>
<td>Nonrandomized clinical trial Nonquantitative systematic review Lower quality RCT Clinical cohort study Case-control study Historical control Epidemiologic study</td>
</tr>
<tr>
<td>C</td>
<td>Consensus Expert opinion</td>
</tr>
<tr>
<td>D</td>
<td>Anecdotal evidence In vitro or animal study</td>
</tr>
</tbody>
</table>


**Project Leader in preparation of this PL Detail-Document:** Melanie Cupp, Pharm.D., BCPS

**References**


## Characteristics of the Various Statins

—Based on U.S. product labeling and relevant studies. Canadian product information given if differs significantly (e.g., more conservative) from U.S. (Full update November 2013)—

### View our helpful PL Chart, Non-Statin Lipid-Lowering Agents

<table>
<thead>
<tr>
<th>Drug</th>
<th>Potency (average decrease in LDL)</th>
<th>Renal Considerations</th>
<th>Liver Function Monitoring</th>
<th>Selected Drug Interactions</th>
<th>Cost/month (U.S./Canada)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>10 mg: 35-39% 20 mg: 43% 40 mg: 50% 80 mg: 55-60%</td>
<td>No dose adjustment necessary for reduced renal function. (Use 10 mg daily in patients with renal disease per Canadian labelling.)</td>
<td>Check liver function tests at baseline and when clinically indicated.</td>
<td>Metabolized by CYP3A4, but less than lovastatin and simvastatin. Some drugs that significantly inhibit its metabolism through CYP3A4 inhibition include amiodarone, erythromycin, clarithromycin, telithromycin, itraconazole &amp; other azoles, nefazodone, protease inhibitors, cyclosporine, and grapefruit juice; atorvastatin dose reduction or discontinuation may be recommended. Consider cautious dosing with niacin or fibrates (avoid gemfibrozil). Rifampin may increase or decrease levels, depending on timing.</td>
<td>10 mg: $7.08 (generic)/$10.17 (generic)</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>20 mg: 22% 40 mg: 25% 80 mg: 35% (as XL product)</td>
<td>In severe renal impairment, use daily doses over 40 mg with caution. (Canadian labelling recommends not using if CrCl &lt;30 mL/min.)</td>
<td>Check liver function tests at baseline (and 8 weeks after initiation or dosage increase, per Canadian labelling) and when clinically indicated.</td>
<td>Metabolized primarily by CYP2C9. Few significant interactions with 2C9 inhibitors. May be less likely to be involved in drug interactions. Use with phenytoin or glyburide can increase levels of both drugs. Consider dose reduction with niacin. Caution with fibrates (avoid gemfibrozil). Max dose 20 mg twice daily with cyclosporine or fluconazole. Rifampin decreases levels.</td>
<td>80 mg XL: $162.24/$49.39</td>
</tr>
<tr>
<td>Drug</td>
<td>Potency (average decrease in LDL)1,2,8</td>
<td>Renal Considerations</td>
<td>Liver Function Monitoringc</td>
<td>Selected Drug Interactions</td>
<td>Cost/month (U.S./Canada)b</td>
</tr>
<tr>
<td>---------------</td>
<td>---------------------------------------</td>
<td>----------------------</td>
<td>---------------------------</td>
<td>---------------------------------------------------------------------------------------------</td>
<td>--------------------------</td>
</tr>
</tbody>
</table>
| Lovastatin (Mevacor, generics) | 10 mg: 21%  
20 mg: 24-27%  
40 mg: 30-31%  
80 mg: 40-42% (as 40 mg BID) | If CrCl <30 mL/min, use daily doses over 20 mg with caution. | Check liver function tests at baseline (and periodically, per Canadian labelling [more frequent with 40 mg or more]) and when clinically indicated.4 | Metabolized by CYP3A4. Contraindicated with strong CYP3A4 inhibitors including erythromycin, clarithromycin, telithromycin, itraconazole, ketoconazole, posaconazole, voriconazole, protease inhibitors, and nefazodone. Avoid grapefruit and cyclosporine (cyclosporine contraindicated [Canada]). Do not exceed 40 mg daily with amiodarone. Do not exceed 20 mg daily with diltiazem, verapamil, danazol, dronedarone, or niacin >1000 mg/day (Canada), or 40 mg daily with extended-release niacin (Niaspan). Consider dose reduction with ranolazine. Caution with fibrates (avoid gemfibrozil; do not exceed 20 mg daily with fibrates [Canada]). | 40 mg: $<5  
(generic)/ $29.11  
(generic) |
| Pitavastatin (Livalo) (U.S. only) | 1 mg: 29%  
2 mg: 36-39%  
4 mg: 41-45% | For glomerular filtration rate (GFR) 15-59 mL/min/1.73m², including hemodialysis, initial daily dose is 1 mg, max daily dose is 2 mg. | Check liver function tests at baseline and when clinically indicated.4 | Not significantly metabolized by cytochrome P450 and may be less likely to be involved in drug interactions. Contraindicated with cyclosporine. Limit dose to 1 mg daily with erythromycin or 2 mg daily with rifampin. Consider dosage reduction with niacin. Caution with fibrates (avoid gemfibrozil). | 2 mg: $150 |
<table>
<thead>
<tr>
<th>Drug(^a)</th>
<th>Potency (average decrease in LDL)(^1,2,8)</th>
<th>Renal Considerations</th>
<th>Liver Function Monitoring(^c)</th>
<th>Selected Drug Interactions</th>
<th>Cost/month (U.S./ Canada)(^b)</th>
</tr>
</thead>
</table>
| Pravastatin (Pravachol, generics) | 10 mg: 22%  
20 mg: 29%  
40 mg: 34%  
80 mg: 37% | In significant renal impairment, start with 10 mg daily.  
(Canadian labelling advises caution with daily doses of 40 mg or more in renal impairment.) | Check liver function tests at baseline (and 12 weeks after initiation or dosage increase, per Canadian labelling), and when clinically indicated.\(^4\) | Not significantly metabolized by cytochrome P450 and may be less likely to be involved in drug interactions.  
Do not exceed 20 mg once daily with cyclosporine.  
Do not exceed 40 mg once daily with clarithromycin.  
Caution with fibrates (avoid gemfibrozil).  
Consider dose reduction with niacin >=1000 mg/day. | 40 mg: $18.82  
generic/  
$18.65  
generic |
<table>
<thead>
<tr>
<th>Drug(^a)</th>
<th>Potency (average decrease in LDL)(^1,2,8)</th>
<th>Renal Considerations</th>
<th>Liver Function Monitoring(^c)</th>
<th>Selected Drug Interactions</th>
<th>Cost/month (U.S./Canada)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simvastatin (Zocor, generics)</td>
<td>5 mg: 26% 10 mg: 29% 20 mg: 38% 40 mg: 30-41% 80 mg: 36-47%</td>
<td>In severe renal impairment, starting dose is 5 mg daily with close monitoring. (Per Canadian labelling, caution with doses &gt;10 mg daily with severe renal impairment [CrCl &lt;30 mL/min].)</td>
<td>Check liver function tests at baseline and when clinically indicated.(^4) (Per Canadian labelling, for patients to be titrated to 80 mg, check prior to dosage increase, three months later, then periodically [e.g., semiannually] for the first year.)</td>
<td>Metabolized by CYP3A4. Contraindicated with strong CYP3A4 inhibitors including erythromycin, clarithromycin, telithromycin, itraconazole, ketoconazole, posaconazole, voriconazole, protease inhibitors, and nefazodone. Cyclosporine and danazol contraindicated. Avoid grapefruit. Do not exceed 20 mg daily with amiodarone, amlodipine, ranolazine, or lomitapide. Do not exceed 10 mg daily with diltiazem, verapamil, or dronedarone. Do not exceed 40 mg daily with extended-release niacin (Niaspan), in Chinese patients taking &gt;1 g/day niacin, or with lomitapide in patients who have previously tolerated simvastatin 80 mg. Contraindicated with gemfibrozil. Caution with fibrates (do not exceed 10 mg with fenofibrate [Canada]).</td>
<td>20 mg: $&lt;4 (generic)/$20.26 (generic)</td>
</tr>
</tbody>
</table>

\(a\) The following product labeling was used for the above chart: Lipitor (October 2012), Lescol/Lescol XL (October 2012), Mevacor (October 2012), Livalo (October 2013), Pravachol (October 2012), Crestor (August 2013), Zocor (October 2013), Niaspan (March 2013), Lipitor Canada (May 2013), Lescol/Lescol XL Canada (September 2013), Mevacor Canada (April 2013), Pravachol Canada (January 2013), Crestor Canada (May 2013), Zocor Canada (March 2013).

\(b\) U.S. cost is wholesale average cost (WAC). Canadian cost is wholesale cost. Cost is for generic if available.

\(c\) Tell statin users to stop the statin and report symptoms of liver injury (e.g., jaundice, abdominal pain, etc) right away. Stop the statin in the event of evidence of liver injury (e.g., elevated direct bilirubin level, hepatomegaly, jaundice, increased prothrombin time).\(^5,6\) If the statin cannot be excluded as a cause of liver injury, do not restart a statin.\(^5\) But if elevated transaminase levels are the only problem, experts recommend continuing the statin.\(^5\) There’s no proof that dose reduction is necessary.\(^5\) If transaminases exceed three times the upper limit of normal, repeat the test.\(^6\) In asymptomatic patients with transaminases less than five times normal and no evidence of liver injury, the repeat test can be deferred for six months.
In the meantime, stop alcohol and hepatotoxic medications, encourage weight loss, and control diabetes. If still elevated, rule out other causes and consider decreasing the dose or stopping the statin.

**Abbreviations:** ACS = acute coronary syndrome; CHD = coronary heart disease; HDL = high-density lipoprotein cholesterol; LDL = low-density lipoprotein cholesterol; MACE = major adverse cardiac event (cardiac death, non-fatal MI, or revascularization); MI = myocardial infarction; OATP = organic anion transporting polypeptide; PCI = percutaneous coronary intervention; TIA = transient ischemic attack. Evidence is Level A for all studies except CARDS, FLORIDA, TREADMILL [Level A/B] and GREACE and L-CAD [Level B].

---

**Clinical Benefit of Statins (Study acronym in parentheses; FDA-labeled indications are underlined. Full update April 2012.)**

**Atorvastatin (Lipitor)**

- **Primary prevention of CHD:** Reduces non-fatal MI and fatal CHD, and stroke in patients with hypertension and total cholesterol <250 mg/dL (ASCOT).

- **Primary prevention of CHD in diabetes:** Reduces stroke and MI in patients with type 2 diabetes, an additional CHD risk factor, and LDL <160 mg/dL (CARDS).

- **Secondary prevention of CHD:** 80 mg/day reduced risk of major cardiovascular events in patients with CHD and LDL <130 mg/dL vs 10 mg. No overall mortality difference (TNT).

- **Secondary prevention of CHD:** 80 mg/day reduced risk of non-fatal cardiovascular events vs simvastatin 40-80 mg/day in patients with CHD and previous MI (mean LDL 121.5 mg/dL) (IDEAL).

- **Secondary prevention of CHD:** Reduced risk of coronary morbidity and mortality, and stroke in open-label comparison with usual care of patients with LDL >100 mg/dL (GREACE). (*Note: GREACE not used to support this indication.)

- 80 mg/day begun within 1 to 4 days after ACS reduced recurrent ischemic events and stroke over 4 months (MIRACL).

- In ACS, intense lipid lowering (median LDL 62 mg/dL) lowers risk of death/major cardio events more than moderate lipid lowering (median LDL 95 mg/dL) (PROVE-IT).

- Regresses/slows progression of atherosclerosis (ASAP, ARBITER, REVERSAL).

- Unclear benefit in peripheral arterial disease (TREADMILL).
<table>
<thead>
<tr>
<th><strong>Fluvastatin (Lescol)</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ Slows progression of atherosclerosis in patients with CHD and mild to moderate hypercholesterolemia (LCAS).</td>
<td></td>
</tr>
<tr>
<td>▪ <strong>Secondary prevention of CHD:</strong> Reduces need for revascularization. Dose of 40 mg twice daily reduced risk of MACE when begun within days after PCI in patients with average cholesterol levels (LIPS).</td>
<td></td>
</tr>
<tr>
<td>▪ Did not reduce MACE in renal transplant recipients, but secondary endpoints of cardiac death and MI were reduced (ALERT).</td>
<td></td>
</tr>
<tr>
<td>▪ No benefit for early treatment of ACS with 80 mg/day (FLORIDA).</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Lovastatin (Mevacor)</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ <strong>Primary prevention of CHD:</strong> Reduces first acute coronary event, MI, unstable angina, and revascularization in patients with average LDL (AFCAPS/ TexCAPS).</td>
<td></td>
</tr>
<tr>
<td>▪ Slows progression of coronary atherosclerosis in CHD (CCAIT, FATS, MARS). Improvement also in carotid arteries (ACAPS).</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Pitavastatin (Livalo)</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ Pitavastatin 4 mg and atorvastatin 20 mg similarly reduce nonculprit coronary plaque volume post-ACS (JAPAN-ACS).</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Pravastatin (Pravachol)</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ <strong>Primary prevention of CHD:</strong> Reduces cardiovascular death, MI, and revascularization in patients with high LDL and multiple risk factors (WOSCOPS).</td>
<td></td>
</tr>
<tr>
<td>▪ <strong>Secondary prevention of CHD:</strong> Reduces recurrent MI, coronary death, revascularization, and stroke/TIA across range of cholesterol levels (CARE, LIPID).</td>
<td></td>
</tr>
<tr>
<td>▪ Slows progression of coronary atherosclerosis in CHD; improvement also in carotid arteries (REGRESS, PLAC I, PLAC II, KAPS).</td>
<td></td>
</tr>
<tr>
<td>▪ Failed to show benefit in hypertensive patients (ALLHAT-LLT), but result probably due to high non-study statin use in usual care group.</td>
<td></td>
</tr>
<tr>
<td>▪ Preliminary study found lower risk of MACE with early therapy of ACS (L-CAD).</td>
<td></td>
</tr>
<tr>
<td>▪ Reduced composite of coronary death, non-fatal MI, and stroke in high-risk patients &gt;70 years old, but no benefit for stroke alone; result attributed to short study duration (PROSPER).</td>
<td></td>
</tr>
</tbody>
</table>
**Rosuvastatin (Crestor)**  
- Regression of atherosclerosis with intensive statin therapy in patients with angiographic coronary disease.
- 40 mg/day reduced LDL (mean 60.8 mg/dL), raised HDL (mean 49.0 mg/dL), and reduced percent mean atheroma volume by 0.98% (ASTEROID).
- Slows progression of atherosclerosis (METEOR).
- Primary prevention of CAD: Reduces MI, stroke, and cardiovascular death in patients with LDL <130 mg/dL and hs-CRP >2 mg/L (JUPITER).

**Simvastatin (Zocor)**  
- Primary and secondary prevention of CHD: Reduces risk of total mortality, non-fatal MI, stroke, and revascularization in patients at high risk of coronary events, but with normal cholesterol (including LDL <100 mg/dL, women, diabetes, and peripheral arterial disease) (HPS).
- Slows progression of atherosclerosis in patients with CHD and normal to high cholesterol (MAAS, SCAT).
- Combined with niacin reduces major coronary events in patients with CHD and HDL <35 mg/dL (HATS).
- Reduces vascular events (HPS) and development/progression of intermittent claudication (4S) in peripheral arterial disease.

c. In patients with CHD or CHD risk-equivalent (diabetes, peripheral arterial disease, history of stroke or other cerebrovascular disease).

**Statin Clinical Trials**
- ASTEROID - A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden: *JAMA* 2006;295:1556-65.
LCAS - Lipoprotein and Coronary Atherosclerosis Study: Am J Cardiol 1997;80:278-86.
Levels of Evidence
In accordance with the trend towards Evidence-Based Medicine, we are citing the LEVEL OF EVIDENCE for the statements we publish.

<table>
<thead>
<tr>
<th>Level</th>
<th>Definition</th>
</tr>
</thead>
</table>
| A     | High-quality randomized controlled trial (RCT)  
       High-quality meta-analysis (quantitative systematic review) |
| B     | Nonrandomized clinical trial  
       Nonquantitative systematic review  
       Lower quality RCT  
       Clinical cohort study  
       Case-control study  
       Historical control  
       Epidemiologic study |
| C     | Consensus  
       Expert opinion |
| D     | Anecdotal evidence  
       In vitro or animal study |


Project Leader in preparation of this PL Detail-Document: Melanie Cupp, Pharm.D., BCPS

References

Statin-Associated Muscle Symptoms

Background
As many as 30% of patients taking a statin report muscle aches or weakness.1 A thorough understanding of this side effect by health care professionals may minimize unnecessary statin dose reduction or discontinuation of these life-saving medications, while reducing the risk of life-threatening outcomes. This article discusses proposed mechanisms, risk factors, prevention, monitoring, and management of statin myopathy.

Mechanism and Risk Factors
According to the American College of Cardiology/American Heart Association/National Heart, Lung, and Blood Institute Clinical Advisory on the Use and Safety of Statins, myopathy is a general term for any muscle disease. Myalgia refers to muscle pain or weakness without increased creatine kinase, whereas myositis includes elevated creatine kinase. Rhabdomyolysis is defined as muscle symptoms, very high creatine kinase (10 times the upper limit of normal), and increased serum creatinine, often with dark urine and myoglobinuria.2 Other groups use different terminology.3,4 Patients may use terms like weakness, cramping, tenderness, soreness, stiffness, or heaviness to describe their symptoms. Symptoms are usually symmetrical and often involve proximal muscles.5 In the PRIMO study, the thighs or calves are the predominant site of complaints in over a quarter of sufferers.4

Risk factors for statin myopathy include being elderly, small size, high statin dose, liver or renal disease, diabetes, uncontrolled hypothyroidism, and interacting medications.3 The mechanism of statin myopathy is unclear. It may involve statins’ inhibition of the production of substances needed for muscle cells to function normally. These substances include dolichols, isoprenylated proteins, and coenzyme Q10, which participate in cellular respiration. Another theory involves altered muscle cell membrane function as the result of decreased cell membrane cholesterol content. However, myopathy risk is not related to cholesterol levels. There is evidence that increased LDL receptor sensitivity caused by statins could cause increased intake of fat or plant sterols into the muscle.3

Evidence from the PRIMO study suggests that fluvastatin carries the lowest risk of myopathy followed by pravastatin. Myalgia occurred in 10.9% of patients receiving pravastatin (Pravachol) 40 mg daily and in 5.1% of patients receiving fluvastatin (Lescol XL) 80 mg daily (p<0.001). Muscle symptoms were reported in 14.9% of patients receiving atorvastatin 40 mg or 80 mg daily (p=0.04, compared to pravastatin), and in 18.2% of patients receiving simvastatin at a dose of 40 mg or 80 mg daily (p<0.001, compared to pravastatin). The apparently lower risk of myalgia with fluvastatin and pravastatin may be explained by their low propensity for drug interactions (see below) and/or, in theory, their relatively low distribution into muscle due to their hydrophilic nature. In addition, fluvastatin has low systemic bioavailability (i.e., it has high first-pass hepatic elimination) and is highly bound to serum proteins. Rosuvastatin is also hydrophilic and has a relatively low propensity for drug interactions, but it has a long half-life.4

Drug Interactions
The risk of myopathy is increased when statins are coadministered with medications that inhibit their metabolism. Interactions vary among the statins due to differences in their metabolic pathways. Atorvastatin (Lipitor), lovastatin (Mevacor), and simvastatin (Zocor) are CYP3A4 substrates and when coadministered with potent CYP3A4 inhibitors the incidence of myopathy is increased by about five-fold.9 The extent of interaction between atorvastatin and CYP3A4 inhibitors is less than that with lovastatin and simvastatin.3 Lovastatin and simvastatin are termed “sensitive substrates” because their levels
may be increased five-fold or higher by CYP3A4 inhibitors. Fluvastatin is primarily metabolized by CYP2C9 and to a lesser extent by CYP3A4 and CYP2D6. Pravastatin is not significantly metabolized by the cytochrome P450 system and does not interact with other CYP substrates. Rosuvastatin (Crestor) and pitavastatin (Livalo) also aren’t extensively metabolized by the cytochrome P450 system. Statins are substrates for P-glycoprotein; therefore, drugs that inhibit P-glycoprotein (e.g., cyclosporine, diltiazem, etc) may increase statin levels.

Other medications increase risk because they themselves have been associated with myopathy (e.g., cyclosporine, danazol, niacin, fibrates). The increased risk of myopathy is well recognized when statins and fibric acid derivatives are coadministered since both classes of drugs have the potential for inducing myopathy. However, the risk is less with fenofibrate than gemfibrozil. This may be because gemfibrozil inhibits hepatic glucuronidation of statins, thereby interfering with statin elimination.

In managing statin interactions, choosing a noninteracting medication or switching to a noninteracting statin (i.e., for chronic therapy) may be the safest or easiest option. For certain statin interactions, reducing the statin dose may be an acceptable management technique. In patients with stable cardiovascular disease, interactions between lovastatin or simvastatin and strong CYP3A4 inhibitors (e.g., clarithromycin, itraconazole) are managed by stopping the statin as soon as the interacting drug is started. Recommendations vary, but some experts suggest restarting the statin three days or so after the interacting drug has been discontinued. See our chart for more detailed information about clinically significant statin drug interactions, including mechanisms and management.

Management

When statin therapy is initiated, clinicians can consider checking a baseline creatine kinase level as a point of reference, especially in those at high risk of myopathy. Routine monitoring is not necessary in most patients. Increases are common, particularly with physical exertion. Surveillance may be helpful in patients with liver or renal insufficiency or in patients taking interacting medications.

Symptomatic patients should have creatine kinase level checked. Some experts recommend checking a thyroid-stimulating hormone level to rule out hypothyroidism as a cause of myalgia. It has also been suggested that vitamin D deficiency should be ruled out as a cause of muscle symptoms. In one report, statin users with muscle symptoms had lower vitamin D levels than statin users without muscle symptoms. Elevated creatine kinase levels were not more common among the patients with myalgia. Vitamin D supplementation was given to patients with myalgia plus 25-hydroxyvitamin D levels less than 32 ng/mL. Myalgia resolved in over 90% of these patients despite statin continuation.

Symptoms, creatine kinase level, and development of risk factors determine the necessity of statin discontinuation. Statins (and niacin or fibrate, if applicable) should be discontinued if creatine kinase becomes markedly increased (i.e., 10 or more times the upper limit of normal), especially in symptomatic patients. Others recommend stopping statins in patients with severe muscle symptoms regardless of creatine kinase results. Statins should also be held in the event of rhabdomyolysis; sepsis; hypotension; dehydration; major surgery; trauma; severe metabolic, endocrine, or electrolyte disorders; or uncontrolled seizure disorders.

Canadian labeling for lovastatin and simvastatin recommends holding these statins beginning a few days before major elective surgery.

Asymptomatic patients with a creatine kinase <5 times the upper limit of normal in whom other causes (e.g., physical exertion) have been excluded should simply be educated to report symptoms. If the creatine kinase is ≥5 to <10 times the upper limit of normal, asymptomatic patients should be educated about symptoms and retested monthly or bimonthly.

Symptomatic patients with a creatine kinase <10 times the upper limit of normal should have symptoms and creatine kinase checked weekly until resolution. If creatine kinase worsens, consider statin discontinuation or dose reduction. Others recommend using symptoms to guide treatment decisions and as long as symptoms are tolerable they don’t recommend serial creatine kinase monitoring in these patients.

Assuming benefits of continuing the statin outweigh the risk of myopathy, patients with...
tolerable symptoms can try coenzyme Q10. Efficacy studies have found conflicting results. However, some patients and cardiologists feel it is beneficial. It is likely safe when dosed appropriately. A dose of 100 mg once daily or 200 mg divided two or three times daily (to minimize gastrointestinal side effects) has been recommended.

If statin discontinuation is indicated, the risks and benefits of restarting the statin can be reviewed once the patient’s signs and symptoms have resolved. This can take two months or more. For patients who suffered acute renal failure or a creatine kinase over 10,000 units/L, a nonstatin alternative should be considered. Patients with less serious sequelae can be rechallenged with the same statin, preferably at a lower dose, or an alternate regimen can be tried. Some patients may tolerate fluvastatin, alone or with ezetimibe (Zetia), a low-dose statin plus ezetimibe, or extended interval dosing using a more potent, longer-acting statin (rosuvastatin, atorvastatin). Studied or suggested regimens include rosuvastatin 5 mg to 20 mg once weekly; rosuvastatin 5 mg twice weekly; rosuvastatin at a dose of 2.5 mg to 10 mg three times weekly; rosuvastatin 5 mg or 10 mg daily; atorvastatin or rosuvastatin every other day; or 10 mg atorvastatin twice weekly plus 10 mg ezetimibe daily. Sometimes, patients can tolerate statins for several weeks before symptoms occur. These patients can be given “pulse” therapy (e.g., four weeks on, one or two weeks off), depending on their individual tolerance [Evidence level D; anecdotal evidence].

**Commentary**

Alternate statin dosing regimens reportedly can provide good LDL reduction with improved tolerability. When deciding on an alternative lipid-lowering regimen in a patient with statin myopathy, consider the evidence of benefit. For example, the effect of reduced frequency regimens (e.g., every other day) on cardiovascular morbidity and mortality has not been studied. Statin doses used in secondary prevention studies showing a mortality benefit were moderate (e.g., pravastatin 40 mg, simvastatin 20 mg). Patients taking a low statin dose may need additional LDL lowering. The addition of ezetimibe (Zetia) or a bile acid sequestrant (e.g., cholestyramine [Questran, others], colestipol [Colestid], colesevelam [Welchol-U.S.; Lodalis-Canada]) to a statin may reduce LDL by up to an additional 20% to 25% in some cases. Of the nonstatins, bile acid sequestrants have the best evidence for cardiovascular event prevention. If patients cannot tolerate a statin, a bile acid sequestrant, niacin, or ezetimibe can be considered either as monotherapy or in combination. For example, the combination of ezetimibe plus a bile acid sequestrant can reduce LDL by about 40%.

Also consider the risk/benefit ratio. For example, rechallenge with a statin in a patient with a history of statin-associated rhabdomyolysis should be avoided, especially if the indication for the statin is primary prevention [Evidence level C; expert opinion]. Diet and lifestyle changes to improve cardiovascular risk are especially important interventions in this situation.

Another consideration is the cardiovascular risk of stopping a statin. Stopping a statin for up to six weeks in a stable patient appears safe. For example, simvastatin could be held to allow treatment of an infection with clarithromycin. (Alternately, a noninteracting antibiotic [e.g., moxifloxacin (Avelox)] or statin [e.g., rosuvastatin (Crestor)] could be substituted). The cardiovascular risk of stopping a statin is higher in unstable patients. Morbidity and mortality is increased in acute myocardial infarction (MI) and ischemic stroke patients whose statins are discontinued. This association may be seen quickly. In one study there was increased risk of in-hospital death in patients with non-ST segment elevation MI whose statin was discontinued. In addition, stopping statin therapy in acute ischemic stroke patients resulted in early neurologic deterioration and poorer outcomes. Therefore, statins should only be discontinued in acute MI or stroke when clearly indicated.

As the population ages, more patients will be at risk of statin myopathy. Advanced age is a risk factor, and the elderly tend to take more medications that could potentially interact. To provide the best margin of safety, heed drug interaction warnings and dosing recommendations, weighing cardiovascular benefit against myopathy risk. Users of this PL Detail-Document are cautioned to use their own professional judgment and consult any other necessary or appropriate sources prior to making decisions.
clinical judgments based on the content of this document. Our editors have researched the information with input from experts, government agencies, and national organizations. Information and internet links in this article were current as of the date of publication.

Levels of Evidence
In accordance with the trend towards Evidence-Based Medicine, we are citing the LEVEL OF EVIDENCE for the statements we publish.

<table>
<thead>
<tr>
<th>Level</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>High-quality randomized controlled trial (RCT) High-quality meta-analysis (quantitative systematic review)</td>
</tr>
<tr>
<td>B</td>
<td>Nonrandomized clinical trial Nonquantitative systematic review Lower quality RCT Clinical cohort study Case-control study Historical control Epidemiologic study</td>
</tr>
<tr>
<td>C</td>
<td>Consensus Expert opinion</td>
</tr>
<tr>
<td>D</td>
<td>Anecdotal evidence In vitro or animal study</td>
</tr>
</tbody>
</table>


Project Leader in preparation of this PL Detail-Document: Melanie Cupp, Pharm.D., BCPS

References


32. Third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III) final report. *Circulation* 2002;106:3143-421.


