

# Statin Adverse Effects

## Sorting out the Evidence

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Studies have assessed the incidence of everything from myopathy to diabetes and cataracts, but findings have been inconsistent. Here's help making sense of the evidence.

### PRACTICE RECOMMENDATIONS

- Advise patients starting statin therapy to stop taking the medication and call your office immediately if they develop severe muscle pain or weakness, as statins are associated with a small increased risk for rhabdomyolysis. **B**
- Obtain a baseline creatine kinase level for patients with an increased risk for musculoskeletal disorders; routine monitoring is needed only for those who experience muscle pain or weakness while on statin therapy. **C**
- Prescribe statins for patients with chronic kidney or liver disease when indicated; statin therapy is not associated with an increased risk for renal or hepatic failure. **B**

### Strength of recommendation (SOR)

- A** Good-quality patient-oriented evidence
- B** Inconsistent or limited-quality patient-oriented evidence
- C** Consensus, usual practice, opinion, disease-oriented evidence, case series

### CASE

Mr L., a 57-year-old obese patient (BMI > 40) who had not been to a clinician in a decade, comes to see you after a health fair screening revealed dyslipidemia (LDL cholesterol, 188 mg/dL; HDL cholesterol, 32 mg/dL; total cholesterol, 240 mg/dL; triglycerides, 100 mg/dL). His blood pressure (BP) is 146/90 mm Hg, and his fasting glucose is 101 mg/dL. Labs drawn that day reveal an A1C of 5.9%, alanine aminotransferase (ALT) of 45 U/L, and aspartate aminotransferase (AST) of 62 U/L. In taking his history, you discover that Mr L. also has a notable family history of heart disease.

Mr L. agrees to take a low-dose statin, and you prescribe atorvastatin 10 mg and a thiazide diuretic. You advise the patient to contact you immediately if he develops significant myalgia, jaundice, dark urine, or symptoms of hyperglycemia such as excessive thirst or urination, and to schedule a follow-up visit in eight weeks.

Long recognized as the bedrock of hyperlipidemia therapy, statins achieved even greater prominence when the American College of Cardiology/American Heart Association (ACC/AHA) issued a new cholesterol guideline<sup>1</sup> late last year. The ACC and AHA now recommend statins for a wider range of patients, often at a higher starting dose.

Based on the new recommendations, the use of statins is likely to rise.<sup>2</sup> (A statin—rosuvastatin—is already the nation's most widely prescribed medication.<sup>2</sup>) Thus, it is more important than ever for clinicians to know about the risks associated with statins and to be able to assess the benefits of therapy for individual patients.

A 2013 retrospective cohort study of more than 100,000 patients on statins found that 17% developed adverse effects (AEs). Therapy was withheld, at least temporarily, for 10% of study participants (60% of those experiencing AEs).<sup>3</sup> At the same time, the authors of a large meta-analysis (135 randomized controlled trials [RCTs] and > 240,000 patients) reported that AEs associated with statins as a class were uncommon. The meta-analysis also found that the overall

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**TABLE 1** Statin Therapy: Monitoring for Muscle and Hepatic Symptoms

Before starting statin	SOR*
Obtain history of muscle symptoms <sup>†</sup>	B
Get baseline ALT/AST	B
Check baseline CK in patients with increased risk for adverse muscle effects <sup>‡</sup>	C
During treatment	
Routine CK is not needed	A
Measure CK in patients with muscle symptoms	C
Check hepatic function if symptoms suggest hepatotoxicity (eg, unusual fatigue or weakness, loss of appetite, abdominal pain, dark urine, or yellowing of the skin or sclera)	C
Recommendations <ul style="list-style-type: none"> <li>• If <i>severe</i> muscle symptoms occur, discontinue the statin; measure CK and serum creatinine and perform a urinalysis to check for myoglobinuria to rule out rhabdomyolysis</li> <li>• If <i>mild to moderate</i> muscle symptoms occur, discontinue the statin and evaluate for conditions that increase the risk for muscle symptoms</li> <li>• If muscle symptoms resolve and no contraindication exists, resume the statin (at same or lower dose) to establish a causal relationship</li> <li>• If a causal relationship is found, discontinue the original statin; start a low dose of a different statin once muscle symptoms resolve</li> <li>• If the low dose is tolerated, gradually increase as tolerated</li> </ul>	B

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; CK, creatine kinase; SOR, strength of recommendation.

\* SOR definitions can be found on page 41.

<sup>†</sup> Muscle symptoms include pain, tenderness, stiffness, cramping, weakness, or generalized fatigue.

<sup>‡</sup> Risk factors include patient/family history of statin intolerance or muscle disease, age > 75, or concomitant drug therapy that might increase the risk for myopathy.

Source: *Circulation*. 2014.<sup>1</sup>

discontinuation rate for statin users—5.7%—was not significantly different from that of patients receiving placebo.<sup>4</sup>

Such discrepancies regarding particular risks, as well as the overall incidence of AEs and discontinuation rates, make the evidence difficult to sort out. We created this update with that in mind.

### MUSCULOSKELETAL SYMPTOMS ARE MOST COMMON

Musculoskeletal symptoms are the most common AEs reported by patients who are taking statins.<sup>5</sup> These range from muscle weakness, fatigue, and pain to (rarely) rhabdomyolysis—a life-threatening condition characterized by severe muscle pain, muscle weakness, a 10-fold increase in creatine kinase (CK), and increased serum creatinine, often with myoglobinuria.<sup>5</sup>

Patients with myopathy—an umbrella term for any muscle disease—may report stiffness, weakness, tenderness, soreness, cramping, or heaviness. Symptoms are usually symmetrical and often involve the proximal limbs and trunk.<sup>6</sup> Studies indicate that exercise increases the risk for statin-induced myalgia—muscle pain or weakness without an increase in CK—and that patients taking statins are more prone to exercise-related injury.<sup>7,8</sup>

A *baseline CK* is recommended for patients with an increased risk for muscular disorders.<sup>1</sup> Risk factors include a personal or family history of statin intolerance or muscle disease, age older than 75, low levels of vitamin D, and concomitant use of medications that may increase the risk for myopathy (see Table 1).<sup>1</sup> Routine monitoring of CK is not recommended, but CK levels should be obtained for those who exhibit muscle symptoms while on statin therapy.<sup>1</sup>

**TABLE 2 Beware of These Drug Interactions**

Statin(s)	Drugs to avoid	Dose reduction recommended	Caution advised
Atorvastatin, lovastatin, simvastatin	Potent CYP3A4 inhibitors (azole antifungals, boceprevir, clarithromycin, erythromycin, nefazodone, protease inhibitors, telaprevir) and inducers (carbamazepine, dexamethasone, nevirapine, phenobarbital, phenytoin, rifampin, St. John's wort)  Cyclosporine Gemfibrozil	Other common CYP3A4 inhibitors (amiodarone, danazol, diltiazem, dronedarone, grapefruit juice, isoniazid, verapamil)  Amlodipine* Ranolazine*	Colchicine Fenofibrate Warfarin
Fluvastatin	Gemfibrozil	Cyclosporine Fluconazole	CYP2C9 inhibitors/inducers† Colchicine Fenofibrate Warfarin
Pitavastatin	Gemfibrozil Cyclosporine		CYP2C9 inhibitors/inducers† Colchicine Fenofibrate Protease inhibitors Warfarin
Pravastatin	Gemfibrozil		Colchicine Cyclosporine Fenofibrate Warfarin
Rosuvastatin	Gemfibrozil	Cyclosporine Protease inhibitors	CYP2C9 and CYP2C19 inhibitors/inducers† Colchicine Fenofibrate Warfarin

Note: This is a partial list.

\* With simvastatin only.

† CYP2C9 inhibitors: amiodarone, azole antifungals, fluoxetine, sulfamethoxazole/trimethoprim; CYP2C9/CYP2C19 inducers: carbamazepine, phenobarbital, phenytoin, rifampin; CYP2C19 inhibitor: fluvoxamine.

Sources: Elsevier/Gold Standard;<sup>12</sup> FDA.<sup>13</sup>

*continued on page 46 >>*

>> *continued from page 43*

### What the studies show

The incidence of myalgia reported in clinical studies is highly variable, ranging from less than 1% to 20%.<sup>1,9,10</sup> The ACC/AHA guideline reports only one additional case of myopathy per 10,000 statin users compared with those on placebo and cites a rhabdomyolysis occurrence rate of less than 0.06% over five years.<sup>1</sup>

A 2006 systematic review estimated the absolute risk for rhabdomyolysis to be 3.4 per 100,000 person-years, but the incidence was 10 times higher for patients taking both a statin and gemfibrozil.<sup>11</sup> (See Table 2,<sup>12,13</sup> page 43, for more on drug interactions.) But both the meta-analysis cited earlier<sup>4</sup> and a previous systematic review<sup>14</sup> (35 RCTs and > 74,000 patients) found that statins as a class do not increase the incidence of myalgia or rhabdomyolysis.

Differences in the way muscular disorders are defined has been suggested as one reason for the discrepancies.<sup>10</sup> In addition, many clinical trials exclude patients at higher risk for statin-associated AEs, such as those with renal or hepatic insufficiency, prior muscular complaints, poorly controlled diabetes, or potential drug interactions.<sup>1</sup>

**An FDA advisory.** In a safety communication last updated in February 2012, the FDA cautioned against starting patients on the highest dose of simvastatin (80 mg).<sup>15</sup> The warning is based on a large study (N = 12,064) that found an increased risk for myopathy (0.9%) and rhabdomyolysis (0.2%) in patients on the 80-mg dose versus those taking 20 mg (0.02% and 0%, respectively).<sup>16</sup>

With the ACC/AHA now recommending intensive therapy (atorvastatin 40-80 mg or rosuvastatin 20-40 mg) to achieve an LDL reduction greater than 50% for many patients,<sup>1</sup> it is important to be aware that this risk is specific to simvastatin. A recent meta-analysis of studies directly comparing patients receiving intensive statin therapy with those on low to moderate doses did not find any increased risk in rhabdomyolysis associated with more intensive therapy when those taking 80-mg simvastatin were excluded.<sup>17</sup>

**The bottom line:** Although rhabdomyolysis is rare, its severity—a fatality rate of 10%<sup>11</sup>—makes it critical to educate patients about the disorder and instruct them to stop taking the statin and call the office immediately if they develop severe muscle pain or weakness.

### Recommend CoQ10 for statin-induced myopathy

Although the exact mechanism of statin-induced myopathy is unknown, the most likely explanation

is a depletion of coenzyme Q10 (CoQ10), which has negative effects on mitochondrial energy production.<sup>18</sup> While studies using CoQ10 to treat this AE have been small and had mixed results, the overall evidence suggests that it decreases the development and/or severity of symptoms.<sup>18-20</sup>

In fact, CoQ10 supplementation is the only treatment that has shown promise in treating statin-induced muscle symptoms.<sup>18-20</sup> Doses of about 100 mg bid have been found to be beneficial and safe; no clinically relevant AEs have been seen with doses lower than 300 mg/d.<sup>18,20,21</sup> A large placebo-controlled study is currently evaluating a 600 mg/d dose of CoQ10 in patients with statin-induced myopathy.<sup>19</sup>

### CASE

On his next visit, Mr L. reports a new ache in his left shoulder and upper back, which he describes as mild but annoying. He also tells you his memory seems to be getting worse and that he has developed an odd tingling in his hands. These symptoms began about a month after he started the medications, Mr L. says. He also began a new exercise program, but his BMI is unchanged.

On examination, you find the affected shoulder and upper back modestly and diffusely tender to palpation but with no decline in strength. Mr L.'s BP has fallen to 134/84 mm Hg, and his fasting glucose is 105 mg/dL. Lab tests reveal an LDL of 144 mg/dL and HDL of 36 mg/dL, A1C of 6.1%, ALT of 105 U/L, AST of 61 U/L, and a normal CK.

You recommend 100 mg CoQ10 bid. Because it is available only OTC, you advise the patient to look for a product whose purity and potency have been verified by an external source, such as the US Pharmacopeial Convention. You also prescribe metformin 500 mg bid for insulin resistance, refer the patient to a nutritionist and diabetes specialist, and order tests to evaluate his other symptoms.

### HEPATIC EFFECTS ARE RARE

Historically, statins have been linked to potential hepatotoxicity, with case reports of serum transaminase elevation, cholestasis, hepatitis, and acute liver failure. It is now recognized that hepatic AEs are rare and that statins are not associated with a risk for acute or chronic liver failure.<sup>1,11</sup> In patients with coronary heart disease, the incidence of hepatotoxicity with statin use is reported to be less than 1.5% over the course of five years and appears to be dose-dependent.<sup>1</sup>

In 2012, the FDA revised the labeling for most statins, relaxing its earlier recommendations for

**TABLE 3** Additional statin adverse effects

Organ system	Adverse effects (frequency)
Nervous	Headache (2%-17%) Asthenia (1%-4%) Dizziness (1%-4%) Fatigue (1%-4%)
Respiratory	Upper respiratory tract infection (1%-16%) Pharyngitis (3%-13%) Rhinitis (1%-11%) Sinusitis (2%-7%) Bronchitis (2%) Cough (1%-2%)
Gastrointestinal	Abdominal pain (1%-7% for all gastrointestinal effects) Constipation Diarrhea Dyspepsia Flatulence Heartburn Nausea Vomiting
Dermatologic	Rash (1%-4%)

Source: American Society of Health-System Pharmacists. 2013.<sup>50</sup>

monitoring of liver function, clarifying the risk for myopathy, and providing additional information about drug interactions.<sup>13</sup>

Checking transaminase levels before initiating therapy is recommended by both the ACC/AHA and the FDA.<sup>1,13</sup> Routine monitoring is not necessary, the ACC/AHA guideline states, because RCTs have found little evidence of ALT/AST elevation.<sup>1</sup> But here, too, evidence varies. An older meta-analysis (13 trials and nearly 50,000 participants) concluded that as a class, statins have no greater risk for transaminase elevations than placebo.<sup>22</sup> But the 135-RCT meta-analysis<sup>4</sup> found otherwise: Statins did increase the risk for transaminase elevation (odds ratio [OR], 1.51) compared with placebo, with differences associated with particular drugs and higher doses associated with more clinically significant elevations.<sup>4</sup> It is important to note, however, that there was signifi-

cant heterogeneity among the studies and no consistent definition of clinical significance.

**The bottom line:** Statins have been shown in multiple prospective studies to be safe for patients with chronic liver disease.<sup>22,23</sup>

### STATIN USE AND DIABETES: IS THERE A LINK?

Recent studies have found an increased risk for new-onset type 2 diabetes in statin users, with a greater risk associated with higher-potency statins, including rosuvastatin and atorvastatin.<sup>4,24</sup> Although the exact mechanism is not known, statins may modify insulin signaling in peripheral tissues or directly impair insulin secretion.

The ACC/AHA guideline reports an excess rate of diabetes of one per 1,000 patient-years for moderate-intensity therapy and three per 1,000 patient-years for high-intensity therapy.<sup>1</sup> The 2013 meta-analysis found that the elevated risk for diabetes was relatively small (OR, 1.09).<sup>4</sup> No difference among various statins was found.

In another meta-analysis—this one encompassing 17 RCTs and more than 110,000 patients—no statistically significant difference in the incidence of new-onset diabetes was seen based on either the specific statin being taken or the intensity of therapy (high vs moderate).<sup>24</sup>

**The bottom line:** Clinicians should monitor patients taking statins for signs and symptoms of hyperglycemia.

### STATINS MAY BE RENOPROTECTIVE

Statin use has been found to be associated with an increased risk for tubular proteinuria—an effect that is both dose- and potency-dependent.<sup>25</sup> Nonetheless, it has been suggested that statins may be a rare example of a drug class that is renoprotective in the long term, despite having an increased rate of proteinuria in the short term.<sup>25</sup>

The evidence? In prospective studies, statin therapy has been shown to slow the progression of kidney disease in diverse patient populations, including renal transplant recipients and those with chronic kidney disease (CKD).<sup>26,27</sup>

The Kidney Expert Panel of the National Lipid Association (NLA) has concluded that statins do not appear to cause significant proteinuria or acute kidney injury. The panel does not recommend routine monitoring for proteinuria or kidney function in statin users unless otherwise indicated but does recommend a lower dose for patients with CKD.<sup>28</sup>

**The bottom line:** Kidney Disease Improving Global Outcomes guidelines recommend that patients who have CKD, but are not on dialysis, be treated with statin therapy. Statins are contraindicated for patients on dialysis, as clinical trials have failed to show significant cardiovascular benefit.<sup>29</sup>

### INTRACEREBRAL HEMORRHAGE: STATINS INCREASE RECURRENCE RISK

In recent years, there has been considerable concern about a statin-induced increased risk for intracerebral hemorrhage (ICH). In a major prospective study in which patients were put on high-dose statin therapy or placebo after an acute ischemic or hemorrhagic stroke, the overall incidence of a recurrent stroke was significantly lower in the statin group.<sup>30</sup> Among those who'd had an ICH, however, the recurrence rate was 73% higher for patients taking statins.

A subanalysis that looked only at patients who'd had a hemorrhagic stroke as their initial event (n = 93) found that the absolute risk for recurrent ICH was 15.6% for patients randomized to atorvastatin versus 4.2% for those on placebo.<sup>31</sup> Despite being based on a small subset of the original study group, multivariate analysis indicated the increased risk was statistically significant (hazard ratio [HR], 1.69).

A subsequent decision analysis study based on these results proposed that patients with a history of spontaneous deep ICH would need an exceedingly high 10-year cardiovascular event risk (> 40%) for the benefits of statin therapy to outweigh the risk.<sup>32</sup> The risk is particularly high for those with a history of lobar ICH, which has an extremely high recurrence rate. However, subsequent retrospective and observational studies have found that patients who were already on statins when the ICH occurred had less severe strokes and more favorable outcomes, with a lower mortality rate at 90 days post-ICH.<sup>33-35</sup>

A 2010 ICH guideline from the AHA/American Stroke Association states that there is "insufficient data to recommend restrictions on use of statin agents" for patients who have had an ICH.<sup>36</sup>

**The bottom line:** Clinicians should carefully evaluate the anticipated cardiovascular risk for patients who have had a hemorrhagic stroke to determine whether statin therapy would be beneficial.

### OTHER SERIOUS ADVERSE EFFECTS: WHICH REPORTS ARE ACCURATE?

Statin use has been associated with a number of other serious AEs. Some reports appear to be accu-

rate; others do not hold up after a close look at the evidence.

**Malignancy.** A potential link between statins and an increased risk for malignancy has been considered for years. A large trial (N = 5,804) from 2002 found a correlation between pravastatin and an increased risk for new cancer diagnoses compared with placebo (HR, 1.25).<sup>37</sup> But a 10-year follow-up did not substantiate this finding, and it is now believed that the original result may have been due to chance.<sup>38</sup> Numerous other meta-analyses and systematic reviews have found no link between statin use and malignancy.<sup>39-41</sup>

**Cataracts.** Potential ocular effects have been widely studied and debated in recent years. Observational studies reporting an association between statin use and cataracts have had conflicting results, with some showing statins as protective<sup>42-45</sup> and others finding an increased risk.<sup>46,47</sup> However, a recent propensity-score matched analysis found that statin users do indeed have an increased risk for cataracts.<sup>48</sup> The authors concluded that for primary prevention, the risk-benefit equation for statin use should include this added risk.<sup>48</sup>

In addition, a review of the databases of the National Registry of Drug-Induced Ocular Side Effects, the World Health Organization, and the FDA from 1987 to 2008 indicates that statin therapy may also cause diplopia, ptosis, and ophthalmoplegia.<sup>49</sup>

**Peripheral neuropathy.** Despite case reports of statin-induced peripheral neuropathy, the NLA's Neurology Expert Panel states that statins do not appear to cause this condition. If a patient receiving statin therapy develops peripheral neuropathy, a full work-up for other causes should be initiated before modification of statin therapy is considered, the panel advises.<sup>28</sup>

Statins have also been linked to headache and dizziness, respiratory symptoms, gastrointestinal problems, and rash (see Table 3, previous page).<sup>50</sup>

### WHICH DRUG? POTENTIAL DIFFERENCES IN STATINS

A meta-analysis with more than 240,000 participants evaluated patients taking seven different statins (atorvastatin, fluvastatin, lovastatin, pravastatin, pitavastatin, rosuvastatin, and simvastatin), looking at AEs of the drugs both collectively and individually.<sup>4</sup> As noted earlier, the overall discontinuation rate due to AEs for all statins was 5.7%. Discontinuation rates for each agent were not reported.<sup>4</sup>

The researchers did report, however, that atorvastatin and rosuvastatin had the highest discontinuation rates; atorvastatin and fluvastatin had the highest incidence of transaminase elevations (OR, 2.6 and 5.2, respectively); and pravastatin and simvastatin appeared to be the best-tolerated and safest statins, with the lowest discontinuation rates. However, higher doses of simvastatin (> 40 mg/d) significantly increased the risk for CK and transaminase elevations (OR, 4.1 and 2.8, respectively),<sup>4</sup> as well as the risk for rhabdomyolysis when taken at the highest dose.<sup>15,16</sup>

### ARE STATINS SAFE FOR THESE PATIENTS?

When considering statin therapy, there are some patient populations that warrant particular concern:

**Women of childbearing age.** Statins are contraindicated in women who are pregnant or breastfeeding<sup>1</sup> and should not be initiated in women who are trying to conceive.

**Children and adolescents (ages 8-18 years).** Statins have been shown to be safe and effective for children and adolescents with familial hyperlipidemia. No effect on growth or maturation has been seen.<sup>51</sup> As with adults, however, higher statin doses and the use of concomitant interacting drugs increase the risk for AEs.

**Asians.** The new ACC/AHA guideline suggests taking Asian ancestry into consideration when prescribing statins because Asians may be more sensitive to medications metabolized by the CYP450 system.<sup>1</sup> However, there are no reports of an increased risk for AEs in Asian patients on statins.<sup>52</sup>

### Patient factors that increase risk

Risk factors for statin-induced AEs include<sup>1</sup>

- Multiple and/or serious comorbidities (eg, hypothyroidism, impaired renal or hepatic function, rheumatic disorders)
- Unexplained ALT elevation more than 3x the upper limit of normal
- History of prior statin intolerance or concomitant use of drugs that affect statin metabolism
- Age older than 75
- Preexisting muscle disorders
- Low vitamin D levels.

If a patient who would clearly benefit from statin therapy develops an AE requiring discontinuation, a retreatment—with the same drug or a different statin—is generally recommended once the symptoms resolve.<sup>1</sup>

### CASE

The risk for elevated serum transaminases, insulin resistance, cognitive impairment, and neuropathy associated with statin use is minimal, and further evaluation revealed that Mr L.'s recent symptoms had other causes. The elevated transaminases were due to fatty liver disease, the cognitive impairment was secondary to sleep apnea (both linked to his obesity), and the tingling in his hands was the result of carpal tunnel syndrome caused by his exercise regimen.

When he returns in six months, Mr L. reports that he has been working with both a nutritionist and an athletic trainer. He has sustained a 15-lb weight loss. He is still taking atorvastatin 10 mg; after he began taking CoQ10, his muscle pain resolved. The patient's cholesterol and transaminase levels are normal, and the cognitive impairment and peripheral neuropathy he reported at his last visit have improved significantly. **CR**

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