Emerging data suggest that the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) offer important benefits for the large population of individuals at high risk for coronary heart disease. This population encompasses a sizable portion of individuals who are also at high risk for drug-drug interactions due to their need for multiple medications. In general, statins are associated with a very small risk for myopathy (which may progress to fatal or nonfatal rhabdomyolysis); however, the potential for drug-drug interactions is known to increase this risk in specific high-risk groups. The incidence of myopathy associated with statin therapy is dose related and is increased when statins are used in combination with agents that share common metabolic pathways. Of particular concern is the potential for interactions with other lipid-lowering agents such as fibrates and niacin (nicotinic acid), which may be used in patients with mixed lipidemia, and with immunosuppressive agents, such as cyclosporine, which are commonly used in patients after transplantation. Clinicians should be alert to the potential for drug-drug interactions to minimize the risk of myopathy during long-term statin therapy in patients at high risk for coronary heart disease.
greatly from combination lipid-lowering therapy. Yet combinations of statins and fibrates are known to increase the risk of myopathy.

The escalating use of statin therapy in patients with high global risk, the withdrawal of cerivastatin from the market, and the public concern about the risk for myopathy led to this review.\textsuperscript{6,10,11} The intentions of this article are to define the scope of statin-related myopathy, to consider the risks of myopathy in the context of the clinical benefits of statin therapy, and to identify patient subgroups who are potentially at increased risk for this complication. A heightened suspicion for myopathy in high-risk patients, coupled with patient education, can reduce both the frequency and morbidity associated with statin-induced myopathy.

**BENEFITS OF STATIN THERAPY**

The clinical benefits of statins have been demonstrated in data from 7 major randomized controlled trials (RCTs), including nearly 57,000 patients. All 7 of these major RCTs have established that there is no relationship between lowering cholesterol levels with statin therapy and increased mortality from any cause.\textsuperscript{2,3,12}

The first 5 major RCTs\textsuperscript{13-17} to be completed compared simvastatin, pravastatin, or lovastatin with placebo in more than 4000 patients for periods of 5 or more years. Of these 5 trials, 3 (the Scandinavian Simvastatin Survival Study [4S],\textsuperscript{13} the Cholesterol and Recurrent Events Trial [CARE],\textsuperscript{14} and the Long-Term Intervention with Pravastatin in Ischaemic Disease [LIPID] trial)\textsuperscript{15} were secondary prevention trials and 2 (the West of Scotland Coronary Prevention Study [WOSCOPS]\textsuperscript{14} and the Air Force/Texas Coronary Atherosclerosis Prevention Study [AFCAPS/TexCAPS]\textsuperscript{17}) were primary prevention trials. A meta-analysis\textsuperscript{16} of these 5 RCTs, including more than 30,000 patients, determined that the overall proportional risk reduction with statin therapy, compared with placebo, was 31% for major coronary events, 29% for coronary deaths, 27% for cardiovascular deaths, and 21% for total mortality.

More recently, data have been reported for 2 additional RCTs: the Heart Protection Study (HPS) and the Lescol Intervention Prevention Study (LIPS). Data from the HPS,\textsuperscript{2} which is the largest study to date, demonstrate benefits of statin therapy in patients (both primary and secondary prevention) at high risk for cardiovascular events. The HPS randomized 20,536 individuals in the United Kingdom aged 40 to 80 years with total cholesterol levels greater than 135 mg/dL (3.5 mmol/L) to receive simvastatin (40 mg/d) or placebo and followed survivors for an average of 5.5 years. Results showed a 12% reduction in total mortality, a 17% reduction in vascular mortality, a 24% reduction in CHD events, and a 27% reduction in strokes.\textsuperscript{2} Substantial benefits were seen in subpopulations, including women, people older than 70 years, and individuals with LDL-C levels less than 116 mg/dL (3.0 mmol/L). The HPS protocol encouraged the subjects’ physicians to prescribe a non–study statin at their discretion, which they did for approximately one third of the study population. Thus, the actual benefit of statin therapy to participants has been estimated to be as much as 50% greater than the reported intention-to-treat results.

The LIPS\textsuperscript{3} compared the effects of fluvastatin, 80 mg/d, with those of placebo in 1677 patients (ages, 18-80 years; total cholesterol level >135 mg/dL [3.5 mmol/L] with an upper cutoff of 270 mg/dL [7.0 mmol/L]; mean baseline LDL-C, 131 mg/dL [3.4 mmol/L]) following successful completion of their first percutaneous coronary intervention. In these patients, fluvastatin therapy resulted in a risk reduction of 22% in major adverse coronary events compared with placebo. Benefits were more pronounced in patients with diabetes (47% reduction in major adverse coronary events) and in those with multivessel disease (34% reduction in major adverse coronary events).

**POTENTIAL RISKS OF STATIN THERAPY**

The reported rates of serious adverse events (SAEs) among statins as a class have been very low (<1%) and include a slight risk for elevation of liver enzymes and myopathy.\textsuperscript{18} The risk for reversible elevation of liver transaminases (defined by alanine aminotransferase and/or aspartate aminotransferase levels >3 times the upper limit of normal [ULN]) is approximately 1% for all statins.\textsuperscript{19} At doses investigated in clinical trials, these rates were not significantly different from those for placebo.\textsuperscript{12} The rates of elevated liver transaminase levels reported in product information literature ranged from 0.2% to 2.3%, increasing in a curvilinear relation to the statin dose. Product information for all of the statins recommends that liver function tests be performed before the initiation of treatment or dose increase.

**Statin-Associated Myopathy and Rhabdomyolysis**

At the outset of a discussion regarding drug-related myotoxicity, it is important to define 4 conditions: myalgia, elevated creatine kinase (CK) levels with or without symptoms, myopathy, and rhabdomyolysis. Myalgia is a patient-reported symptom of muscle soreness or pain that has been associated with the use of all statins and is also common among placebo-treated patients. Although the physician must investigate any patient report of myalgia appropriately, most are not associated with any increase in CK values. Thus, statistical reports of myalgia found in clinical trial reports or product information are not helpful in determining risk for myopathy.

Elevated CK levels are biochemical markers of the muscle damage associated with myopathy from any cause. Reference values for total CK in adults vary by analytical method and reference population. In the clinical setting, asymptomatic elevations of CK level of less than 5 × ULN may be considered benign, whereas elevations of 5 to 10 × ULN require evaluation. Myopathy has traditionally been defined as CK level greater than 10 × ULN with symptoms (eg, generalized myalgia, fatigue, or weakness). However, the definition of myopathy varies among studies and reports of statin-related myopathy are not based on a consistent definition. Likewise, reports of rhabdomyolysis have been confounded by its varied definitions. Rhabdomyoly-
Rhabdomyolysis is a clinical syndrome that results from severe and widespread injury to skeletal muscle and the subsequent accumulation of toxic muscle products in the blood and urine. Although initially defined by the US Food and Drug Administration (FDA) as a CK level greater than 10,000 U/L, more recently rhabdomyolysis has been defined by the FDA as an appropriate diagnosis only when organ damage (typically renal insufficiency) occurs in association with elevated CK levels. Severe myopathy and rhabdomyolysis are often characterized by marked elevations of CK levels (often >100 × ULN). Rhabdomyolysis is accompanied by findings such as myoglobinuria, myoglobinemia, and evidence of target-organ damage, such as decreased renal function or acute renal failure. If untreated, rhabdomyolysis can almost always be reversed by early diagnosis and treatment (FDA) as a CK level greater than 1000 U/L, more recently rhabdomyolysis-related deaths have been reported with all statins, and rhabdomyolysis-related deaths have been reported with all statins except for fluvastatin.

Case reports of myopathy associated with lovastatin or simvastatin began to appear in the literature around 1988; some involved concomitant use of gemfibrozil, cyclosporine, or erythromycin. In 1990, Pierce and colleagues published an article describing 12 reported cases of myopathy or rhabdomyolysis associated with concomitant use of lovastatin and gemfibrozil that had been reported to the Spontaneous Reporting System of the FDA. The risk appeared to be greatly increased in patients with renal insufficiency who were taking cyclosporine. In the 12 cases reported, the median CK level was 15,250 U/L; 4 patients had myoglobinuria, and 5 had acute renal failure. The symptoms of all 12 patients resolved when both drug therapies were discontinued and patients were treated supportively. Subsequently, the package inserts of all statins have included warnings regarding risk for rhabdomyolysis when used in combination with gemfibrozil or cyclosporine. Cerivastatin was the only statin that had a contraindication instead of a warning for combination therapy with gemfibrozil.

Staffa and colleagues summarized all cases of fatal rhabdomyolysis reported to the FDA prior to June 26, 2001, for which they could confirm a temporal association between statin use and rhabdomyolysis. By associating the number of cases with the number of prescriptions dispensed in the United States (according to data from National Prescription Audit Plus), the authors were able to assign a reporting rate per million prescriptions. There were 73 deaths and more than 480 million prescriptions, and the overall rate of reported deaths per 1 million prescriptions was 0.15 (Table 1). Based on a hypothetical average prescription length of 6 months, this would translate to approximately 0.03 deaths per 100,000 patient-years.

However, it has recently become evident that the magnitude of the problem was markedly greater for cerivastatin than for other statins. Cases of rhabdomyolysis involving the concomitant use of gemfibrozil and cerivastatin led to a change in cerivastatin prescribing information in 1999 to include an unequivocal warning against prescribing these 2 agents concurrently. In May 2001, a “Dear Doctor” letter was widely distributed, prohibiting the concomitant administration of the 2 agents. Nonetheless, additional cases of rhabdomyolysis with this combination continued to be reported through 2001.

Omar and Wilson recently published a review of all reports of statin-associated rhabdomyolysis cases reported to the FDA’s Adverse Events Reporting System (AERS) database between November 1997 and March 2001.

### Table 1. Reported Cases of Fatal Rhabdomyolysis and Numbers of Prescriptions for All Statins Dispensed in the United States Since These Products Were Launched

<table>
<thead>
<tr>
<th>Approval year</th>
<th>Lovastatin</th>
<th>Pravastatin</th>
<th>Simvastatin</th>
<th>Fluvastatin</th>
<th>Atorvastatin</th>
<th>Cerivastatin</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1987</td>
<td>19</td>
<td>3</td>
<td>14</td>
<td>0</td>
<td>6</td>
<td>31</td>
<td>73</td>
</tr>
<tr>
<td>1991</td>
<td>1991</td>
<td>14</td>
<td>3</td>
<td>0</td>
<td>6</td>
<td>31</td>
<td>73</td>
</tr>
<tr>
<td>1993</td>
<td>1993</td>
<td>3</td>
<td>14</td>
<td>0</td>
<td>6</td>
<td>31</td>
<td>73</td>
</tr>
<tr>
<td>1996</td>
<td>1996</td>
<td>3</td>
<td>14</td>
<td>0</td>
<td>6</td>
<td>31</td>
<td>73</td>
</tr>
<tr>
<td>1997</td>
<td>1997</td>
<td>3</td>
<td>14</td>
<td>0</td>
<td>6</td>
<td>31</td>
<td>73</td>
</tr>
</tbody>
</table>

†Reporting rate (ie, the number of fatal cases divided by the number of prescriptions dispensed). Reporting rates are not incidence rates.

*Adapted from Staffa et al.*

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2000, showing 601 cases of statin-associated rhabdomyolysis; 38 listed death as the outcome and many involved 1 or more drug-drug interactions (Table 2). While this information is extremely valuable, there are important limitations to the interpretation of adverse events reported through the AERS, primarily because cases cannot be viewed within an accurate context of drug exposure. Simvastatin was first marketed in 1987 and clearly has had far greater patient exposure than cerivastatin, which was initially marketed in dosages of 0.1 to 0.3 mg/d in 1998. Further, both underreporting and overreporting of SAEs are very likely to occur. Thus, neither precise actual occurrences nor incidence rates can be derived from these data.

### Incidence of Myopathy Reported in Clinical Trials

A more statistically accurate picture may be gleaned by reviewing the extent of CK elevations and myopathy reported in clinical trials. Important caveats in reviewing safety data from clinical trials, however, are that many types of patients excluded from trials receive these agents in clinical practice and that patients in clinical trials differ from those seen in general practice in that the former are generally better informed and monitored and perhaps more compliant. Overall, myopathy occurred in approximately 0.1% to 0.2% of patients who received statins in clinical trials. The rate of CK elevations greater than 10×ULN reported in phase 3 clinical trials of cerivastatin was significantly greater than that of other statins and was dose dependent (placebo, 0.0% [n=198]; 0.4 mg/d, 1.0% [n=194]; 0.8 mg/d, 1.3% [n=774]). Importantly, the frequency of CK levels greater than 10×ULN was increased in more susceptible individuals; it was 5.6% in women older than 65 years.

In the Extended Clinical Evaluation of Lovastatin (EXCEL) trial, which enrolled more than 8000 patients, myopathy—defined as the combination of muscle symptoms with CK elevations greater than 10×ULN—was seen in 0.0%, 0.1%, and 0.2% of patients receiving lovastatin dosages of 20 mg/d or 20 mg twice daily, 40 mg/d, and 80 mg/d, respectively. Pooled data from nearly 9000 patients who received fluvastatin or placebo in clinical trials between 1987 and 2001 showed no difference between fluvastatin monotherapy and placebo for CK elevations greater than 10×ULN, which occurred in 0.2%, 0.2%, 0.3%, and 0.0% of patients receiving placebo or fluvastatin dosages of 20 mg/d, 40 mg/d, and 80 mg/d, respectively.

In the meta-analysis cited previously, LaRosa and colleagues reported that in approximately 70,000 patient-years of statin therapy, there was only 1 reported episode of myopathy; this was in a patient receiving simvastatin, 20 mg/d, in 45.

In the HPS, CK levels greater than 10×ULN were identified in 0.09% [n=194]; 0.8 mg/d, 1.3% [n=774]). Importantly, the frequency of CK levels greater than 10×ULN was increased in more susceptible individuals; it was 5.6% in women older than 65 years.

### Table 2. Profile of 601 Reports of Rhabdomyolysis Associated With 6 Statins

<table>
<thead>
<tr>
<th>Statin</th>
<th>No. of Cases (% of Total)</th>
<th>No. of Cases Associated With Potentially Interacting Drugs†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simvastatin</td>
<td>215 (35.8)</td>
<td>Mibefradil (48) Fibrates (33) Cyclosporine (21) Warfarin (12) Macrolide antibiotics (10) Digoxin (9) Azole antifungals (4) Chlorothiazide (2) Nefazodone (2) Niacin (2) Tacrolimus (1) Fusidic acid (1)</td>
</tr>
<tr>
<td>Cerivastatin</td>
<td>192 (32.1)</td>
<td>Mibefradil (45) Fibrates (10) Macrolide antibiotics (13) Warfarin (7) Cyclosporine (5) Digoxin (5) Azole antifungals (2)</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>73 (12.2)</td>
<td>Mibefradil (1) Niacin (1) Cholesterol (2) Digoxin (2) Cyclosporine (2) Macrolide antibiotics (1)</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>71 (11.8)</td>
<td>Mibefradil (1) Niacin (1) Cholesterol (1) Digoxin (2) Cyclosporine (2) Macrolide antibiotics (1)</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>40 (6.7)</td>
<td>Mibefradil (3) Niacin (1) Cholesterol (1) Digoxin (2) Cyclosporine (1) Macrolide antibiotics (1) Azole antifungals (6) Niacin (2)</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>10 (1.7)</td>
<td>Mibefradil (1) Niacin (1) Cholesterol (1) Digoxin (2) Cyclosporine (1) Macrolide antibiotics (1) Azole antifungals (6) Niacin (2)</td>
</tr>
</tbody>
</table>

*Adapted from Omar and Wilson.*

†Each case may be associated with 1 or more potentially interacting drugs.
ase levels greater than 1.5 \times \text{ULN} during this phase were also excluded.\textsuperscript{2,41} In LIPS,\textsuperscript{3} there were no elevations in CK levels of 10 \times \text{ULN} or greater or episodes of rhabdomyolysis in the fluvastatin group.

In contrast to the demonstrated safety of statin therapy in clinical trials, in which no patients had fatal rhabdomyolysis or renal failure, a meta-analysis of clinical trials of aspirin as primary prevention estimated that for each 1000 patients treated for 5 years, aspirin would cause 0 to 2 hemorrhagic strokes and 2 to 4 major gastrointestinal tract bleeding events.\textsuperscript{42}

### Differences Among Statins

**Table 3** presents a comparison of the pharmacokinetic profiles of the 5 clinically available statins, as well as the profile for cerivastatin. Statins exhibit differences in half-life, systemic exposure (area under the curve), maximum concentration, bioavailability, protein binding, lipophilicity, clearance, metabolic pathways, presence of active metabolites, and excretion routes.\textsuperscript{43} Fluvastatin is available in both immediate-release and extended-release formulations, which have some differences in pharmacokinetic properties.

With the exception of lovastatin and simvastatin, which are administered as prodrugs, all statins are given as the active \( \beta \)-hydroxyacid form. The extent of absorption of statins varies considerably, from 30\% to 98\%. Following absorption, statins undergo extensive hepatic first-pass metabolism and are excreted mainly via the bile into feces, resulting in low systemic bioavailability.\textsuperscript{45,46} With the exception of atorvastatin,\textsuperscript{47,48} the elimination half-life of all statins is very short (0.5-4.7 hours), and no drug accumulates in plasma on repeated administration.\textsuperscript{43,46,49} The quantity of the administered dose of statin that is excreted in urine varies from negligible amounts for atorvastatin\textsuperscript{47} to 20\% and 30\% for pravastatin and cerivastatin, respectively. With their limited renal excretion, fluvastatin and atorvastatin are the statins least affected by alterations in renal function.\textsuperscript{43} Immediate-release fluvastatin displays nonlinear increases in its area under the curve and maximum concentration at doses greater than 20 mg, suggesting a saturation of the hepatic first-pass effect. Consequently, there are greater than expected systemic drug concentrations in patients receiving higher doses, although this effect appears to be temporary.\textsuperscript{50} Compared with immediate-release fluvastatin (80 mg), extended-release fluvastatin (80 mg) demonstrates a reduced maximum concentration and bioavailability, resulting in lower systemic drug levels.\textsuperscript{31}

### Drug Interactions

Drug-drug interactions with statins are significantly more likely to be associated with myopathy compared with statin monotherapy. For example, one source reported that the incidence of myopathy for lovastatin monotherapy was 0.15\%, but increased to 2\%, 5\%, and 28\% in patients receiving concomitant niacin, niacin plus cyclosporine, or cyclosporine plus gemfibrozil, respectively.\textsuperscript{32} Reported drug interactions with statins that have been associated with rhabdomyolysis are given in **Table 4**.

\begin{table}
\centering
\caption{Clinical Pharmacokinetics of HMG-CoA Reductase Inhibitors*}
\begin{tabular}{llccccccccccc}
\hline
Statin & \( T_{\text{max}} \), h & \( C_{\text{max}} \), mg/mL & Bioavailability, \% & Lipophilicity & Protein Binding & Clearance, \( \text{L/h per kg} \) & Primary Metabolic Pathway & Active Metabolites & \( t_{1/2} \), h & Urinary/Fecal Excretion, \% & Hepatic Extraction, \% \\
\hline
Atorvastatin & 2-3 & 0.27-66 & 0-12 & Yes & 80-90 & 0.25 & CYP3A4 & Yes & 15-30 & 2/70 & >70 \\
Cerivastatin & 1.0 & 0.2 & 20-60 & Yes & >99 & 0.20 & CYP3A4 & Yes & 1.3-3.1 & 30/70 & NA \\
Fluvastatin & 0.5-1.0 & 0.4 & 19-29 & Yes & >99 & 0.49 & CYP2C9 & No & 0.5-2.3 & 6/90 & >68 \\
Fluvastatin & 4.0 & 4.0 & 55 & Yes & >99 & 3.8 & CYP2C9 & No & 4.7 & NA & >68 \\
Lovastatin & 1.0-3.0 & 0.2 & 5 & Yes & >95 & 0.26-1.10 & CYP3A4 & Yes & 2.9 & 10/83 & >70 \\
Pravastatin & 0.9-1.6 & 0.9-1.6 & 45-55 & Yes & 43-55 & 0.81 & NS & No & 1.3-2.8 & 20/71 & 44-66 \\
Simvastatin & 1.3-2.4 & 0.5-1.0 & 10-34 & Yes & 94-98 & 0.45 & CYP3A4 & Yes & 2.3 & 13/58 & 78-87 \\
\hline
\end{tabular}
\footnotesize{Abbreviations: \( C_{\text{max}} \), maximum concentration; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; NA, not available; NS, not significant; \( t_{1/2} \), terminal elimination half-life; \( T_{\text{max}} \), time to maximum concentration; XL, extended release.}
\footnotesize{*Based on a 40-mg oral dose, with the exception of fluvastatin XL (80 mg) and cerivastatin (0.2 mg). Adapted from Corsini et al.\textsuperscript{43}}
\end{table}

\begin{table}
\centering
\caption{Clinically Reported Drug Interactions With Statins Associated With Rhabdomyolysis*}
\begin{tabular}{cccccccc}
\hline
Drug & Atorvastatin & Cerivastatin & Fluvastatin & Lovastatin & Pravastatin & Simvastatin \\
\hline
Fibrates & + & + & + & + & + & + \\
Cyclosporine & + & + & + & + & + & + \\
Niacin & + & + & + & + & + & + \\
Macrolide antibiotics & + & + & + & + & + & + \\
Digoxin & + & + & + & + & + & + \\
Antifungals & + & + & + & + & + & + \\
Warfarin & + & + & + & + & + & + \\
\hline
\end{tabular}
\footnotesize{*Adapted from Omar and Wilson.\textsuperscript{4} Minus sign indicates not reported; plus sign, reported.}
\end{table}
With the exception of pravastatin, which is transformed enzymatically in liver cytosol, statins are extensively metabolized via cytochrome P450 (CYP) pathways. Lovastatin, simvastatin, atorvastatin, and cerivastatin use mainly the CYP3A4 pathway. Fluvastatin has minimal CYP3A4 activity; its metabolism occurs mainly via CYP2C9 (Table 4).33,51

Most of the clinically important drug-drug interactions that occur with statins are attributable to the concurrent use of statins that are recognized by CYP3A4 and other agents that are potent inhibitors or substrates of this enzyme—in particular, the azole antifungals, some macrolide antibiotics, and cyclosporine. Other CYP3A4 substrate agents (eg, the calcium channel antagonists) may compete for the enzyme, thereby also potentially increasing the serum concentration of the statin. An interaction also occurs between statins and coumarin anticoagulants8; the coadministration of statins to patients receiving warfarin causes a small increase in the anticoagulant effect of warfarin that requires monitoring of the international normalized ratio and potentially a reduction in warfarin dosage. The mechanism of the interaction between statins and warfarin is uncertain; given that both CYP3A4 and CYP2C9 isoenzymes are involved in the metabolism of warfarin, competition with statins at this level may be a contributing factor in the potentiation of warfarin effects.5 Cases of rhabdomyolysis have been reported with the combination of warfarin and any statin,4 but it is not clear whether these cases were due to a warfarin-statins interaction. However, it should be noted that the risk for myopathy also appears to increase when statins are combined with drugs that may not be metabolized via the CYP3A4 pathway, such as fibrates and niacin. Drug interactions at the excretion level might potentially occur as a consequence of competition for carrier-mediated transport across the bile canalicular membrane.

In addition, changes in the absorption and excretion of drugs independent of CYP metabolism can alter drug disposition and may contribute to the interaction potential of statins. A newly recognized class of active drug transporters, P-glycoproteins,54 are known to affect the disposition and bioavailability of many drugs including 3A4 substrates. P-glycoproteins are transmembrane proteins that function as drug efflux pumps that actively transport drugs from intestinal, renal, brain, and hepatic cells.54 Lovastatin and simvastatin are very potent and effective inhibitors of P-glycoprotein transport, whereas atorvastatin and pravastatin have less inhibitory activity.55,56 In contrast, fluvastatin is not a substrate of P-glycoprotein.57 Digoxin is a P-glycoprotein substrate, and its narrow therapeutic range makes any drug-drug interaction important. Acute interactions have been observed with simvastatin,58 and coadministration of atorvastatin, 80 mg/d, and digoxin for 20 days increased systemic exposure to digoxin by inhibition of P-glycoprotein59; therefore, monitoring digoxin levels is warranted with these agents. Administration of a single 40-mg dose of fluvastatin to patients receiving long-term treatment with digoxin did not result in any clinically significant effect on the digoxin steady-state pharmacokinetics.60 However, cases of rhabdomyolysis have been reported with the coadministration of digoxin and all statins,4 although it is not clear whether these cases were related to a digoxin-statins interaction.

When statins are administered concomitantly with other potentially myotoxic drugs or with agents that may increase the plasma concentration of statins, the risk for myopathy increases. Cases of substantial increases in serum drug concentrations ofLovastatin and simvastatin have been reported following clinically significant drug interactions.18 Spach and colleagues18 reported a 3-fold increase in the serum concentration of lovastatin (40 mg/d) when given concomitantly with erythromycin. Ayanian and colleagues61 reported an 8-fold increase in the serum concentration oflovastatin (60 mg/d) in combination with erythromycin and diltiazem, and Mousa and colleagues62 reported a 3.6-fold increase in the concentration of simvastatin (20 mg/d) in combination with diltiazem. Interactions have been reported for fluvastatin in combination with the CYP2C9 substrate warfarin,63 and an increased serum concentration of fluvastatin has been reported when it is coadministered with diclofenac or fluconazole.33,64

**Statin Interactions With Cyclosporine**

In patients after transplantation, the combination of statins and calcium-channel blockers (in particular, cyclosporine) often results in increased serum levels of the statin, with the potential for an increased risk for myopathy and rhabdomyolysis, particularly when higher doses of statins are used. Cases of rhabdomyolysis have been reported in patients after transplantation taking cyclosporine with all statins except fluvastatin and pravastatin.30,65-70 Cyclosporine increases plasma exposure to atorvastatin by approximately 6-fold,71 lovastatin by up to 20-fold,72 pravastatin by 5- to 23-fold,72 simvastatin (20 mg/d) by 3- to 5-fold,74,75 cerivastatin (0.2 mg/d) by 3- to 5-fold,76 and fluvastatin by approximately 2-fold.53,72,73,77 The increase in pravastatin bioavailability in the presence of cyclosporine, despite the lack of CYP3A4 interactions, may be due to competition for biliary excretion by these 2 agents resulting in reduced biliary clearance of pravastatin.78,79

Despite the risk for statin-cyclosporine interactions, treating dyslipidemia is crucial in the posttransplantation population because cardiovascular disease is a major cause of death in these patients, accounting for nearly half of all deaths in kidney graft recipients.80 Dyslipidemia often worsens during the posttransplantation period, with increases in total cholesterol of 25% to 30% commonly found in renal transplant patients, along with concomitant increases in triglyceride and LDL-C levels.81 Because of the significant clinical benefits of statin therapy in this population, therapy is recommended with close follow-up. In 1992, Ballantyne and colleagues82 reported that 4 of 5 patients after heart transplantation who
were treated with high-dose lovastatin (40-80 mg/d) in combination with another lipid-lowering agent developed rhabdomyolysis and 2 developed acute renal failure. However, lovastatin monotherapy at a dosage of 20 mg/d was well tolerated and did not result in myopathy in 15 similar patients.

Low-dose statin therapy in combination with cyclosporine was well tolerated in heart transplant patients in 2 small open-label trials. Shortly after heart transplantation, Kobashigawa and colleagues85 randomly assigned 97 patients to pravastatin (20-40 mg/d) or no statin. The pravastatin group had a better survival rate after 12 months (94% vs 78%; \( P = .03 \)), and there were no episodes of CK elevations or myopathy in either group. Similarly, Wenke and colleagues86 randomly assigned 72 heart transplant patients to receive simvastatin (5-15 mg/d) or no statin. The simvastatin group had a significantly higher survival rate (88.6% vs 70.3%; \( P = .05 \)) and lower incidence of graft complications at 4 years than did patients randomized to no statin. In a 12-month open-label study comparing simvastatin, 20 mg/d, and pravastatin, 40 mg/d, in heart transplant patients receiving cyclosporine (N=87),87 there were similar clinical benefits to the 2 trials mentioned previously; however, myopathy or rhabdomyolysis occurred in 6 (13.3%) of the simvastatin-treated patients but in none of the pravastatin-treated patients. Based on these studies, it is recommended that heart transplant recipients receiving cyclosporine should not receive more than 10 mg/d of simvastatin, 20 mg/d of lovastatin, or 40 mg/d of pravastatin, nor should a statin be taken in combination with other lipid-lowering agents.86,87

Fluvastatin (at dosages of up to 80 mg/d) has been studied extensively in renal transplant recipients. No instances of rhabdomyolysis have been observed during clinical trials in which patients received fluvastatin and cyclosporine concomitantly.88-90 Fluvastatin is currently being investigated in the ongoing Assessment of Lescol in Renal Transplantation (ALERT) trial,89 which is an RCT designed to assess the effect of fluvastatin (40-80 mg/d) vs placebo on major adverse coronary events and all-cause mortality in renal transplant recipients (N=2100) with mild to moderate hypercholesterolemia. Results of the 6-year trial are expected in early 2003. Following the withdrawal of cerivastatin, ALERT investigators reviewed blinded safety data for all adverse events reported at a mean follow-up of 4 patient-years. Overall, there was only 1 reported asymptomatic CK level greater than 10×ULN, and there were no cases of rhabdomyolysis.

**Statin-Fibrate Combination Therapy**

Monotherapy with fibrates appears to pose an independent risk for myopathy that is greater than the risk posed by statin monotherapy. An analysis of data from 17 219 general practice patients in the United Kingdom90 found that the incidence rate for myopathy observed for the total population was 2.3 per 10 000 patient-years (95% confidence interval, 1.2-4.4), whereas the incidence rate for the population without hyperlipidemia and not taking lipid-lowering agents was 0.2 per 10 000 patient-years (95% confidence interval, 0.1-0.4). Although rare, myopathy occurred more frequently in patients using either statins or fibrates than in the general population; however, current fibrate users were 5.5 times more likely to develop myopathy than were current statin users.

Fibrates are particularly effective in reducing triglyceride levels and raising high-density lipoprotein cholesterol (HDL-C) levels and have been shown to reduce clinical events in patients with low HDL-C levels.91 Because patients with mixed hyperlipidemia can rarely be treated successfully with a single drug, statin-fibrate combination therapy may offer a therapeutic advantage in improving lipid profiles, although the potential clinical benefits of this combination have not been reported. Mixed hyperlipidemia is frequently identified in patients with diabetes; it is characterized by a highly atherogenic lipid pattern of increased total cholesterol and triglyceride levels in combination with decreased HDL-C level.92 For these patients, the absolute risk for a cardiovascular disease event is high, and the benefits of combination therapy are likely to be substantially greater than the risk for an SAE.

Drug interactions between statins and fibrates occur frequently, resulting in a relatively large number of reports of severe myopathy and rhabdomyolysis in patients treated with this combination.20 In a review of 36 clinical trials published between 1988 and 2000 (including RCTs [n=10], retrospective studies [n=5], open-label studies [n=21], and a number of trials of very short duration) with a total combined population of 1674 patients, combination drug therapy with a statin and a fibrate appeared to be associated with an overall 0.12% incidence of myopathy, defined as myalgia with CK levels greater than 10×ULN.93 Of the studies reviewed, 20 used gemfibrozil and 10 used bezafibrate; the 2 cases of myopathy involved gemfibrozil use. In a subsequent clinical trial, the combination of fluvastatin and bezafibrate was not associated with myopathy or relevant CK elevations in 333 patients with mixed hyperlipidemia who were followed up for 6 months.93 However, in a 12-month open-label study, myopathy was reported in 2 of 148 patients with type 2 diabetes who received the combination of simvastatin and bezafibrate.94

Myopathy related to the statin-fibrate combination appears likely to occur by more than a single mechanism and does not always involve CYP3A4 pathways. For example, gemfibrozil was shown to increase plasma concentrations of Lovastatin without inhibiting CYP3A4, whereas bezafibrate demonstrated no significant effect on the pharmacokinetics of Lovastatin.95 Although all fibrates have been associated with cases of CK elevations and myopathy in combination with statins, the risk for the development of myopathy may be greater for gemfibrozil compared with bezafibrate or fenofibrate use. The concomitant use of gemfibrozil and atorvastatin, Lovastatin, pravastatin, or simvastatin has been associated with case reports of rhabdomyolysis, although no cases have been reported for fluvastatin.
statin in combination with gemfibrozil.4,24,102 No significant pharmacokinetic differences were observed when comparing the combination of fluvastatin and gemfibrozil with each drug alone.103

Cardiologists and lipidologists are the primary prescribers of statin-fibrate therapy, but primary care providers, particularly in the United States, also increasingly prescribe the combination. In 1998, a consensus paper on the clinical use of fibrates in the treatment of dyslipidemia and CHD affirmed the benefits of statin-fibrate therapy in patients with type IIB hyperlipidemia104; however, it cautioned that this combination should not be used by the following groups: elderly patients (older than 70 years), patients taking multiple medications, patients with renal disease or other severe illnesses, and patients who may not fully understand the risks of therapy. Fibrate monotherapy may impair liver function independently; therefore, patients with impaired liver function should not receive combination statin-fibrate therapy. Furthermore, fibrates, which are excreted primarily through the kidneys, may increase the risk for myopathy in patients with even mild renal impairment.

**Statin-Niacin Combination Therapy**

Nicotinic acid (niacin) monotherapy is used infrequently to lower LDL-C level, primarily because it is poorly tolerated at the high doses required for monotherapy. However, as with the statin-fibrate combination, statin-niacin therapy is used to augment reductions in LDL-C and triglycerides and increases in HDL-C. In 5 major clinical trials, various combinations of statins and niacin preparations have demonstrated efficacy in reducing cardiovascular and total mortality and in slowing the progression of coronary lesions.105

Niacin monotherapy has not been associated with myopathy. Clinical trials in which patients have received niacin in combination with fluvastatin, pravastatin, or simvastatin have also not reported myopathy106-108; however, the number of patients in these trials was low. A recent open-label study did not find any cases of myopathy with a new drug formulation containing once-daily extended-release niacin and lovastatin.109 The concomitant administration of fluvastatin with niacin demonstrated no effect on the bioavailability of either drug.60 However, in case reports, niacin has been associated with rhabdomyolysis in combination with lovastatin, pravastatin, or simvastatin use, but not with atorvastatin or fluvastatin.4,24,102 No significant pharmacokinetic differences were observed when comparing the combination of fluvastatin and gemfibrozil with each drug alone.103

While hepatic toxicity with statin-niacin therapy has been minimal, transaminase elevations are frequently encountered, particularly with the use of a sustained-release niacin preparation given twice daily. As with monotherapy with either agent, patients being treated with statin-niacin combination therapy should have liver transaminase levels monitored and should be cautioned to report any symptoms that suggest myopathy.

**Calcium Channel Antagonists**

Many patients with hypercholesterolemia are also hypertensive and may be receiving antihypertensive therapy with calcium channel antagonists. Of particular note is the interaction of statins with mibefradil, which was withdrawn from the global market because of a range of serious drug-drug interactions.6 Several cases of statin-associated rhabdomyolysis were reported in patients receiving mibefradil.112 Verapamil and diltiazem, which are weak inhibitors of CYP3A4,113 have been shown to increase the plasma concentration of simvastatin up to 4-fold, and diltiazem has been shown to increase the plasma concentration of lovastatin to the same magnitude.55,114,115

A review of data115 from clinical outcome trials in which more than 12,000 patients received simvastatin for several years revealed that approximately one third of patients randomized to simvastatin were receiving concomitant therapy with a calcium channel antagonist. There was no evidence that the concomitant use of calcium channel antagonists, including diltiazem and verapamil, increased the risk of simvastatin-associated myopathy in these trials.113

However, more recently, enhanced cholesterol reduction has been reported with simvastatin use in combination with diltiazem, and 2 cases of rhabdomyolysis have also been reported in association with this combination,116,117 suggesting a need for some caution in using the 2 agents simultaneously.

**COMMENT**

The risk of statin therapy must be considered in view of the remarkable clinical benefits associated with this class of drugs. Patients at highest risk for CHD obtain the greatest absolute benefits from statin therapy. Based on the findings from the HPS,2,118 if 1 million high-risk patients were to initiate statin therapy, approximately 5000 deaths would be prevented annually. This would translate into approximately 70 to 100 fewer myocardial infarctions, strokes, or revascularization operations for every 1000 patients with CHD, other vascular disease, or diabetes who were treated with statins for 5 years (7% to 10% absolute risk reduction). Based on the much larger population of people at risk for CHD who might benefit from statin therapy, 70,000 to 100,000 fewer major vascular events can be expected to occur for every million patients treated with statins.

The absolute risk for SAEs with statin therapy is low. The estimated prevalence of CK levels greater than 10×ULN with statin monotherapy is approximately 0.12%.24 In contrast, reports of SAEs with cerivastatin, alone and in combination with a fibrate or cyclosporine, were at least 20 times higher than with other statins, leading to the withdrawal of cerivastatin from the world market. The rate of myopathy noted in phase 2 and 3 clinical trials with cerivastatin was based on lower dosages than those used in phase 4 trials. Higher dosages (0.4 mg/d and 0.8 mg/d) were also often used in clinical practice, and despite clearly specified warnings in the product label and letters sent to physicians, cerivastatin was often prescribed in combination with a fibrate.5,33,38,70,119-124 In the AERS data reported by Staffa and colleagues,1 cerivastatin was associated...
Table 5. Safety Considerations in Prescribing Statins in Primary Care Settings

**DO**

- Exercise due caution when prescribing statins.
- Check baseline renal function and thyroid function (TSH) prior to initiating statin therapy.
- Check ALT and AST levels prior to prescribing a statin and prior to any planned increase in statin dose.
- Consider the potential for drug-drug interactions when prescribing statins.
- Be alert for patient characteristics that may increase the risk for myopathy during statin therapy, such as advanced age (particularly elderly women), renal or liver impairment, diabetes with evidence of hepatic fatty changes, hypothyroidism, drugs of abuse (amphetamine, phencyclidine, heroin, cocaine), surgery, trauma, ischemia-reperfusion, debilitated status, excessive alcohol intake, heavy exercise.
- Provide patient education regarding recognition and reporting of symptoms of myopathy during statin therapy.
- Counsel patients to discontinue statin therapy if they become acutely ill or are admitted to the hospital.
- Consider discontinuation of statin therapy during a short course of a macrolide antibiotic (eg, azithromycin, clarithromycin, or erythromycin).
- Consider myopathy when a statin-treated patient complains of unexplained, generalized muscle pain, tenderness, or weakness. Joint pain, nocturnal leg cramps, or localized pain are not symptoms of myopathy.
- Consider the possibility of myopathy in elderly patients who report only weakness, since these patients are less likely than younger patients to experience muscle pain.
- Check CK levels when a patient reports symptoms of myopathy.
- If CK levels are less than 5 × ULN, repeat measurement in 1 week.
- If CK levels are elevated to 5 × ULN or greater, discontinue statin therapy and monitor serum CK levels.
- Assess for signs of dehydration or renal compromise in patients with myopathy.
- Consider referral for patients requiring combination lipid-lowering therapy or document the need for this therapy, such as lack of response to monotherapy in a high-risk patient.
- When adding a statin to the regimen of a patient already receiving a fibrate, initiate at the lowest starting dose of statin.
- Consider the differences in pharmacokinetic profiles among statins, particularly in patients requiring long-term therapy with drugs that are CYP3A4 substrates, inhibitors, or both.

**DON’T**

- Prescribe statin-fibrate combination therapy in patients with the following conditions: impaired liver or renal function (creatinine level >2.0 mg/dL [176 mmol/L]), cyclosporine or tacrolimus therapy, long-term macrolide antibiotic therapy or azole antifungal therapy, advanced age (>70 y), skeletal muscle conditions.
- Prescribe high-dose statin therapy for elderly patients and patients with renal insufficiency, or in combination with fibrates or cyclosporine.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; TSH, thyroid-stimulating hormone; ULN, upper limit of normal.

with 3.16 reports of fatal rhabdomyolysis per 1 million prescriptions (approximately 0.63 deaths per 100 000 patient-years, based on a hypothetical average prescription duration of 6 months), whereas for lovastatin, simvastatin, atorvastatin, pravastatin, and fluvastatin, the rates were 0.19, 0.12, 0.04, 0.04, and 0.00 cases, respectively, per 1 million prescriptions (approximately 0.04, 0.02, 0.01, 0.01, and 0.00 deaths, respectively, per 100 000 patient-years). However, as we begin to treat more patients with high global risk, risk for SAEs is likely to increase because of factors such as increased age and multiple therapies.

Although statins as a class share a common mechanism of action, the clinical experience with cerivastatin has shown that SAE rates differ substantially. Further research is needed to better understand the molecular mechanisms involved with statin-induced rhabdomyolysis and which pharmacological properties are critical in determining the risk for rhabdomyolysis.

Careful patient selection, education, and follow-up can reduce the risk of statin therapy while optimizing the benefits (Table 5). Clearly, the combination of a statin with a fibrate, particularly gemfibrozil, has been a major problem and should not be used in patients at increased risk because of age or comorbidities. Clinical trials are needed to determine the absolute benefits and risks of combination therapy with statin plus fibrate or statin plus niacin vs monotherapy in high-risk patients. Risk for myopathy and rhabdomyolysis has also been shown to be increased with the use of cyclosporine, a potent inhibitor of CYP3A4, suggesting that risk for SAEs in patients requiring multiple medications may be reduced with statins that are not primarily metabolized through the CYP3A4 pathway (fluvastatin or pravastatin). However, drug-drug interactions have not been demonstrated in all cases of myopathy, and other presently unknown factors may also be involved in the development of myopathy, such as disease states or genetic polymorphism.

Education and follow-up are essential to preventing SAEs with statin therapy. Many of the reported cases of rhabdomyolysis in patients receiving cerivastatin and gemfibrozil might have been averted if clinicians had heeded warnings to avoid the use of this combination and if patients had been better informed about the warning signs. Statin-associated myopathy should be suspected when a statin-treated patient complains of unexplained, generalized muscle pain, tenderness, or weakness. Likewise, patients should be taught to recognize symptoms of myopathy and report them promptly. If myopathy is suspected, statin therapy should be discontinued and serum CK levels should be monitored. Early diagnosis and treatment of symptomatic CK elevations, including cessation of drug therapies potentially related to myopathy, can prevent the progression to rhabdomyolysis.

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From Baylor College of Medicine, Houston, Tex (Dr Ballantyne); Department of Pharmacological Sci-
REFERENCES


