Safety and Statins: Pharmacologic and Clinical Perspectives

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Among the 20 leading prescription drugs in the United States, 3 agents—atorvastatin (Lipitor), simvastatin (Zocor), and pravastatin (Pravachol)—are of the class known formally as 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors and informally as statins.

Statins are a primary form of therapy for patients with unhealthy lipid profiles, especially elevations in low-density lipoprotein (LDL) cholesterol.

Collectively, statins represent the number 1 category of prescribed drug in the United States in terms of dollar volume (more than $14 billion annually) and the number 3 category in terms of new prescription volume (more than 120 million annually).[1,2]

With approximately 15 million people in the United States taking a statin at any given time, even infrequent adverse events can affect tens of thousands of patients. Overall, the record of safety with statins has been good. The main adverse effects are myotoxicity and hepatotoxicity, both of which appear to be dose related.

Statin-induced Myotoxicity

Myotoxicity, the most common form of statin-induced toxicity, has traditionally been defined by 2 criteria: the presence of muscle symptoms and elevations in creatine kinase (CK) levels. In general, the incidence is much higher for the milder forms of statin-induced myotoxicity than for the more severe forms.[3]

Definitions

Myalgia refers to muscle aches, soreness, or weakness, with minimal or no elevation in CK. These symptoms may be specific in terms of discomfort at certain locations or general in terms of overall weakness. The onset of myalgia does not automatically dictate a change in therapy if CK levels remain normal, but close monitoring of CK levels is advisable.

Myopathy refers to muscle symptoms associated with elevations in CK at least 10 times the upper limit of normal (ULN). Statin dose reduction, switching to a different statin, or discontinuation of statin therapy is indicated in such cases to allow resolution of symptoms and recovery of normal laboratory values.

Rhabdomyolysis refers to myopathy extensive enough to cause spillage of myoglobin into the urine; this nephrotoxic substance can induce acute renal failure. Rhabdomyolysis is typically associated with extreme elevations in CK, to values exceeding 10 000 U/L, which is more than 50 times ULN. This condition is potentially fatal, but the incidence is low (<0.1%).

These traditional definitions are not absolute. A normal CK level does not rule out muscle pathology, and muscle symptoms associated with CK elevations less than 10 times ULN are also clinically relevant and may warrant a revision in therapy.

Risk Factors

A variety of factors may contribute to the

Table 1. Risk Factors for Statin-induced Myotoxicity*

Factor	Comment
High or increasing doses of statins	Risk of myotoxicity is dose related.
Pharmacokinetic interactions with CYP450 inhibitors, resulting in increased concentration of active statin	Relevant mainly to lipid-soluble statins that require metabolic transformation via CYP450 isoenzymes to water-soluble form for renal excretion.
Pharmacodynamic interactions with other myotoxic agents, resulting in additive adverse effects	Examples include concomitant therapy with a second statin or with fibrates or niacin.
Female sex, older age (especially age >65 years)	These variables are associated with statin concentrations that are higher than expected for a given dose.
Renal insufficiency, hypothyroidism	These conditions contribute independently to the risk of myotoxicity.

CYP450 indicates cytochrome P450.
*Adapted from Pasternak RC, et al.[4]

risk of statin-induced myotoxicity (**Table 1**).[4] Two types of drug–drug interaction are associated with increased risk. Pharmacokinetic interactions result from concomitant use of a drug whose binding affinity for an isoenzyme of the cytochrome P450 (CYP) system is stronger than that of a statin whose metabolism depends on the same isoenzyme. With the metabolism of the statin blocked because it cannot bind to its enzyme, the amount of active statin present in the body is greater than would otherwise be expected at the given dosage, resulting in an increased risk of toxicity. Pharmacodynamic interactions result from concomitant use of other drugs that also have the capacity to induce myotoxicity (such as fibrates and niacin, which are often used in combination with statins to correct adverse lipid profiles). The result is an additive adverse effect.

Other risk factors that may contribute to a higher risk of myotoxicity include the type of statin used (specifically, its degree of lipid solubility) and the doses given. Female sex and older age may be associated with statin levels that are higher than expected for the given dose. Hypothyroidism (which by itself may cause myalgia and mild elevation in CK) and renal insufficiency may also predispose patients to statin myopathy.

Statin-induced Hepatotoxicity

Several factors may place patients at increased risk for hepatotoxicity, starting with high doses of statins (**Table 2**).[5] Asymptomatic baseline elevations in transaminase values pose an increased risk, and statins should not be used at all in patients with preexisting hepatitis. More typically, baseline liver function tests are normal when patients start taking a statin, but show minor elevations (to <3 times ULN) on retesting after the start of treatment. According to some postmarketing surveillance studies, approximately 70% of these statin-induced elevations will spontaneously fall back into the normal range even as treatment continues.[5] In cases in which the transaminase elevation persists, the physician must decide whether to reduce the dose of the statin, switch to a different statin, or discontinue statin therapy entirely.

As with myotoxicity, the risk of hepatotoxicity is also increased by pharmacodynamic interactions with other potentially hepatotoxic compounds, including fibrates, niacin, acetaminophen, and alcohol. Pharmacodynamic interactions between drugs that act as CYP450 inhibitors and statins that depend on CYP450

Table 2. Risk Factors for Statin-induced Hepatotoxicity*

Factor	Comment
High or increasing doses of statins	Highest statin doses are associated with the highest rate of discontinuations because of hepatotoxicity (transaminase levels elevated to ≥3 times ULN).
Preexisting hepatitis	Statins are contraindicated in patients with active liver disease.
Preexisting elevations in transaminase levels	Statins are contraindicated in patients with persistent elevation in transaminase levels. (Minor elevations to <3 times ULN induced by statin therapy resolve spontaneously in approximately 70% of patients, but persistent therapy-induced elevations may require reduction or cessation of statin use.)
Concurrent use of hepatotoxic substances	Examples include acetaminophen, alcohol, fibrates, niacin.
Concurrent use of cytochrome P450 inhibitors	Examples include macrolide antibiotics, azole antifungals, cyclosporine, and calcium channel blockers.

ULN indicates upper limit of normal.
*Adapted from Tolman KG.[5]

isoenzymes for metabolism also increase risk. Although pharmacokinetic interactions are more commonly associated with myotoxicity, published case reports of myotoxicity caused by this mechanism frequently mention marked elevations in transaminase values.

## Statin Lipophilicity and the Risk of CYP450 Interactions

The metabolic properties of the statins differ and this affects the risk of drug–drug interactions. Atorvastatin, pravastatin, fluvastatin (Lescol), and rosuvastatin (Crestor) are given in the active acid form. Active acid refers to the pharmacophore, the component of the chemical structure responsible for the activity that defines the statins as a class—binding to the HMG-CoA reductase enzyme to produce lowering of LDL cholesterol. In contrast, lovastatin (Mevacor, Altocor) and simvastatin are administered in inactive form as lactones, some portion of which is then hydrolyzed into the active acid form to produce their clinical effects. In terms of elimination from the body, the lactone forms are highly lipid soluble and require CYP450-mediated conversion to a water-soluble form, whereas the active acid forms undergo glucuronidation in the liver. Additional groups on the molecular structure of the drugs define other specific characteristics that distinguish the various statins from each other. These characteristics include lipophilicity, binding affinity to HMG-CoA reductase, and relative selectivity for the liver as the site of clinical action versus muscle tissue as the site of adverse effects (**Figure 1**).

Lipophilicity is especially important in terms of the likelihood of pharmacokinetic interactions that can lead to statin toxicity. Statins that are highly lipophilic must be metabolized to a water-soluble form for renal excretion. Because that process depends on CYP450 isoenzymes, a lipophilic statin is subject to metabolic inhibition by concomitantly-administered drugs with stronger affinity for the same isoenzyme. In contrast, a water-soluble statin depends less or not at all on the CYP450 system and is therefore less subject to pharmacokinetic interactions.

The CYP450 isoenzyme involved in the

Figure 1. Several statins are administered in active acid form that can bind to HMG-CoA reductase. Simvastatin and lovastatin are administered in lactone form and must first undergo conversion to active acid form to produce their clinical effects.
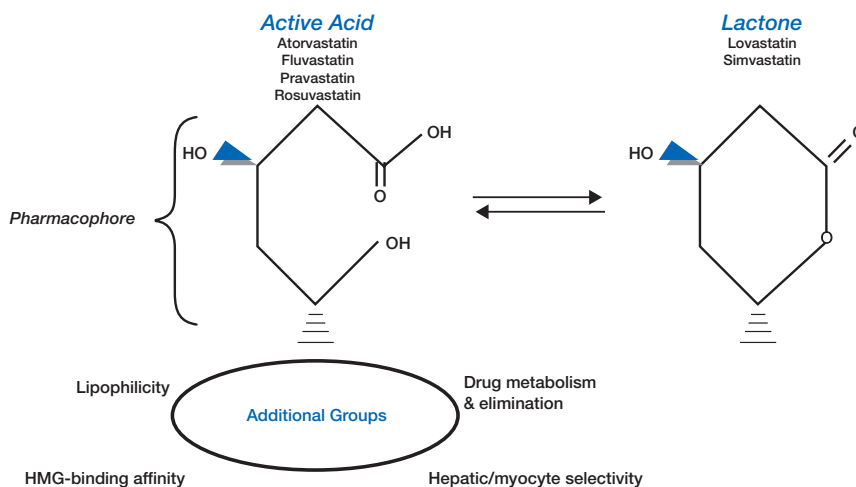

HMG-CoA indicates 3-hydroxy-3-methylglutaryl coenzyme A.

metabolism of the greatest number of different drugs is labeled CYP3A4. CYP3A4 accounts for the majority of CYP450 isoenzymes in the liver and also in the gut wall. Most pharmacokinetic interactions occur when 2 or more drugs that are metabolized by the same CYP450 isoenzyme (whether it is CYP3A4 or a different isoenzyme) are given concurrently. The drug with the stronger binding affinity for the isoenzyme will effectively block the metabolism of the drug with weaker binding affinity, resulting in increased

Figure 2. Increase in simvastatin exposure when used in conjunction with verapamil, itraconazole, and erythromycin versus placebo.
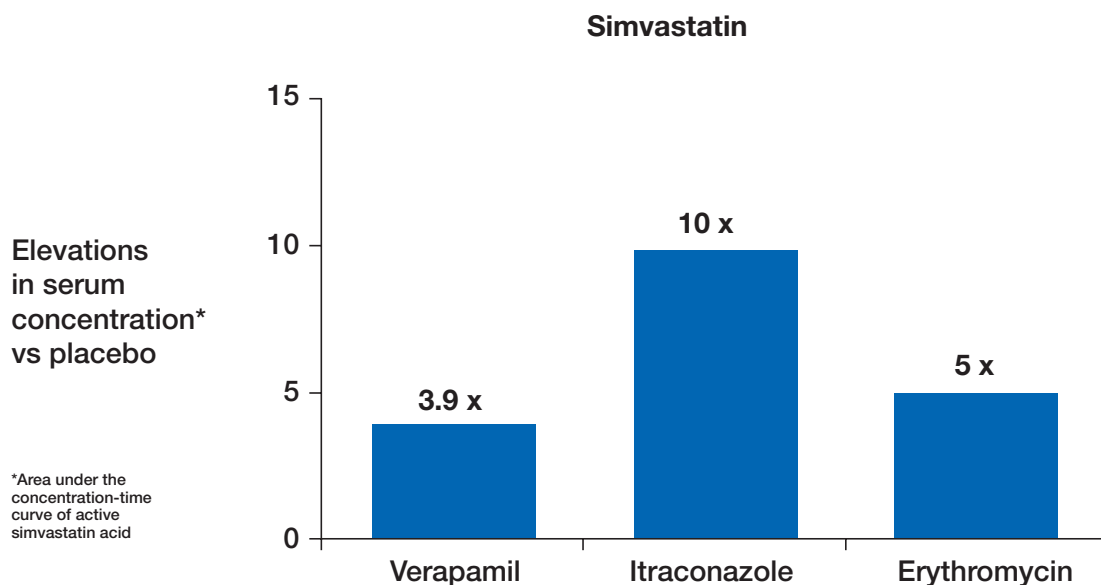
Sources: Kantola T, et al. *Clin Pharmacol Ther.* 1998;64:177-182; Neuvonen PJ, et al. *Clin Pharmacol Ther.* 1998;63:322-341.

Figure 3. Increase in lovastatin exposure when used in conjunction with diltiazem, erythromycin, itraconazole, or cyclosporine versus placebo.

Lovastatin

Elevations in serum concentration* vs placebo

*Area under the concentration-time curve
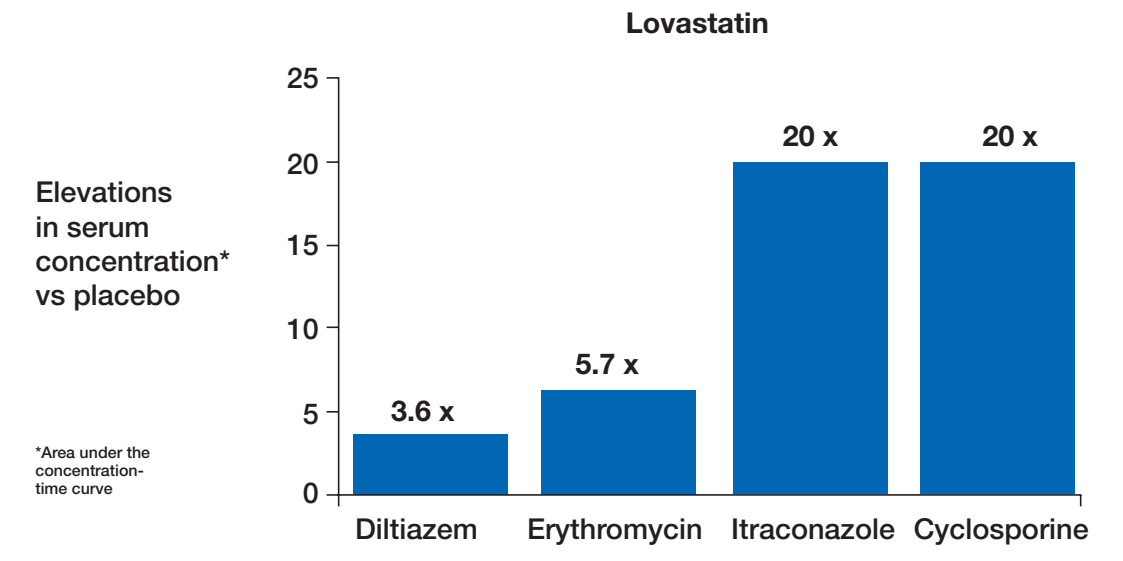
Sources: Olbricht C, et al. *Clin Pharmacol Ther.* 1997;62:311-321; Neuvonen PJ, et al. *Clin Pharmacol Ther.* 1996;60:54-61; Azie NE, et al. *Clin Pharmacol Ther.* 1998;64:369-377; Bottorff MB, et al. *Pharmacotherapy.* 1997;17:184-185.

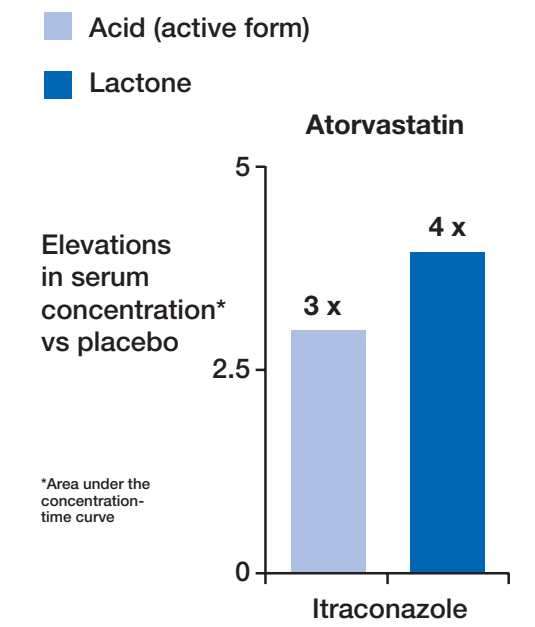concentrations of active (nonmetabolized) drug and an increased risk of toxicity.[6]

The lipid-soluble statins that depend on CYP3A4-mediated metabolism tend to bind rel-atively weakly to the isoenzyme. Therefore, many drugs with stronger binding affinity for CYP3A4 will act as metabolic inhibitors when used concurrently with those statins. In contrast, statins that do not depend on CYP3A4 have a low propensity for causing toxicity as a result of pharmacokinetic interactions.[7]

Atorvastatin, simvastatin, and lovastatin are metabolized by CYP3A4 and are subject to interactions with a long list of substances, including macrolide antibiotics (but not azithromycin), azole antifungals, amiodarone, verapamil and diltiazem (but not the dihydropyridine calcium channel blockers), cyclosporine, protease inhibitors, and grapefruit juice. For example, when simvastatin is used alone, the incidence of myopathy is less than 0.1%; but when used in combination with amiodarone, the incidence rises sharply to 6%.[8]
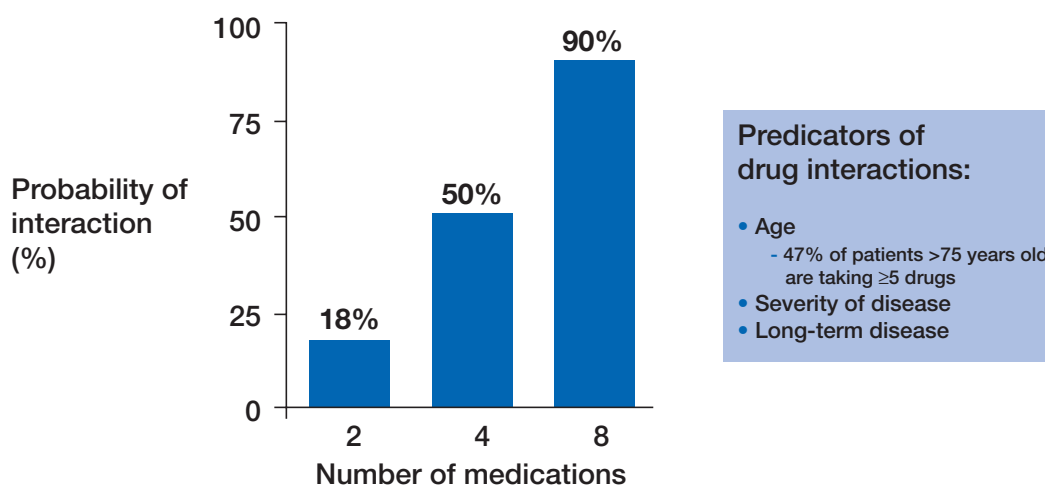
Fluvastatin is metabolized by CYP2C9 and is subject to potential interactions with agents such as amiodarone, gemfibrozil, fluconazole, metronidazole, and fluoxetine. However, in contrast to the relatively weak binding of simvastatin, atorvastatin, and lovastatin for CYP3A4, fluvastatin binds strongly to CYP2C9 and may inhibit the metabolism of the other agents that depend on this isoenzyme, such as warfarin.

Figure 4. Increase in atorvastatin exposure when used in conjunction with itraconazole versus placebo.

Acid (active form)

Lactone

Atorvastatin

Elevations in serum concentration* vs placebo

*Area under the concentration-time curve

Source: Kantola T, et al. Clin Pharmacol Ther. 1998;64:58-65.

Figure 5. The likelihood of drug–drug interactions rises sharply with the number of medications in use. Other factors affecting the likelihood of clinically relevant interactions include age and the severity and chronicity of disease.

Predicators of
drug interactions:

- Age
  - 47% of patients >75 years old
    are taking ≥5 drugs
- Severity of disease
- Long-term disease

Sources: Williams, et al. *Ir J Med Sci.* 1999; Weideman, et al. *Hosp Pharm.* 1998;33:835-840.

Because rosuvastatin is relatively water-soluble, increased drug levels may result from severely diminished renal function. Approximately 10% of its elimination results from metabolism by CYP2C9 and CYP2C19. Interactions can occur with gemfibrozil (an inhibitor of both isoenzymes, resulting in an approximate doubling of rosuvastatin exposure),[9] and theoretically with fluconazole, fluoxetine, fluvoxamine, and omeprazole as well. In addition, rosuvastatin drug levels are roughly twice as high in Japanese and Chinese people living in Asia than in Caucasian people living in Europe or North America.[9] These differences may be caused by environmental factors or may, in part, reflect the fact that a genetic inability to produce CYP2C19 is found in 10% to 20% of the Japanese population compared with 3% to 5% of the Caucasian population[10]; further study of these differences is needed.

Pravastatin is water soluble and does not depend on CYP450-mediated metabolism; it does, however, undergo acid hydrolysis and hepatic conjugation, and elimination occurs through renal and biliary excretion. In patients with diminished renal function, nonrenal mechanisms tend to increase in compensation, preventing accumulation and increased drug concentrations.

To quantify the effects of pharmacokinetic interactions between CYP3A4-dependent statins and CYP3A4 inhibitors, simvastatin exposure, measured as area under the concentration-time curve, was increased 4- to 10-fold when the statin was used in conjunction with known CYP3A4 inhibitors versus placebo (**Figure 2**).[11,12] Similarly, lovastatin exposure was increased 3.6- to 20-fold when used in conjunction with CYP3A4 inhibitors versus placebo (**Figure 3**).[13-16] Exposure to atorvastatin in active acid and lactone forms was increased 3- and 4-fold when used in conjunction with itraconazole versus placebo (**Figure 4**).[17] Because atorvastatin is less dependent than simvastatin or lovastatin on metabolism via CYP3A4, it may be less sensitive to pharmacokinetic interactions with CYP3A4 inhibitors.

Other Types of Statin Interactions

As previously stated, the active acid forms of the statins undergo hepatic glucuronidation, and the fibrates block glucuronide. It is now known that gemfibrozil is a more potent glucuronide blocker than fenofibrate.[18] When gemfibrozil is given concurrently with simvastatin or lovastatin, the statin levels increase

roughly 3-fold. Fenofibrate, in contrast, has no effect on statin concentrations.

The interactions between statins and warfarin are complex. Warfarin goes through several different CYP450 pathways, any of which might serve as a source of interactions with statins. However, whereas most of the interactions previously described result in inhibited statin metabolism, interactions with warfarin tend to work in the opposite direction and inhibit warfarin metabolism. The clinical result is an increase in the international normalized ratio (INR), a standardized measure of prothrombin time. The CYP3A4-dependent statins (simvastatin, lovastatin, and atorvastatin) all have the potential to raise the INR in patients taking warfarin; the effect is variable, and monitoring INR is important to determine whether the warfarin dosage must be adjusted.

Fluvastatin, metabolized through the CYP2C9 pathway, can also interfere with warfarin metabolism and raise the INR.[19] Rosuvastatin can raise the INR without raising warfarin concentrations, which implies that its effect is not mediated through the CYP450 system but is more likely caused by a partial displacement of warfarin from its protein-bound state in circulation.[20] Pravastatin is unique among the statins in that it produces no change in the INR in patients taking warfarin, which demonstrates its lack of involvement in the CYP450 pathways and an absence of effects on warfarin protein binding.

Selecting Statin Therapy

Patients most often start receiving statin therapy for the purpose of lowering concentrations of LDL cholesterol; other goals in improving the lipid profile include elevating high-density lipoprotein (HDL) cholesterol and lowering triglycerides. Subsequent clinical decisions are made if any of these goals are not met by the initially chosen regimen.[21] For example, if LDL cholesterol remains elevated, options include increasing the dose of the statin or adding niacin to the statin, although these strategies would incur an increased risk

of toxicity. Other agents that may be added to the statin regimen are fenofibrate (although it is relatively weak in terms of reducing LDL cholesterol), ezetimibe (a cholesterol absorption inhibitor), and bile acid sequestrants. If the HDL cholesterol remains low or triglycerides remain high, fibrates or niacin may be added, but again at the cost of an increased risk of toxicity. Another option for reducing triglyceride levels is the addition of fish oils (omega-3 fatty acids) to the regimen.

An additional safety concern when drugs are added to a statin regimen is that the likelihood of interactions rises sharply with polypharmacy. When more than 2 drugs are taken, the theoretical number of possible interactions is computed as N! divided by 2(N−2)! (the exclamation point indicates the factorial of the number: for example, 4!=4x3x2). Realistically, the likelihood of an interaction when 8 drugs are taken is roughly 90% (**Figure 5**) (Williams, et al. *Ir J Med Sci*. 1999; Weideman, et al. *Hosp Pharm*. 1998;33:835-840). Interactions are not always serious or clinically apparent, but it is obvious that as more drugs compete for common CYP450 pathways, the risk of a clinically-relevant interaction increases. For patients taking multiple medications, it is especially important to select agents that are least likely to incur an additional risk of interaction; for patients who require the addition of lipid-lowering pharmacotherapy to a drug regimen that is already complex, the preferred agents would be the statins that are least dependent on the CYP450 system in general and on CYP3A4 in particular.

Conclusion

The American Heart Association's (AHA) position statement[22] on avoiding medication errors in cardiac patients includes 2 principles that are pertinent to the foregoing discussion.

First, it states "know thoroughly the drugs you prescribe." As discussed, statins differ considerably among themselves in terms of their dependence on CYP450-mediated metabolism and their propensity to become involved in

drug–drug interactions. In prescribing these agents, it is important to understand subtle differences between them, which may have clinical consequences.

Second, the AHA advises that physicians should try to "anticipate and prevent drug interactions" before they occur, as opposed to responding to them after they occur. This point is especially important in patients who require lipid-lowering therapy, at least some of whom are also taking other cardiac drugs and/or antidiabetic medications. To this end, it is important to remain aware of potential interactions and to maintain close collaborative partnerships with other members of the interdisciplinary healthcare team. ■

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