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Original Contribution

A clinician's guide to statin drug-drug interactions

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Abstract: The statins are widely used worldwide to reduce risk for cardiovascular events in both the primary and secondary prevention settings. Although generally quite safe, the statins can be associated with a variety of serious side adverse effects, including myalgia, myopathy, and changes in plasma enzymes of hepatic origin. Although rare, the most serious of these is rhabdomyolysis. Several drugs can interfere with the metabolism and disposal of the statins, thereby increasing risk for adverse events. It is important that clinicians treating patients with statins be aware of the potential for drug-drug interactions between each statin and specific other drugs and take measures to prevent them. The prediction of potential drug-drug interactions derives from basic pharmacokinetic principles. Certain drug interactions are predicted by measuring the effect of interacting drugs on blood plasma concentrations of the statin. Individual patient variations resulting in part from polymorphisms in the metabolizing enzymes confound some of these predictions. Based on these known effects, a new classification for predicting statin drug interactions is proposed. This report discusses likely prescription and nonprescription interactions as well as potential alternatives for special populations.
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The metabolism of statins is described by basic pharmacokinetic principles. Pharmacokinetic measures involve the rate of absorption, distribution, metabolism, and excretion for these molecules. With the exception of lovastatin and simvastatin, which are given as prodrugs, all statins are administered in the active hydroxyl acid form (Fig. 1). Once ingested, various other factors affect their absorption, distribution, metabolism, and excretion. Statins are moderately to well absorbed, with the time to reach peak plasma concentration averaging about 4 hours. When consumed with food, lovastatin is more efficiently absorbed. Rosuvastatin, pitavastatin, and simvastatin are not affected by food, whereas fluvastatin, pravastatin, and atorvastatin have a reduced absorption with food. Once absorbed into the portal venous system, while all statins undergo extensive first-pass metabolism, the rate of this first-pass hepatic uptake inversely relates to the systemic bioavailability. Therefore, the lower systemic

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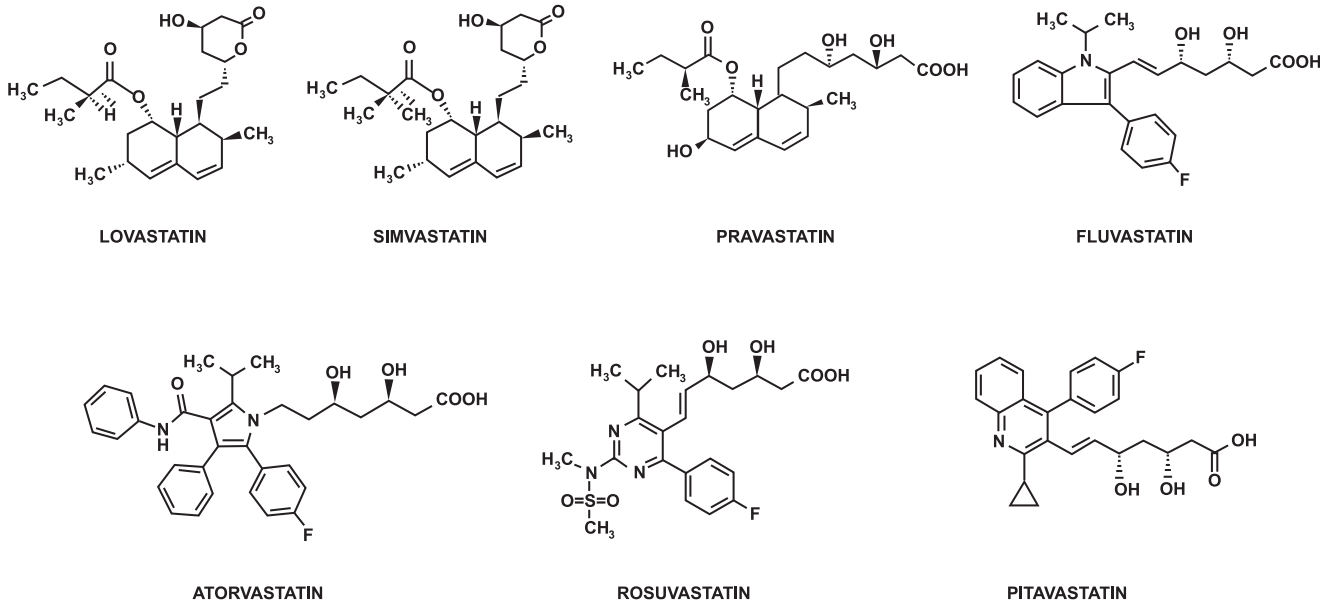

Figure 1 Chemical structures of statins. Type I naphthalene statins (lovastatin, pravastatin, simvastatin); type II non-naphthalene (atorvastatin, pitavastatin, rosuvastatin, fluvastatin). Lovastatin and simvastatin are prodrugs.

bioavailability of fluvastatin (19%–29%) may suggest a more efficient first-pass metabolism. Pravastatin is the only statin not protein bound, which imparts a low systemic exposure to the medication.[1]

Statins undergo a complex metabolic fate, beginning with absorption, followed by hepatic uptake, metabolism, and eventually elimination from the liver into either the systemic circulation or the biliary tract (Fig. 2).[2] During the absorption process, most statins are substrates for the P-glycoprotein (P-gp) efflux transporter, which reduces absorption into the portal circulation. Enterocyte cytochrome P450 (CYP) may metabolize some statins before eventual absorption into the portal circulation. Hepatic uptake is mediated by several transporters, including organic anion transporting polypeptide 1B1 (OATP1B1), which facilitates metabolism by additional CYP enzymes (phase I metabolism) and glucuronidation (phase II metabolism). Additional efflux transporters on the canalicular membranes of hepatocytes facilitate biliary excretion.

Some interacting drugs, such as cyclosporine, inhibit multiple sites of statin disposition (Table 1),[3] resulting in larger increases in serum concentrations and subsequent risk for myopathy. Cyclosporine is an inhibitor of OATP1B1, OATP1B3, P-gp, and adenosine triphosphate

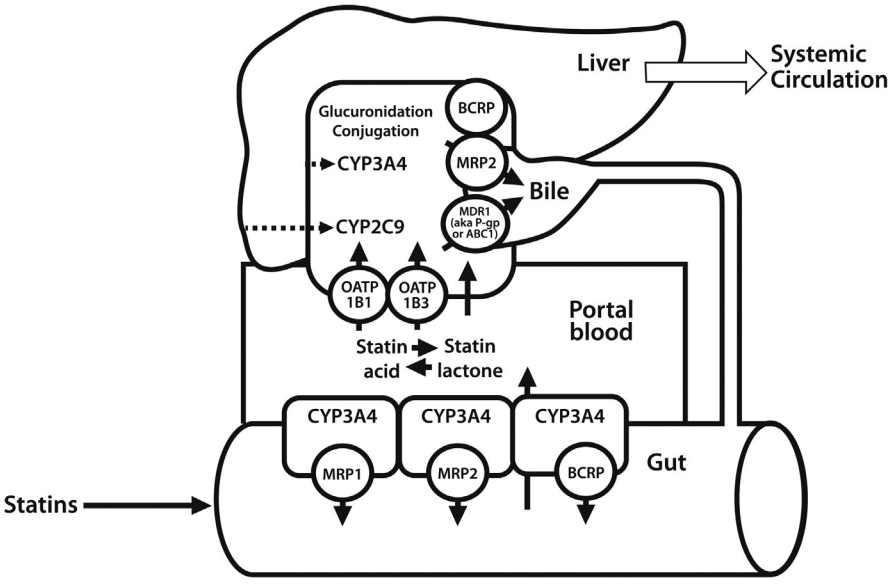

Figure 2 Metabolic fate of statins. BCRP, breast cancer–resistant protein, encoded by gene ABCG2; MDR1, multidrug-resistant protein 1; MRP2, multidrug-resistant–associated protein 2, encoded by gene ABCC2; OATP1B1, organic anion transporter protein 1B1, formerly known as OATP2, encoded by SLCO1B1 gene; OATP1B3, organic anion transporter protein 1B3, encoded by the SLCO1B3 gene; P-glycoprotein, P-gp, encoded by the ABCB1 gene. Adapted from Niemi et al.[2]

Table 1 Transporters and enzymes involved in statin metabolism

Statin	Transporters and enzymes affecting metabolism
Simvastatin	CYP3A4 (intestinal and hepatic)
Lovastatin	OAT1B1
	P-gp
	MDR1
	BCRP
Atorvastatin	BCRP (intestinal)
	CYP3A4 (intestinal and hepatic)
	OAT1B1 and OAT2B1
	P-gp
Rosuvastatin	BCRP (intestinal)
	CYP2C9 (minor)
	OAT1B1 and OAT1B3
	NTCP
	OAT2B1
Pravastatin	BCRP (intestinal)
	OAT1B1 and OAT1B3
	OAT2B1
Fluvastatin	BCRP (intestinal)
	OATP1B1
	OAT1B3
	OAT2B1
	CYP2C9
	CYP3A4
Pitavastatin	BCRP (intestinal)
	MDR1
	OAT1B1 andOAT1B3
	OATP2B1
	CYP2C9 (minor)

BCRP, breast cancer–resistant protein; CYP, cytochrome P450; MDR1, multidrug-resistant protein; OAT, organic anion transporters; OATP, organic anion transporting polypeptides; P-gp, p-glycoprotein.
Adapted from Harper et al.[3]

cassette transporter subfamily G, member 2 (ABCG2 or breast cancer–resistant protein [BCRP]). Transporters are membrane proteins that move drugs (and other chemicals) in and out of cells (Table 2).[4] As such, transporters are an important determinant of statin disposition and a source of drug interactions when transporter inhibitors are coadministered with a statin. All statins are substrates for OATP1B1, which provides statin access into the hepatocyte both for pharmacologic activity and subsequent metabolism and elimination. In addition, genetic polymorphisms in the solute carrier organic anion transporter family member 1B1 gene (*SLCO1B1*) have been associated with a higher statin exposure and increased risk for myopathy.[2,5–8]

Individual variation in enzyme induction, inhibition, and patient response

Although traditional models attribute statin metabolism to the cytochrome hepatic systems, more contemporary theories involve classification of potential pathways as follows:

a lipophilic lactone prodrugs such as simvastatin are predominantly CYP metabolized;
b polar statins such as rosuvastatin and pravastatin are substrates of transporters including the hepatic OATPs, sodium/taurocholate cotransporting peptides (NTCP), and the renal OATPs; and
c statins such as fluvastatin that are metabolized by CYP and access the hepatocyte by active transport.

In addition, all statins have affinity to the multi-drug-resistance protein (MRP2), P-gp, the bile salt export pump, and the BCRP. The latter transporters may have a minor role in statin drug interactions. Finally, there appears to be a delicate balance between these transporter proteins and CYP metabolism.[2,5–7]

P-gp is a member of the ATP binding cassette-subfamily B. P-gp is the 170-kD protein product of the multidrug resistance gene ABCB1 (*MDR1*). Many compounds can alter the function and/or expression of P-gp, providing mechanisms for several clinically important drug-drug interactions (DDIs), which were unexplained or attributed solely to inhibition of CYP. Verapamil, cyclosporine, erythromycin, ketoconazole, and tamoxifen are examples of agents that have demonstrated either in vitro or in vivo inhibition of P-gp function. An interesting feature of P-gp is the interaction with drug-metabolizing enzymes, specifically the 3A4 isozyme of CYP (CYP3A4). P-gp and CYP3A4 share many substrates and inhibitors and have a common tissue distribution. After entering the enterocyte, a compound with affinity for P-gp or as a substrate for CYP3A4 may be absorbed directly into the systemic circulation, metabolized by CYP3A4 in the enterocyte, or secreted back into the intestinal lumen by P-gp. Drugs pumped back into the lumen may be reabsorbed at a distal site and exposed again to any of the 3 fates previously described. This may create a cycling effect (enteroenteric recycling) and increase the mean residence time in the intestinal lumen and interaction, in the case of statins, with 3-hyroxy-3-methyglutaryl coenzyme A reductase. Fluvastatin and pravastatin consistently demonstrate no significant inhibition of P-gp transport. Rosuvastatin acid or its lactone do not appear to be substrates for P-gp, leaving the effect of P-gp largely with lovastatin, simvastatin, and atorvastatin.[9]

What appears to be the conundrum in understanding variations in statin tolerance are single-nucleotide polymorphisms in individuals and specific patient populations. The *OATP1B1 (SLBO1B1)* and *BCRP (ABC2)* genes have been studied most extensively.[8,10] In diploid carriers of the OAT1B1 521T > single-nucleotide polymorphism (174Val > Ala variant rs4149056), therapeutic doses of 5 statins showed altered pharmacokinetics (Tables 3A, B).[8] Fluvastatin has no apparent association with variations in implied OATP1B1 function from studies in different genetic groups. The results in Table 3, however, only partially translate into day-to-day clinical scenarios with regard to

Table 2 Membrane transporters

Transporter/alias (gene)	Organ or cells	Comment
P-gp/MDR1 (ABCB1)	Intestinal enterocyte Hepatocyte (canalicular) Kidney proximal tubule	Drug absorption, distribution, and excretion Source of drug interaction
BCRP (ABCB2)	Intestinal enterocyte Hepatocyte (canalicular) Kidney proximal tubule	Drug absorption, distribution, and excretion Genetic polymorphisms Source of drug interaction
OATP1B1/OATP2 (SLCO1B1)	Hepatocyte (sinusoidal)	Drug distribution, excretion Genetic polymorphisms Source of drug interaction
OATP1A2/OATP-A (SLCO1A2)	Cholangiocyte Distal nephron	Drug distribution, excretion
OATP2B1/OATP-B (SLCO2B1)	Hepatocytes (sinusoidal)	Drug distribution, excretion Source of drug interaction

ABCRP, breast cancer–resistant protein; CYP, cytochrome P450; MDR1, multidrug-resistant protein; OAT, organic anion transporters; OATP, organic anion transporting polypeptides; P-gp, p-glycoprotein; SLCO2B1, gene for solute carrier organic anion transporter family member 2B1.

Adapted from Giacomini et al.[4]

muscle side effects. It may apply most often to simvastatin and atorvastatin.

Differences in the ABC2 gene may explain some ethnic differences. It has been suggested that 1% to 4% of African Americans, 5% to 10% Caucasians, and 35% to 45% of Asians carry variations in the *ABCG2 (BCRP)* gene. These changes suggest differences in the absorption of rosuvastatin, simvastatin-lactone, fluvastatin, and atorvastatin, but not simvastatin acid (active moiety) or pravastatin (Table 4).[8–16]

Focus on drugs that have the highest potential to interact with statins

Although multiple pathways have been shown to play a role in statin DDIs, the CYP3A4 and CYP2C9 pathways have been most commonly described. Focusing on simvastatin, the potential for DDIs involves complete inhibition of intestinal CYP3A4-mediated metabolism in addition to OATP1B1-mediated uptake of the statin acid. Based on this mechanism, cyclosporine, telithromycin, and posaconazole are also likely to produce similar multiple-fold increases in areas under the curve (AUCs). Although a critical interaction, the combination of gemfibrozil and simvastatin perhaps is less daunting because gemfibrozil only inhibits OATP1B1 in turn because neither gemfibrozil, nor its glucuronide, are CYP3A4 inhibitors.

Atorvastatin may be more complex because of the passive absorption of atorvastatin acid. Cyclosporine enterocyte concentrations and BCRP intestinal inhibition would result in full inhibition of CYP3A4, causing the interaction. Yet for the other atorvastatin interactions, there is less involvement of BCRP and a greater involvement of

Table 3A Comparison of peripheral blood plasma concentrations of different statins in individuals with homozygous (OATP1B1) 521CC (dysfunctional) compared with those with fully functional homozygous (OATP1B1) 521 TT (fold AUC changes are based on group mean AUC 0–∞)*

Statin	AUC change
Simvastatin acid	3.21-fold ↑ (+221%)
Pitavastatin	3.08-fold ↑ (+208%)
Atorvastatin	2.45-fold ↑ (+145%)
Pravastatin	1.91-fold ↑ (+91%)
Rosuvastatin	1.62-fold ↑ (+61%)
Fluvastatin	1.19-fold ↑ (+19%, ns)

AUC, area under the curve; ns, not significant; OATP, organic anion transporting polypeptide.

*Heterozygous individuals with the c.521 TC genotype generally show smaller AUC value increases than individuals with the c.521CC genotype.

Adapted with permission from Elsby et al.[8]

Table 3B Comparison of postdosing plasma concentrations of different statins in homozygous BCRP 421AA individuals compared with homozygous BCRP 421CC individuals (fold AUC changes are based on group mean AUC 0–∞)*

Drug	AUC change
Rosuvastatin	2.44-fold ↑ (+144%)
Simvastatin acid	1.22-fold ↑ (+22%)
Simvastatin lactone	2.11-fold ↑ (+111%)
Atorvastatin lactone	1.94-fold ↑ (+94%)
Atorvastatin acid	1.72-fold ↑ (+72%)
Fluvastatin	1.72-fold ↑ (+72%)
Pravastatin	1.13-fold ↓ (ns)
Pitavastatin	1.05-fold ↑ (+5%, ns)

AUC, area under the curve; BCRP, breast cancer–resistant protein; ns, not significant.

Adapted with permission from Elsby et al.[8]

Table 4 Predicted vs observed fold increases in various statins and enzyme systems*

Statin	Perpetrator drug	Predicted fold increase in AUC from inhibition of composite pathways			CYP3A4 hepatic	Clinically predicted fold increase in AUC
		BCRP (intestine)	CYP3A4 (intestine)	OAT1B1		
Simvastatin	Cyclosporine		1.67	4.5 (56)	1.0 (0.09)	7.5
	Telithromycin		1.67	1.2 (0.2)	2.0 (1.6)	4.0
	Posaconazole		1.67	NI	1.7 (0.9)	4.0
Atorvastatin	Cyclosporine	1.72 (174)	1.45	3.2 (103)	NA	8.0
	Lopinavir/ritonavir	NA, low solubility	1.45	1.9 (2.3) 1.1 (0.14)	1.0 (0.16)	2.9
	Clarithromycin	NI	1.45	2.0 (2.7)	1.1 (0.4)	3.2
	Itraconazole	NI	1.45	NI	1.0 (0.4)	1.45
		BCRP (intestine)		**OAT1B3**	**CYP2C9**	
Fluvastatin	Cyclosporine	1.72 (100)		1.8 (19)	NI	3.2
	Fluconazole	NI		NI	1.7 (9.9)	1.7
Statin	Precipitating drug	BCRP (intestine)	Active uptake (OATP1B1:NTCP:OATP1B3) (f_e = 0.38:0.21:0.11 = 0.7)	OAT3	Overall predicted fold increase in AUC	Clinically observed fold increase in AUC
Rosuvastatin	Cyclosporine	2.0 (100)	3.2 (56)	NI	6.4	7.1
	Gemfibrozil	NI	1.5 (OATP1B) (2.0)	1.2 (2.1)	1.8	1.9
	Lopinavir/ritonavir	No effect-low solubility	1.5 (OATP1B) (1.9 if all inhibited) (2.3)	NA	1.5 (1.9)	2.1
	Atazanavir/ritonavir	2.0 (25)	1.6 (OATP1B) (3.5)	NA	3.2	3.1
		Efflux (intestine)	**OATP1B1**	**OAT3**		
Pravastatin	Cyclosporine	2.9	2.0 (103)	NI	5.8	3.82
	Clarithromycin	NI	1.6 (2.7)	NI	1.6	2.1
	Gemfibrozil	NI	1.3 (0.9)	1.4 (2.6)	2.1	2.0
			OAT			
Pitavastatin	Cyclosporine		4.2 (39)		4.2	4.55
	Erythromycin		1.5 (0.7)		1.5	2.8
	Gemfibrozil		1.5 (0.8)		1.5	1.45

AUC, area under the curve; BCRP, breast cancer–resistant protein; CYP3A4, cytochrome P450 isozyme 3A4; DDI, drug-drug interaction; IC50, half maximal inhibitory concentration; Ki, reversible inhibition constant; NA, not applicable; NI, not an inhibitor; OAT, organic anion transporter; OATP, organic anion transporting polypeptide.

*(number), ratio of $_{\text{inlet max, unbound}}/IC_{50}$ or Ki (>0.1 indicates potential for interaction); [number], ratio of $[I_2]/IC_{50}$ or Ki (>10 indicates potential for interaction).

Adapted with permission from Elsby et al.[8]

combined OATP1/CYP3A4 interaction. Fluvastatin interactions are predominately related to complete inhibition of CYP2C9. The AUC changes for fluvastatin involve OAT1B3 and BCRP. There is a strong likelihood that pharmacogenetic differences in intestinal BCRP are the cause of the fluvastatin/cyclosporine interaction. Pitavastatin is largely eliminated through OATP1B1. Although this is a common pathway for erythromycin and gemfibrozil, the AUC changes in these drug combinations with pitavastatin are less than predicted. The cause may be only partial inhibition of OATP1B1.

Multiple mechanisms including complete inhibition of various OATPs (1B1 and OAT3 enzyme systems, inhibition of intestinal efflux, and intestinal BCRP and possibly other proteins) may be responsible for increased blood levels of statins (Table 4).[8] These cannot always be accurately predicted by pharmacokinetic modeling. Pravastatin and gemfibrozil theoretically would produce a DDI by completely inhibiting OAT1B1; however, gemfibrozil is also able to inhibit the renal transporter OAT3. This suggests the possibility that the drug interaction involves mediation of both the hepatic and renal pathways. Similarly, the interaction of cyclosporine and pravastatin cannot be attributed solely to OAT1B1 inhibition. Therefore, other potential mechanisms of intestinal efflux may be responsible.

The cyclosporine induced changes in rosuvastatin AUC are likely related to inhibition of all active uptake (OATP1B1, NTCP, and OATP1B3) in addition to intestinal BCRP. The gemfibrozil/rosuvastatin DDI could be related to inhibition of both OATP1B1/3 and OAT3. There may be issues with this theory in day-to-day clinical practice, where many patients may not present with the DDI.

Following the previous discussion, it is important to know how the statins and their potential interactants affect intestinal, hepatic, and possibly renal efflux pumps. There are likely pharmacogenetic differences among various cohorts involving differing hepatic uptake (via OATP1B1/3 and NTCP), first-pass metabolism via CYP3A4, absorption via BCRP, and renal elimination by OAT3. Understanding more definitively how these drugs affect or are affected by these enzyme and transport systems can be useful in DDI prediction. Although not fully recognized until studying cerivastatin interactions, glucuronidation is now identified as a common metabolic pathway for the conversion of active open acid forms of several statins (including atorvastatin and rosuvastatin) to their lactone form. Catabolism of lactone forms of statins is common to CYP3A4 enzyme activity.

Suggested nomenclature for classifying statin drug interaction

There appears to be a concentration-dependent relationship between the risk of myopathy/myonecrosis (clinical rhabdomyolysis) and the serum concentration of a statin. As such, we propose adopting the system shown in Figure 3 for the clinician to apply drug interaction studies with the relative risk to an exposed patient.[17] An interaction resulting in less than a 2-fold increase in statin AUC, a marker for systemic exposure, would be classified as "mild" risk. Interactions producing more than a 2- but less than 5-fold increase in systemic exposure would be classified as "moderate." A strong interaction would result in a 5-fold or higher increase in statin exposure. This system should only be used as a guide, because an individual patient's response may be dictated by other clinical features, such as inherent susceptibility to statin-related myopathy, unidentified genetic predisposition, and history or presence of other predictors of statin muscle side effects (eg, hypothyroidism, vitamin D deficiency, electrolyte disturbances, low baseline muscle mass).[11]

Understanding package labeling

The US Food and Drug Administration (FDA) label repository maintains copies of all statin labeling.[18] The repository first used the portable document format and then transitioned to the new technology called the "structured product label" for use in the National Library of Medicine. Changes up until 2008 were minor, adding only new indications, drug interactions, or adverse reactions. With the possible exception of the 2001 cerivastatin (Baycol) recall, warning information was sparse. Starting with its review of ezetimibe/simvastatin (Vytorin) in the Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression study, the FDA began issuing study review communications and commenced major labeling changes for the various statins. In 2011, dosing limits on simvastatin were established and the labeling for both lovastatin and simvastatin was revised. Subsequent labeling changes included obviating the need for routine liver transaminase monitoring, suggested dosing limits on concomitant statin prescription with either niacin, amiodarone, or calcium channel blockers, and warnings regarding statin-induced cognitive impairment and diabetes mellitus. The FDA is assuming a greater role in postmarketing surveillance and keeping package labeling current with contemporary literature.[19–21]

Using the concepts presented here, the 2012 simvastatin (Zocor) package insert can be examined as an example.[22] The values of the geometric mean ratio, AUC, and maximum concentration are determined separately. Each dose is compared with the reference dose on a pairwise basis. The geometric mean ratios for each dose level are

AUC ratio increase	>1.25 - <2.0	>2.0 - <4.9	>5.0
Rank of inhibition of various CYP enzymes	Weak	Moderate	Strong

Figure 3 A proposed ranking of significance with respect to area under the curve (AUC) changes and drug-drug interaction possibilities. AUC, area under the curve; CYP, cytochrome P450. Adapted from Rodrigues et al.[17]

Table 5 Simvastatin drug interactions[22]

Coadministered drug and dosing regimen	Simvastatin (mg)	Simvastatin form	Geometric mean ratio (ratio* with/without coadministered drug) No effect = 1.00 AUC
Contraindicated with simvastatin			
Telithromycin† 200 mg QD for 4 d	80 mg	Simvastatin acid‡	12
		Simvastatin	8.9
Nelfinavir† 1250 mg BID for 14 d	20 mg QD for 28 d	Simvastatin acid‡	6.2
		Simvastatin	
Itraconazole† 200 mg QD for 4 d	80 mg	Simvastatin acid‡	AUC not reported C_{max}
		Simvastatin	13.1
Posaconazole			
100 mg (oral suspension) QD for 13 d	40 mg	Simvastatin acid	7.3
		Simvastatin	10.3
200 mg (oral suspension) QD for 13 d	40 mg	Simvastatin acid	8.5
		Simvastatin	10.6
Avoid >1 quart of grapefruit juice with simvastatin			
Grapefruit juice§ (high dose)	60 mg single dose	Simvastatin acid	7
		Simvastatin	16
200 mL of double-strength TID‖			
Grapefruit juice§ (low dose)	20 mg single dose	Simvastatin acid	1.3
		Simvastatin	1.9
8 oz (about 237 mL) of single-strength¶			
Avoid taking with >10 mg simvastatin, based on clinical and/or postmarketing experience			
Verapamil SR 240 mg QD days 1-7 then 240 mg BID on days 8-10	80 mg on day 10	Simvastatin acid	2.3
		Simvastatin	2.5
Diltiazem 120 mg BID for 10 d	80 mg on day 10	Simvastatin acid	2.69
		Simvastatin	3.10
Diltiazem 120 mg BID for 14 d	20 mg on day 14	Simvastatin	4.6
Avoid taking with >20 mg simvastatin, based on clinical and/or post-marketing experience			
Amiodarone 400 mg QD for 3 d	40 mg on day 3	Simvastatin acid	1.75
		Simvastatin	1.76
Amlodipine 10 mg QD x 10 d	80 mg on day 10	Simvastatin acid	1.58
		Simvastatin	1.77
Ranolazine SR 1000 mg BID for 7 d	80 mg on day 1 and days 6-9	Simvastatin acid	2.26
		Simvastatin	1.86
No dosing adjustments required for the following			
Fenofibrate 160 mg QD × 14 d	80 mg QD on days 8-14	Simvastatin acid	0.64
		Simvastatin	0.89
Niacin extended-release** 2 g single dose	20 mg single dose	Simvastatin acid	1.6
		Simvastatin	1.4
Propranolol 80 mg single dose	80 mg single dose	Total inhibitor	0.79
		Active inhibitor	0.79

AUC, area under the curve; BID, twice a day; C_{max}, maximum concentration; TID, 3 times a day; QD, every day; SR, slow release.

*Results based on a chemical assay except results with propranolol as indicated.

†Results could be representative of the following cytochrome P450 3A4 isozyme inhibitors: ketoconazole, erythromycin, clarithromycin, HIV protease inhibitors, and nefazodone.

‡Simvastatin acid refers to the β-hydroxyacid of simvastatin.

§The effect of amounts of grapefruit juice between those used in these 2 studies on simvastatin pharmacokinetics has not been studied.

‖Double strength: 1 can of frozen concentrate diluted with 1 can of water. Grapefruit juice was administered TID for 2 d, and 200 mL together with single-dose simvastatin and 30 and 90 min after single-dose simvastatin on day 3.

¶Single strength: 1 can of frozen concentrate diluted with 3 cans of water. Grapefruit juice was administered with breakfast for 3 d; simvastatin was administered in the evening on day 3.

**Chinese patients have an increased risk for myopathy with simvastatin coadministered with lipid-modifying doses (≥1 g/day niacin) of niacin-containing products. Because the risk is dose-related, it is recommended that Chinese patients not receive simvastatin 80 mg coadministered with lipid-modifying doses of niacin-containing products.

compared with the reference dose. If the confidence intervals include unity, it is implied that the relationship between the test dose and the reference dose is proportional. If the lower confidence interval lies just less than 1.0, this may be an indication that the true response at this level is slightly more than dose-proportional compared with the reference dose level. This concept may be confusing to the understanding of the true potential for clinically significant DDIs.

More recent package inserts for statins (Lipitor, Crestor, Livalo) provide greater clarity.[23–25] The statin AUC, when coadministered with the reference drug, is expressed as an x-fold change and represents a simple ratio between coadministration and statin alone (ie, 1-fold = no change). This concept appears simpler and provides information similar to that in package inserts of other drug classes as well as many clinical prediction models. The modified package inserts for drug coadministered interactions are shown in Tables 5–11.[22–28] These tables are by no means complete, hence current reference sources, such as Table 12[29] and other contemporary drug interaction references should be consulted before prescribing interacting drugs.

Table 13 suggests dose limits for various drugs based on FDA package labeling. As new drugs are approved, the FDA does not always update the statin package inserts, even if a suspected dose limit may occur. It is often best to consult proprietary drug databases that reference these limits for the most up to date information.

Common interacting drugs and over-the-counter medications, supplements, and foods

When the potential for simvastatin/lovastatin interactions is examined, many common drugs can cause clinical issues. Atorvastatin, being less dependent on CYP3A4 for elimination, is not as susceptible to drug interactions by the CYP3A4 pathway. For example, the same CYP3A4 inhibitor will produce a much larger increase in simvastatin AUC compared with the increase in atorvastatin AUC.[30,31] Atorvastatin, although less likely to cause CYP3A4 interactions, has potentially similar drug interactions. If potentially interacting medications must be used, it is wise to choose a statin metabolized through a different enzyme system. Rosuvastatin, pravastatin, pitavastatin, and fluvastatin are associated with fewer potentially severe interactions than those noted previously. Although there are fewer interacting medications involving severe and major drug interactions for the non-CYP3A4 metabolized statins (Table 13), commonalities still exist.

- **Fibrate:** Recently, the American College of Cardiology/American Heart Association guidance on cholesterol management made a strong statement against using gemfibrozil with ANY statin.[32] Gemfibrozil is known to reduce the glucuronidation and elimination of statins. If a fibrate is to be used in combination with a statin, then fenofibrate is generally the fibrate of choice. Each statin has its own limitations with respect to gemfibrozil, and some formularies still allow open gemfibrozil utilization. Understanding the potential for pharmacokinetic interactions between fibrates and statins may be a good guide for practitioners if gemfibrozil is still to be considered (Table 14).
- **Over-the-counter supplements, medications, and foods:** The Natural Medicines Comprehensive Database is the most frequently used resource to investigate over-the-counter supplements/medicines and their effects on statin medications. For ease, the most common interactions can be divided into major (do not use) and moderate (clinical outcome not severe). Concomitant ingestion of alcohol and statins, and other medications

Table 6 Lovastatin drug interactions[26]

		Geometric mean ratio (ratio* with/without coadministered drug)	
		No effect = 1.00 AUC	
Coadministered drug and dosing regimen	Lovastatin (mg)	Lovastatin	Lovastatin acid
Gemfibrozil 600 mg BID for 3 d	40 mg	0.96	2.80
Itraconazole 200 mg QD for 4 d	40 mg on day 4	>36†	22
Itraconazole 100 mg QD for 4 d	40 mg on day 4	>14.8†	15.4
Grapefruit juice (high dose) 200 mL of double strength	80 mg single dose	15.3	5.0
Grapefruit juice (low dose) about 250 mL of single strength for 4 d	40 mg single dose	1.94	1.57
Cyclosporine (dose NA)	10 mg daily for 10 d	5- to 8-fold	ND
			Total lovastatin acid
Diltiazem 120 mg BID for 14 d	20 mg		3.57

AUC, area under the curve; BID, twice a day; NA, not applicable; ND, not determined; QD, every day.
*Results based on a chemical assay.
†Estimated minimum change.

Table 7 Atorvastatin drug interactions[23]

Coadministered drug and dosing regimen	Atorvastatin dose (mg)	Atorvastatin change in AUC*
Cyclosporine 5.2 mg/kg/d, stable dose	10 mg QD for 28 d	↑ 8-fold‡
Tipranavir 500 mg BID/ritonavir 200 mg BID for 7 d	10 mg SD	↑ 9.4-fold‡
Telaprevir 750 mg every 8 h for 10 d	20 mg SD	↑ 7.88-fold‡
Saquinavir 400 mg BID/ritonavir 400 mg BID for 15 d†	40 mg QD for 4 d	↑ 3.9-fold‡
Clarithromycin 500 mg BID for 9 days	80 mg QD for 8 d	↑ 4.4-fold‡
Darunavir 300 mg BID/ritonavir 100 mg BID for 9 d	10 mg QD for 4 d	↑ 3.9-fold‡
Itraconazole 200 mg QD for 4 d	40 mg SD	↑ 3.3-fold‡
Fosamprenavir 700 mg BID/ritonavir 100 mg BID for 14 d	10 mg QD for 4 d	↑ 2.53-fold‡
Fosamprenavir 1400 mg BID for 14 d	10 mg QD for 4 d	↑ 2.3-fold‡
Nelfinavir 1250 mg BID for 14 d	10 mg QD for 28 d	↑ 74%‡
Grapefruit juice 240 mL QD	40 mg SD	↑ 37%
Diltiazem 240 mg QD for 28 d	40 mg SD	↑ 51%
Erythromycin 500 mg QID for 7 d	10 mg SD	↑ 51%
Amlodipine 10 mg, single dose	80 mg	↑ 15%
Cimetidine 300 mg QD for 4 wk	10 mg QD for 2 wk	↓ Less than 1%
Colestipol 10 mg BID for 28 wk	40 mg QD for 28 wk	Not determined
Maalox TC 30 mL QD for 17 d	10 mg QD for 5 d	↓ 33%
Efavirenz 600 mg QD for 14 d	10 mg QD for 3 d	↓ 41%
Rifampin 600 mg QD, 7 d (coadministered)†	40 mg SD	↑ 30%‡
Rifampin 600 mg QD, 5 d (doses separated)†	40 mg SD	↓ 80%
Gemfibrozil 600 mg BID 7 d	40 mg SD	↑ 35%
Fenofibrate 160 mg QD 7 d	40 mg SD	↑ 3%

AUC, area under the curve; BID, twice a day; QD, every day; QID, 4 times a day; SD, single dose.

*Results based on a chemical assay.

†Because of the dual interaction mechanism of rifampin, simultaneous coadministration of atorvastatin with rifampin is recommended, because delayed administration of atorvastatin after administration of rifampin has been associated with a significant reduction in atorvastatin plasma concentrations.

‡Clinically significant.

metabolized through the liver, can result in DDIs. Although no specific quantity recommendations are available, moderate amounts of alcohol (2 standard drinks in a 24-hour period) offer less concern for pharmacokinetic and pharmacodynamic effects than larger amounts. Grapefruit juice contains bergamottin, a natural furanocoumarin, which can inhibit CYP3A4 and OAT. This inhibitory effect can last for up to 24 hours. Either grapefruit juice should be avoided with statins or the quantity consumed should be kept to less than 60 mL. Separating administration of grapefruit juice and statins by 4 hours may limit the interaction.

Like grapefruit, sweet orange (citrus sinensis) juice may inhibit OATP. Tangerines are related to the sweet orange and may also have an interaction. Separation of the fruit or juice from statin administration by 4 hours may be advisable. St John's wort induces CYP3A4. There are noted major interactions between statins and St. John's wort, and this combination should be avoided. St. John's wort mediates P-gp. It will decrease metabolism of simvastatin and possibly atorvastatin, but not likely pravastatin, fluvastatin, or rosuvastatin. Red yeast rice is a popular nonprescription treatment for hyperlipidemia. Red yeast rice has varying amounts of monacolin K (similar to lovastatin). Products are not standardized and no red yeast rice product should be given to a patient taking a prescription statin.

Special populations with potentially increased risk for DDIs

- **Elderly:** More elderly patients are being treated with statins. As muscle mass decreases with aging, there may be an increased risk of myopathy in elderly patients. In addition, polypharmacy is pervasive in the elderly and increases the chance of a DDI. As age increases, metabolizing enzymes may be less functional as well, increasing the likelihood of increased AUC and more DDIs. It is critical that elderly patients on polypharmacy be regularly reevaluated for the risk of DDIs and drug lists be rigorously kept up to date.[33–36] Atorvastatin and rosuvastatin may mildly increase serum concentrations of ethinyl estradiol and norgestrel, which may be used as part of postmenopausal therapies.
- **Chinese/Japanese**: Pharmacokinetic data have shown that Asians taking statins have higher serum levels of these drugs than Caucasians. The FDA has issued caution when treating Chinese patients with simvastatin doses exceeding 20 mg/day administered with niacin.[37] This followed the observation in the Heart Protection Study 2 of increased risk of myopathy in those taking simvastatin 40 mg administered with niacin-containing products (>1 g/day). Rosuvastatin labeling notes higher blood levels in patients of Asian heritage (Filipino, Chinese,

Table 8 Rosuvastatin drug interactions[24]

Coadministered drug and dosing regimen	Rosuvastatin dose (mg)*	Rosuvastatin change in AUC
Cyclosporine (stable dose required 75-200 mg BID)	10 mg/d for 10 d	↑ 10-fold‡
Gemfibrozil 600 mg BID × 7 d	80 mg	↑ 1.9-fold‡
Lopinavir/ritonavir combination 400 mg/100 mg BID for 10 d	20 mg/day for 7 d	↑ 2-fold‡
Atazanavir/ritonavir combination 300 mg/100 mg QD for 7 d	10 mg	↑ 3.1-fold‡
Eltrombopag 75 mg QD for 5 d	10 mg	↑ 3.1-fold
Tipranavir/ritonavir combination 500 mg/200 mg BID for 11 d	10 mg	↑ 26%
Dronedarone 400 mg BID	10 mg	↑ 1.4-fold
Itraconazole 200 mg QD for 5 d	10 mg or 80 mg	↑ 39% ↑ 28%
Ezetimibe 10 mg daily for 14 d	10 mg daily for 14 d	↑ 1.2-fold
Fosamprenavir/ritonavir 700 mg/100 mg BID for 7 d	10 mg	↑ 8%
Fenofibrate 67 mg TID for 7 d	10 mg	↑ 7%
Aluminum and magnesium hydroxide combination antacid administered simultaneously; administered 2 h apart	40 mg 40 mg	↓ 54%‡ ↓ 22%
Erythromycin 500 mg QID for 7 d	80 mg	↓ 20%
Ketoconazole 200 mg BID for 7 d	80 mg	↑ 2%
Itraconazole 200 mg QD for 5 d	10 mg 80 mg	↑ 39% ↑ 28%
Fluconazole 200 mg QD for 11 d	80 mg	↑ 14%

AUC, area under the curve; BID, twice a day; QD, every day; QID, 4 times a day, TID, 3 times a day.
†Mean ratio (with/without coadministered drug and no change = 1-fold) or % change (with/without coadministered drug and no change = 0%); symbols of ↑ and ↓ indicate the exposure increase and decrease, respectively.
*Single dose unless otherwise noted.
‡Clinically significant.

Japanese, Korean, Vietnamese, or Asian-Indian). A 5-mg rosuvastatin initiation dose may be appropriate for this group. Pitavastatin was recently approved based on research in Japanese patients. Differences in Japanese and Caucasian pharmacokinetics with pitavastatin are still under investigation. No specific recommendations appear in the pitavastatin labeling. Atorvastatin and fluvastatin offer no current special population warning for Asian groups. Labeling in Asian countries differs from the higher doses used in the United States. Initiation of therapy with low doses of all statins in Asian and Asian-American patients remains the most prudent approach.[37]

Table 9 Fluvastatin drug interactions[27]

Coadministered drug and dosing regimen	Fluvastatin dose (mg)*	Fluvastatin change in AUC†
Cyclosporine – stable dose BID‡	20 mg QD for 14 wk	↑ 90%
Fluconazole 400 mg QD d 1200 mg BID d 2-4‡	40 mg QD	↑ 84%
Cholestyramine 8 g QD	20 mg QD administered 4 h after a meal plus cholestyramine	↓ 51%
Rifampicin 600 mg QD for 6 d	20 mg QD	↓ 53%
Cimetidine 400 mg BID for 5 d, QD on day 6	20 mg QD	↑ 30%
Ranitidine 150 mg BID for 5 d, QD on day 6	20 mg QD	↑ 10%
Omeprazole 40 mg QD for 6 d	20 mg QD	↑ 20%
Phenytoin 300 mg QD	40 mg BID for 5 d	↑ 40%
Propranolol 40 mg BID for 3.5 d	40 mg QD	↓ 5%
Digoxin 0.1-0.5 mg QD for 3 wk	40 mg QD	No change
Diclofenac 25 mg QD	40 mg QD for 8 days	↑ 50%
Glyburide 5-20 mg QD for 22 d	40 mg BID for 14 d	↑ 51%
Warfarin 30 mg QD	40 mg QD for 8 d	↑ 30%
Clopidogrel 300 mg loading dose on day 10, 75 mg dose on days 11-19	80 mg XL QD for 19 d	↓ 2%

AUC, area under the curve; BID, twice a day; QD, every day.
*Single dose, unless otherwise noted.
†Mean ratio (with/without coadministered drug and no change = 1-fold) or % change (with/without coadministered drug and no change = 0%); symbols of ↑ and ↓ indicate the exposure increase and decrease, respectively.
‡Considered clinically significant.

Table 10 Pravastatin drug interactions[28]

Coadministered drug and dosing regimen	Pravastatin dose (mg)	Pravastatin change in AUC
Cyclosporine 5 mg/kg single dose	40 mg single dose	↑ 282%
Clarithromycin 500 mg BID for 9 d	40 mg QD × 8 d	↑ 110%
Boceprevir 800 mg TID for 6 d	40 mg single dose	↑ 63%
Darunavir 600 mg BID/Ritonavir 100 mg BID for 7 d	40 mg single dose	↑ 81%
Colestipol 10 g single dose	20 mg single dose	↓ 47%
Cholestyramine 4 g single dose	20 mg single dose	
Administered simultaneously		↓ 47%
Administered 1 h before cholestyramine		↑ 12%
Administered 4 h after cholestyramine		↓ 12%
Cholestyramine 24 g daily for 4 wk	20 mg BID for 8 wk	↓ 51%
	5 mg BID for 8 wk	↓ 38%
	10 mg BID for 8 wk	↓ 18%
Fluconazole		
200 mg IV for 6 d	20 mg PO + 10 mg IV	↓ 34%
200 mg PO for 6 d	20 mg PO + 10 mg IV	↓ 16%
Kaletra 400 mg/100 mg BID for 14 d	20 mg daily for 4 d	↑ 33%
Verapamil IR 120 mg for 1 d and verapamil ER 480 mg for 3 d	40 mg single dose	↑ 31%
Cimetidine 300 mg QID for 3 d	20 mg single dose	↑ 30%
Antacids 15 mL QID for 3 d	20 mg single dose	↓ 28%
Digoxin 0.2 mg daily for 9 d	20 mg daily for 9 d	↑ 23%
Probucol 500 mg single dose	20 mg single dose	↑ 14%
Warfarin 5 mg daily for 6 d	20 mg BID for 6 d	↓ 13%
Itraconazole 200 mg daily for 30 d	40 mg daily for 30 d	↑ 11% (compared with day 1)
Gemfibrozil 600 mg single dose	20 mg single dose	↓ 7.0%
Aspirin 324 mg single dose	20 mg single dose	↑ 4.7%
Niacin 1 g single dose	20 mg single dose	↓ 3.6%
Diltiazem	20 mg single dose	↑ 2.7%
Grapefruit juice	40 mg single dose	↓ 1.8%

AUC, area under the curve; BID, twice a day; ER, extended release; IR, immediate release; IV, intravenous; PO, orally; QD, every day; QID, 4 times a day; TID, 3 times a day.

- **HIV:** Recently, the FDA issued warnings about protease inhibitors and non-nucleoside reverse transcriptase inhibitors used in highly active antiretroviral therapy and statins. These are usually specific to the drugs metabolized by CYP3A4. Current National Institutes of Health guidelines recommend fluvastatin, pitavastatin, and

Table 11 Pitavastatin drug interactions[25]

Coadministered drug and dosing regimen	Dose regimen	Pitavastatin change in AUC*
Cyclosporine 2 mg/kg/d on day 6	Pitavastatin 2 mg QD	↑ 4.6-fold†
Erythromycin 500 mg 4 times daily for 5 d	Pitavastatin 4 mg single dose on day 4	↑ 2.8-fold†
Rifampin 600 mg QD for 5 d	Pitavastatin 4 mg QD	↑ 29%
Atazanavir 300 mg daily for 5 d	Pitavastatin 4 mg QD	↑ 31%
Darunavir/ritonavir 800 mg/100 mg QD on days 6-16	Pitavastatin 4 mg QD on days 1-5 and 12-16	↓ 26%
Lopinavir/ritonavir 400 mg/100 mg BID on days 9-24	Pitavastatin 4 mg QD on days 1-5 and 20-24	↓ 20%
Gemfibrozil 600 mg BID for 7 d	Pitavastatin 4 mg QD	↑ 45%
Fenofibrate 160 mg daily for 7 d	Pitavastatin 4 mg QD	↑ 18%
Ezetimibe 10 mg daily for 7 d	Pitavastatin 2 mg QD	↓ 2%
Enalapril 20 mg daily for 5 d	Pitavastatin 4 mg QD	↑ 6%
Digoxin 0.25 mg daily for 7 d	Pitavastatin 4 mg QD	↑ 4%
Diltiazem LA 240 mg on days 6-15	Pitavastatin 4 mg QD on days 1-5 and 11-15	↑ 10%
Grapefruit juice for 4 d (quantity not specified)	Pitavastatin 2 mg single dose on day 3	↑ 15%
Itraconazole 200 mg daily for 5 d	Pitavastatin 4 mg single dose on day 4	↓ 23%

BID, twice daily; QD, once daily; LA, long acting.

*Data presented as x-fold change represent the ratio between coadministration and pitavastatin alone (ie, 1-fold = no change). Data presented as % change represent % difference relative to pitavastatin alone (ie, 0% = no change).

†Considered clinically significant.

Table 12 Comparison of drug-drug interactions across all statins

	Level 1 (severe) *Do not use*	Level 2 (major) *Use with caution*	Level 3 (moderate) *Less likely to cause severe drug interaction*	Level 4 (mild) *Unlikely to cause drug interaction*
Simvastatin/lovastatin	Protease inhibitors	Amiodarone	Afatinib	Barbiturates
	Boceprevir	Amlodipine	Aprepitant	Carbamazepine
	Clarithromycin	Conivaptan	Fosaprepitant	Clopidogrel
	Cobicistat	Diltiazem	Bosentan	Nevirapine
	Elvitegravir	Dronedarone	Colchicine	
	Emtricitabine	Efavirenz	Dalfopristin/quinupristin	
	Tenofovir	Other fibrates	Daptomycin	
	Cyclosporine	Fluconazole	Digoxin	Oxcarbazepine
	Danazol	Grapefruit juice	Esomeprazole	Rifabutin
	Delavirdine	Imatinib	Fluvoxamine	Rifapentine
	Erythromycin	Lomitapide	Fosphenytoin	
	Gemfibrozil	Ranolazine	Lansoprazole	
	Itraconazole	Simeprivir	Niacin, niacinamide	
	Ketoconazole	Ticagrelor	Omeprazole	
	Nefazodone	Troleandomycin	Pantoprazole	
	Posaconazole	Verapamil	Phenytoin	
	Red yeast Rice		Quinine	
	Telaprevir		Repaglinide	
	Telithromycin		Rifampin	
	Voriconazole		St. John's wort	
			Warfarin	
Atorvastatin	Posaconazole	Boceprevir	Amiodarone	Barbiturates
	Red yeast rice	Clarithromycin	Antacids	Carbamazepine
	Telithromycin	Conivaptan	Aprepitant	Cimetidine
	Voriconazole	Cyclosporine	Fosaprepitant	Clopidogrel
		Darunavir	Atazanavir	Miconazole
		Delavirdine	Bosentan	Nevirapine
		Digoxin	Colchicine	Oral contraceptives
		Diltiazem	Colestipol	Oxcarbazepine
		Erythromycin	Dalfopristin/quinupristin	Pioglitazone
		Fluconazole	Danazol	Rifabutin
		Fosamprenavir	Daptomycin	Rifapentine
		Gemfibrozil	Efavirenz	Spironolactone
		Grapefruit juice		
		Imatinib	Esomeprazole	
		Itraconazole	Fosphenytoin	
		Ketoconazole	Indinavir	
		Lopinavir/ritonavir	Lansoprazole	
		Nefazodone	Mifepristone	
		Nelfinavir	Niacin, niacinamide	
		Other fibrates	Nilotinib	
		Saquinavir	Omeprazole	
		Simeprivir		
		Telaprevir	Pantoprazole	
		Tipranavir	Phenytoin	
		Troleandomycin	Quinine	
		Verapamil	Ranolazine	
			Rifampin	
			St. John's wort	
			Warfarin	
Rosuvastatin	Red yeast rice	Antacids	Colchicine	Erythromycin
		Atazanavir	Daptomycin	Oral contraceptives
		Clarithromycin	Darunavir	
		Cyclosporine	Indinavir	

(*continued on next page*)

Table 12 (*continued*)

	Level 1 (severe) *Do not use*	Level 2 (major) *Use with caution*	Level 3 (moderate) *Less likely to cause severe drug interaction*	Level 4 (mild) *Unlikely to cause drug interaction*
		Fosamprenavir Gemfibrozil and other fibrates Lopinavir/Ritonavir Nelfinavir Ritonavir Saquinavir Simeprivir Telithromycin	Itraconazole Niacin, niacinamide Warfarin	
Pravastatin	Red yeast rice	Bile acid resins Clarithromycin Cyclosporine Darunavir Erythromycin Gemfibrozil and other fibrates Simeprivir Telithromycin	Boceprevir Colchicine Daptomycin Itraconazole Niacin, niacinamide Orlistat Warfarin	
Fluvastatin	Red yeast rice	Cyclosporine Erythromycin Gemfibrozil and other fibrates Telithromycin	Amiodarone Antiretroviral protease inhibitors Cholestyramine Cimetidine Colchicine Daptomycin Delavirdine Diclofenac Digoxin Efavirenz Ethanol Fluconazole Fluoxetine Fluvoxamine Glyburide Imatinib Niacin, niacinamide Nilotinib Omeprazole Phenytoin Ranitidine Rifampin Sulfinpyrazone Sulfonamides Voriconazole Warfarin	Clopidogrel Irbesartan Rifabutin Rifapentine Zafirlukast
Pitavastatin	Cyclosporine Red yeast rice	Atazanavir Darunavir Erythromycin Fosamprenavir Gemfibrozil and other fibrates Lopinavir; Ritonavir Rifampin Ritonavir Saquinavir Simeprivir Telithromycin Tipranavir	Colchicine Niacin, niacinamide Raltegravir	Warfarin

Adapted with permission from Clinical Pharmacology [database online]. Tampa, FL: Elsevier/Gold Standard, Inc.; 2013.[29]

Table 13 Dose limits of various statins with respect to various interacting medications[21–29,47]

Statin/interactant	Simva	Lova	Atorva	Rosuva	Prava	Fluva	Pitava
Ketoconazole	Avoid	Avoid					
Posaconazole	Avoid	Avoid					
Boceprevir	Avoid	Avoid	No mention				
Simeprevir	Caution	Caution	Caution	Caution	Caution		Caution
Nefazodone	Avoid	Avoid					
Cyclosporine	Avoid	Avoid	Avoid	5 mg/d	20 mg/d	20 mg/d	
Gemfibrozil	Avoid	Avoid	Avoid	10 mg/d	Avoid	Caution	Avoid
Danazol	Avoid	Avoid					
Tipranavir			Avoid				
Telaprevir			Avoid				
HIV protease inhibitor	Avoid	Avoid	20 mg*	10 mg*			
Verapamil diltiazem	10-mg limit						
Clarithromycin			20-mg limit	40-mg limit			
Itraconazole			20-mg limit				
Fosamprenavir ± ritonavir			20-mg limit				
Nelfinavir			40-mg limit				
Fluconazole						20 mg/d	
Amiodarone	20-mg limit						
Amlodipine							
Ranolazine							
Grapefruit juice	Avoid large quantity	Avoid large quantity					
Niacin	Limit to 1 g/d	Limit to 1 g/d	Limit to 1 g/d	Limit to 1 g/d	Limit to 1 g/d		
Erythromycin							1 mg/d
Rifampin							2 mg/d

atorva, atorvastatin; fluva, fluvastatin; lova, lovastatin; pitava, pitavastatin; prava, pravastatin; rosuva, rosuvastatin; simva, simvastatin.

pravastatin (except for pravastatin with darunavir/ritonavir) over lovastatin and simvastatin. Atorvastatin and rosuvastatin may be used with caution. In combination with non-nucleoside reverse transcriptase inhibitors, some statins may have increased efficacy, whereas others may have decreased efficacy (Table 15).[38,39]

- **Hepatitis C and nonalcoholic fatty liver disease (NAFLD):** Hepatitis C is a leading cause of liver failure and transplantation. Data have already demonstrated the increased cardiovascular risk of patients with hepatitis C. In this condition, statins may not only help prevent cardiovascular disease but may also block the protein synthesis necessary for hepatitis C replication. One study suggested that simvastatin administered as monotherapy has the strongest antiviral activity, lovastatin and fluvastatin have a moderate antiviral effect, and pravastatin has no antiviral activity. With respect to worrisome DDIs with antiviral drugs as part of new therapy for hepatitis C, boceprevir, classified as a nonstructural protein 3/4A protease inhibitor should not be given with simvastatin or lovastatin. Boceprevir is a potent inhibitor of CYP3A4. An atorvastatin/boceprevir interaction has not been noted. Conversely, telaprevir, also an NS3/4A protease inhibitor, is contraindicated with simvastatin, lovastatin, and atorvastatin. Non-CYP3A4 statins should be used when patients are subjected to treatment with these newer agents. Statins do not appear to affect the concentrations of sofosbuvir.

Table 14 Statin/fibrate combination therapy: pharmacokinetic interactions[22–28,46,47]

Statin	Gemfibrozil	Fenofibrate
Atorvastatin	↑ in C_{max} (expected)	No change
Simvastatin	↑ in C_{max} by 2-fold	No change
Pravastatin	↑ in C_{max} by 2-fold	No change
Rosuvastatin	↑ in C_{max} by 2-fold	No change
Fluvastatin	No change	No change
Lovastatin	↑ in C_{max} by 2.8-fold	No change
Pitavastatin	↑ in C_{max} by 41%	Unknown

C_{max}, maximum concentration.

Simeprevir on the other hand inhibits OATP1B1. Rosuvastatin dose should be initiated at 5 mg once daily and not exceed 10 mg daily. Atorvastatin should be started at the lowest dose and not exceed 40 mg daily. Simvastatin doses should be kept lowest as needed and no data is noted with pitavastatin, lovastatin, or lovastatin and doses should also be kept as low as possible.[28]

Using statins in patients with NAFLD has long been a subject of controversy. NAFLD includes disorders ranging from simple hepatic steatosis to nonalcoholic steatohepatitis and cirrhosis. Covered in another article in this publication, it should be noted that changes in alanine aminotransferase often occur independently of statin therapy. Most recently, the FDA has obviated the need for routine liver function testing because minor elevations have

Table 15 Drug interactions between highly active antiretroviral therapy regimens and other drugs[39]

Drug	PI	Effect on PI or concomitant drug concentrations	Recommendation
Atorvastatin	ATV/r	↑ atorvastatin possible	Titrate atorvastatin dose carefully and use lowest dose necessary
	ATV		
	DRV/r	DRV/r + atorvastatin 10 mg similar to atorvastatin	Titrate atorvastatin dose carefully and use the lowest necessary dose. Do not exceed 20 mg atorvastatin daily
	FPV/r	40 mg administered alone;	
	FPV	FPV ± RTV ↑ atorvastatin AUC 130% to 153%;	
	SQV/r	SQV/r ↑ atorvastatin AUC 79%	
	LPV/r	LPV/r ↑ atorvastatin AUC 488%	Use with caution and use the lowest atorvastatin dose necessary
	TPV/r	↑ atorvastatin AUC 836%	DO NOT COADMINISTER
Lovastatin	All PIs	Significant ↑ lovastatin expected	Contraindicated. Do not coadminister
Pitavastatin	All PIs	ATV ↑ pitavastatin AUC 31% and C_{max} ↑ 60% ATV: no significant effect LPV/r ↓ pitavastatin AUC 20% LPV: no significant effect	No dose adjustment necessary
Pravastatin	DRV/r	Pravastatin AUC ↑ 81%	Use lowest possible starting dose of pravastatin with careful monitoring
	LPV/r	Pravastatin AUC ↑ 33%	No dose adjustment necessary
	SQV/r	pravastatin AUC ↓ 47% to 50%	No dose adjustment necessary
Rosuvastatin	ATV/r	ATV/r ↑ rosuvastatin AUC 3-fold and	Titrate rosuvastatin dose carefully and use the lowest necessary dose. Do not exceed 10 mg rosuvastatin daily
	LPV/r	C_{max} ↑ 7-fold LPV/r ↑ rosuvastatin AUC 108% and C_{max} ↑ 366%	
	DRV/r	rosuvastatin AUC ↑ 48% and C_{max} ↑ 139%	Titrate rosuvastatin dose carefully and use the lowest necessary dose while monitoring for toxicities
	FPV ± RTV	No significant effect on rosuvastatin	No dosage adjustment necessary
	SQV/r	No data available	Titrate rosuvastatin dose carefully and use the lowest necessary dose while monitoring for toxicities
	TPV/r	rosuvastatin AUC ↑ 26% and C_{max} ↑ 123%	No dose adjustment necessary
Simvastatin	All PIs	Significant ↑ simvastatin level; SQV/r 400 mg/400 mg BID ↑ simvastatin AUC 3059%	CONTRAINDICATED, do not coadminister

Concomitant drug class/name	NNRTI	Effect on NNRTI or concomitant drug concentrations	Recommendations
Fluvastatin	ETR	↑ fluvastatin possible	↑ fluvastatin possible
Lovastatin	EFV	Simvastatin AUC ↓ 68%	Adjust simvastatin dose according to lipid responses, not to exceed the maximum recommended dose. If EFV used with RTV-boosted PI, simvastatin and lovastatin should be avoided
Simvastatin			
	ETR	↓ Lovastatin possible	Adjust lovastatin or simvastatin dose according to lipid responses, not to exceed the maximum recommended dose. If ETR or NVP used with RTV-boosted PI, simvastatin and lovastatin should be avoided
	NVP	↓ Simvastatin possible	
Pitavastatin	EFV,	No data	No recommendation
	ETR		
	NVP		
	RPV		
Pravastatin, rosuvastatin	EFV	Pravastatin AUC ↓ 44% rosuvastatin: no data	Adjust statin dose according to lipid responses, not to exceed the maximum recommended dose.
	ETR	No significant effect expected	No dosage adjustment necessary

ABC, abacavir; APV, amprenavir; ATV/r, ritonavir-boosted atazanavir; AUC, area under the curve; DRV/r, ritonavir- boosted darunavir; ETR, etravirine; EFV, efavirenz; FPV/r, ritonavir-boosted fosamprenavir; LPV/r, ritonavir-boosted lopinavir; NFV, nelfinavir; NNRTI, non-nucleoside reverse transcriptase inhibitor; NVP, nevirapine; PI, protease inhibitor; RAL, raltegravir; RPV, rilpivirine; RTV, ritonavir; SQV/r, ritonavir-boosted saquinavir; T20, enfuvirtide; TDF, tenofovir disoproxil fumarate; TPV/r, ritonavir-boosted tipranavir.

Table 16 Safety of statins in chronic kidney disease

- Atorvastatin and fluvastatin are minimally excreted by the kidneys
- Dosing modifications for other statins (NKF recommendations):[46]
  - ➢ Simvastatin and lovastatin: 50% dose reduction if GFR < 30 mg/mL
  - ➢ Pravastatin: no dose adjustment (package insert: start with 10 mg once daily in renal impairment)
  - ➢ Rosuvastatin: not discussed in NKF guidelines (prescribing information: start at 5 mg and do not exceed 10 mg in severe chronic renal insufficiency [creatinine clearance <30 mL/min] in patients not on dialysis
  - ➢ Pitavastatin: not discussed in NKF guidelines (package insert: patients with moderate and severe renal impairment [GFR 30-59 mL/min/1.73 m^2 and 15-29 mL/min/1.73 m^2 not receiving hemodialysis, respectively] as well as end-stage renal disease receiving hemodialysis: initial, 1 mg orally daily and maximum 2 mg daily)

GFR, glomerular filtration rate; NKF, National Kidney Foundation.

led to physicians inappropriately discontinuing statin therapy, putting patients at increased risk of cardiovascular disease. The currently labeled recommendations for statins should be used with caution in patients with liver disease who consume substantial amounts of alcohol.[40–43]

- **Pediatrics:** Young adults are rarely on interacting medications that would create a clinical dilemma. Some epileptics may be prone to DDIs. As noted previously, some statins may mildly increase serum concentrations of ethinyl estradiol and norgestrel (found in oral contraceptives). The clinical significance is unknown. There is little information with regard to safety issues in children who are on statins for familial hypercholesterolemia (FH). Little is known about safety issues in this population and more data and endpoints are needed. The 4 statins currently approved for use in children with FH by the FDA, all with labeling consistent with the recent American Heart Association pediatric statement in terms of age and when treatment should be started, are lovastatin, simvastatin, pravastatin, and atorvastatin.[44,45]
- **FH:** FH patients present similar challenges with respect to DDIs as other patients on multiple drug regimens. The potential for statin and ezetimibe interactions is minor at best. Statins and bile acid resins have few interactions other than those attributed to the resin class. The potential for myopathic side effects with the higher doses of statins exists, but is similar to the general population.
- **Chronic kidney disease (CKD)/end-stage renal disease:** Statins have been shown to reduce cardiovascular events in those with CKD (stages I-IV), but not for those with end-stage renal disease and receiving hemodialysis. Recommendations for statin dosing in CKD patients is shown in Table 16.[46]

Recommendations for classification of statin drug interactions and labeling

Thus, a recommendation of the National Lipid Association Statin Safety Taskforce would be to unify the FDA-mandated labeling to allow practitioners to readily compare statin drug interactions. Additionally, it is recommended that a system to express the likelihood for a statin DDI be created as an adjunctive tool for practitioners.

Conclusions

Statin absorption, distribution, metabolism, and excretion are complex and vary from statin to statin. The transporters and enzymes involved in these processes are now better understood and serve to explain the mechanisms of statin interactions with a variety of drugs that alter what is otherwise an excellent safety profile. As new drugs enter the US market, understanding these mechanisms allows the clinician to predict the impact new drugs may have on statin disposition, given the effect of a new drug on known transporters and metabolizing enzyme systems.

We propose that clinicians become familiar with the statins they prefer and refer to an individual statin table to identify drugs they often coprescribe that may interact with a particular statin. Once identified, the potential interacting agent can be classified as having mild, moderate, or severe interacting potential. One option would be to avoid the interaction by changing to a different statin or to a therapeutic equivalent to the interacting agent. This is the preferred option for severe interactions. If a combination cannot be avoided, the effected statin should be dosed according to its identified dosing limit. This is the preferred option for interactions with moderate intensity. Patients who receive drug combinations with mild potential for interaction may be carefully monitored for symptoms of statin toxicity because of a low potential for serious side effects.

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