Statin Drug Interactions in Patients with Comorbidities and on Multiple Medications

Matthew K Ito, PharmD, FCCP, FNLA, CLS

Professor of Pharmacy Practice, College of Pharmacy, Oregon State University/Oregon Health & Science University, Portland, Oregon, US

Abstract

Extensive clinical evidence has demonstrated the efficacy of statin treatment in the prevention of cardiovascular disease (CVD). However, nearly half of patients taking statins discontinue their use, largely as a result of side effects. Many patients receiving statins are elderly, and/or have comorbid conditions, increasing the potential for drug-drug interactions (DDIs). Statin DDIs are largely the result of altered drug metabolism via cytochrome P450s (CYPs), glucuronidation or altered drug transport via organic anion-transporting polypeptides (OATPs) and P-glycoprotein (P-gp). There is a need for discussion and education about DDIs within the clinical consultation. Statins that are not significantly metabolized via the CYP system have a reduced risk of DDIs. To date, pitavastatin has shown a low rate of DDIs compared to other available statins metabolized by CYP3A4 isozymes. Its potential for CYP-mediated DDIs has been studied in combination with a wide range of drug classes known to be CYP inhibitors and has been clinically evaluated in patients populations where multiple medications are used, including the elderly, those high risk of CVD, and those taking protease inhibitors. It may also have beneficial effects on parameters of glucose metabolism, and has shown improved outcomes in patients with chronic kidney disease. Knowledge of statin pharmacokinetics, their dose limitations and contraindications, and their mechanisms of DDI allows improved therapeutic choices, avoiding adverse interactions without compromising patient care.

Keywords

Cytochrome P450, drug-drug interaction, p-glycoprotein, organic anion-transporting polypeptide, pitavastatin, statin

Disclosure: Matthew K Ito, PharmD, FCCP, FNLA, CLS, has received honoraria for speaking from GlaxoSmithKline and Kowa/Lilly and for serving on advisory boards for Kowa/Lilly, Aegerion, and Regeneron.

Acknowledgment: Editorial assistance was provided by Katrina Mountfort at Touch Medical Media and was funded by Kowa Pharmaceuticals.

Received: November 20, 2012 **Accepted:** November 27, 2012 **Citation:** *US Endocrinology*, 2012;8(2):104–11 *DOI: 10.17925/USE.2012.08.02.104*

Correspondence: Matthew K Ito, PharmD, FCCP, FNLA, CLS, Department of Pharmacy Practice, College of Pharmacy, Oregon Health & Science University, 3303 SW Bond Ave, CH12C, Portland, OR 97239, US. E: itom@ohsu.edu

Support: The publication of this article was funded by Kowa Pharmaceuticals. The views and opinions expressed are those of the author and not necessarily those of Kowa Pharmaceuticals.

Cardiovascular disease (CVD) is the leading cause of mortality worldwide, and an overwhelming body of clinical evidence has demonstrated the efficacy of statin treatment in the prevention of this condition. Therapeutic goals in the prevention of CVD include management of dyslipidemia and of its complications such as hypertension and diabetes. Statins are the most widely used treatment in the management of dyslipidemia and exert their therapeutic action by competitively inhibiting 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase. Inhibition of this enzyme results in upregulation of low-density lipoprotein (LDL) receptors and a reduction in the plasma levels of LDL cholesterol (LDL-C), non high-density lipoprotein cholesterol (non HDL-C), and apolipoprotein B.[1] Results from a meta-analysis showed that statins reduce the five-year incidence of major coronary events, coronary revascularization, and stroke by about a fifth for each mmol/l reduction in LDL-C.[2]

Despite the known efficacy of statins, high LDL-C remains underdiagnosed and undertreated: it is estimated that 71 million US adults (≥20 years of age) have LDL-C levels greater than the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP-III) goals.[3] In the National Cholesterol Education Program evaluation project utilizing novel E-technology (NEPTUNE) II survey, it was found that patients with diabetes (55 %) and other coronary heart disease (CHD) risk equivalents (40 %) were less likely to have achieved their LDL-C targets than those with CHD (62 %).[4] Therefore, the use of these drugs at conventional doses may be unsatisfactory for LDL-C management in patients with diabetes, other CHD risk equivalents, and CHD. For such patients, administration of statins at high doses, or concomitant use of other agents for dyslipidemia may be considered. However, such options may increase the risk of serious adverse drug reactions.[5]

Table 1: Pharmacokinetic Properties of Statins

	Atorvastatin	Fluvastatin XL	Lovastatin	Pitavastatin	Pravastatin	Rosuvastatin	Simvastatin
Fraction absorbed (%)	30	98	30	75	34	50	60–80
t_{max} (h)	2–3	4	2–4	1.2	0.9–1.6	3	1.3–2.4
C_{max} (ng/ml)	27–66	55	10–20	18.2	45–55	37	10–34
Bioavailability (%)	12	6	5	51	18	20	5
Effect of food on bioavailability (%)	13	0	50	0	30	20	0
Lipophilicity	Yes	Yes	Yes	Yes	No	No	Yes
Transporter substrate	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Protein binding (%)	>98	>99	>95	>99	43–55	88	94–98
Hepatic extraction (%)	>70	>68	>70	Estimated >70	46–66	63	78–87
Systemic metabolites	Active	Inactive	Active	Inactive	Inactive	Active (minor)	Active
Systemic clearance (ml/min)	291.6	4,433	303–1,166	410	945	805	525
Renal clearance (ml/min)	No	No	No	No	>400	226	No
$t_{1/2}$ (h)	15–30	4.7	2.9	13	1.3–2.8	20.8	2–3
Fecal excretion (%)	70	90	83	78	71	90	58
Urinary excretion (%)	2	6	10	<4	20	10	13

All based on a 40 mg oral dose, except fluvastatin XL (extended release, 80 mg) and pitavastatin 2 mg. C_{max} = maximum concentration; h = hours; t_{max} = time to reach maximum concentration; $t_{1/2}$ = terminal elimination half-life. Source: Corsini, 2011.[9]

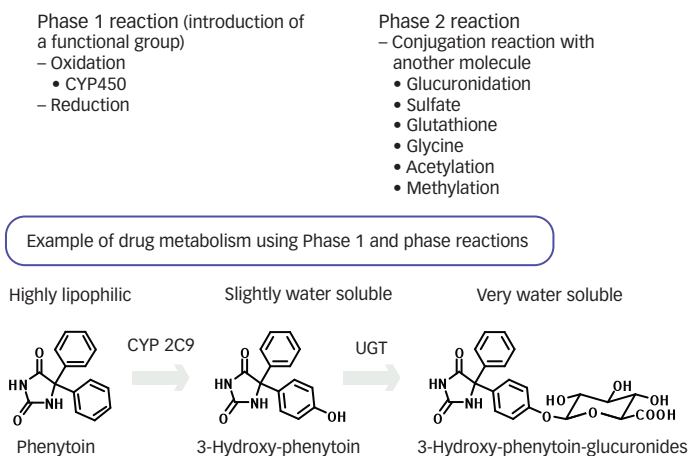
Adverse drug reactions are a significant burden in healthcare and are associated with substantial morbidity, mortality and healthcare costs.[6] Although the rate of adverse affects during statin monotherapy is generally low, in rare cases (0.1–0.2 %), statins may cause myositis,[7] and in extremely rare cases, life-threatening rhabdomyolysis.[7,8] Drug–drug interactions (DDIs) that increase the serum concentration of statins can increase the risk of these muscle-related adverse events.[9] The aim of this article is to discuss the patient populations who are most at risk of statin DDIs, and outline dyslipidemia treatment choices that may reduce the risk of DDIs in these patients.

Molecular Basis of Statin Drug–Drug Interactions

In order to understand the molecular basis of statin DDIs, it is important to take into account the different pharmacokinetic properties that underlie their routes of metabolism and elimination (see *Table 1*).[9,10] Statin DDIs are primarily caused by agents that inhibit their metabolism and transport. The metabolism of drugs generally occurs in two phases (see *Figure 1*). Phase I reactions involve introduction of a functional group to decrease their lipophilicity. This typically involves oxidation resulting in a variety of hydroxyl metabolites. If the drug is sufficiently hydrophilic, it will be eliminated from the body, if not, it will undergo Phase II reactions which involve conjugation with another hydrophilic molecule, further increasing their water solubility. Typical Phase II reactions include glucuronidation, acetylation, methylation, or formation of sulfate, glutathione or glycine conjugates.[11] Of the enzymes involved in Phase I reactions, the cytochrome P-450 (CYP) group is the most important. Within the CYP system, CYP3A4 is the most prevalent isoenzyme and metabolizes more than half of the drugs in current use.[12]

Each of the common Phase I isoenzymes, CYP2C9, 2C19, 2D6 and 3A4/5 interact differently with the different statins because of their differing physiochemical properties. Lovastatin and simvastatin undergo extensive first-pass metabolism via CYP3A4, with atorvastatin being metabolized by CYP34A to a lesser extent. Fluvastatin is metabolized via CYP2C9, with CYP3A4 and CYP2C8 contributing to a lesser extent.[1] More recently developed statins such as rosuvastatin,

Figure 1: Phases of Drug Metabolism



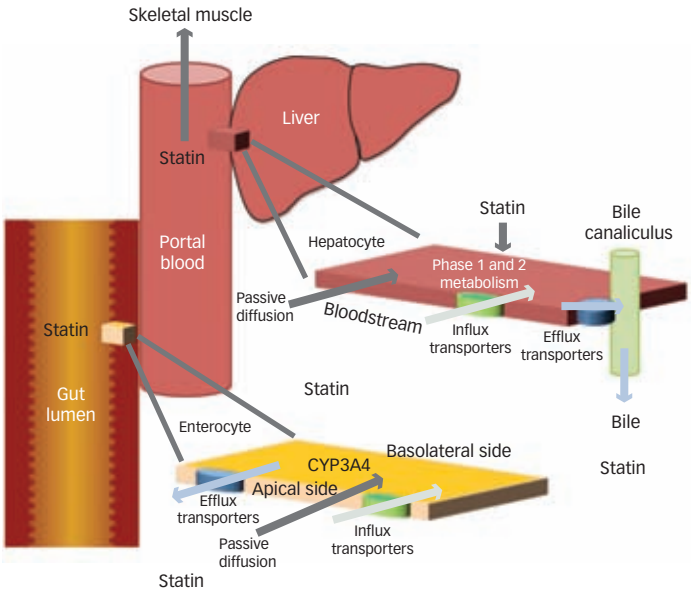
CYP = cytochrome P-450; UGT = uridine 5'-diphospho-glucuronosyltransferase. Source: Ito MK, presented at 2012 American Heart Association Scientific Sessions, Los Angeles, California, US.

and pitavastatin and older statins such as pravastatin, undergo minimal Phase I metabolism and their plasma concentrations are not significantly increased by CYP3A4 inhibitors.[13]

This predominant role of CYP in the metabolism of many statins presents the potential for DDIs with CYP inhibitors, which can result in marked alterations in concentrations of drugs within this class. When lovastatin and simvastatin are used concurrently with a potent CYP3A4 inhibitor such as itraconazole, the statin serum concentration can be increased 10- to 20-fold.[14,15] A retrospective database study found that patients who received statins with a concomitant CYP3A4 inhibitor had a six-fold increased rate of muscle-associated adverse reactions including rhabdomyolysis.[16]

Atorvastatin is also metabolized by CYP3A4, but not as extensively as lovastatin and simvastatin. Accordingly, potent CYP3A4 inhibitors tend to produce two- to four-fold increases in atorvastatin serum concentrations.[17] The relationship between altered plasma

Figure 2: Active and Passive Transport of Statins



CYP = cytochrome P-450.

concentrations and adverse effects or toxicity may not be linear, and therefore caution should be exercised in prescribing certain statins in combination with CYP3A4 inhibitors.[18] Even foodstuffs such as grapefruit juice and fresh grapefruit can inhibit the metabolism of statins as a result of selective downregulation of CYP3A4 in the small intestine.[19,20] Regular consumption of grapefruit juice (200 ml once daily) can increase simvastatin area under the curve (AUC) over three fold.[21] Therefore, grapefruit juice consumption is best avoided when taking a statin metabolized by CYP3A4.[22]

Following reports of muscle-related side effects of statin therapy, particularly simvastatin, the FDA underwent their own surveillance and a review of the Study of the effectiveness of additional reductions in cholesterol and homocysteine (SEARCH) trial.[23] As a result, they have issued a number of safety announcements on potential DDIs, which have included discontinuation of the 80 mg dose of simvastatin and other dose restrictions when taken in combination with strong CYP inhibitors.[24–26] Lovastatin has also been given many dose restrictions by the FDA.[26] These are summarized in *Table 2*.

Of the statins that do not primarily depend on CYP3A4 for metabolic clearance, rosuvastatin is primarily eliminated as the unchanged parent compound but has but has some dependence on CYP2C9 and CYP2C19 for its metabolism.[27,28] Pitavastatin is only minimally metabolized by CYP2C9 and to a lesser extent CYP2C8 and is mainly metabolized by glucuronidation. As a result, it does not interact with CYP3A4 inhibitors, increasing the drug's tolerability profile.[9,29] A large post-marketing study conducted in more than 20,000 patients in Japan[30] found that the rate of adverse drug reactions with pitavastatin treatment was 6.1 %, around half that observed with atorvastatin and rosuvastatin (12.0 and 11.1 % respectively).[9] These included increases in blood creatine phosphokinase, alanine aminotransferase, aspartate aminotransferase gamma-glutamyltransferase, and also myalgia.

Table 2: New US Food and Drug Administration Labeling Restrictions on Simvastatin and Lovastatin

New Simvastatin Label	New Lovastatin Label
Contraindicated with simvastatin: Itraconazole Ketoconazole Posaconazole Erythromycin Clarithromycin Telithromycin HIV protease inhibitors Nefazodone Gemfibrozil Cyclosporine Danazol	Contraindicated with lovastatin: Itraconazole Ketoconazole Posaconazole Erythromycin Clarithromycin Telithromycin HIV protease inhibitors Boceprevir Telaprevir Nefazodone
	Avoid with lovastatin: Cyclosporine Gemfibrozil
Do not exceed 10 mg simvastatin daily with: Verapamil Diltiazem	
Do not exceed 20 mg simvastatin daily with: Amiodarone Amlodipine Ranolazine	Do not exceed 20 mg lovastatin daily with: Danazol Diltiazem Verapamil
	Do not exceed 40 mg lovastatin daily with: Amiodarone
Avoid large quantities of grapefruit juice (>1 quart daily)	Avoid large quantities of grapefruit juice (>1 quart daily)

One pharmacokinetic property shared by all statins is extensive first pass hepatic extraction. Access into the liver is an important step prior to metabolism and elimination of the statins. This is accomplished by two primary mechanisms—active transport and passive diffusion (see *Figure 2*). Organic anion transporting polypeptides (OATPs) form a family of membrane influx transporter proteins that actively transport all statins to some extent.[31] Hydrophilic statins such as pravastatin and rosuvastatin are transported from the portal circulation into the hepatocyte[32] by OATPs. OATP1B1 also appears to have a selective role in pitavastatin transport[33] Atorvastatin, fluvastatin, lovastatin, and simvastatin enter hepatocytes mainly by passive diffusion; however, the acid forms of these statins also utilize active transport mechanisms.[34,35]

Inhibition of hepatic uptake transporters and reduced transport activity have the potential to cause significant DDIs.[34] Cyclosporine inhibits several influx and efflux transporters, including OATP1B3, OATP2B1, as well as CYP3A4[36] and has been shown to increase plasma concentrations of lovastatin.[37] However cyclosporine has been shown to increase plasma concentrations of statins that are not significantly metabolized by CYP3A4; interactions between cyclosporine and rosuvastatin,[38] and pitavastatin[39] have been noted in clinical situations. Furthermore, genetic variability in OATP-encoding genes can result in significant inter-individual differences in pharmacokinetics. For example, a single nucleotide polymorphism in

Table 3: Clinically Significant Drug–Drug Interactions Involving Statins

Interacting Drug	Mechanism of Interaction	Reference
Amiodarone	Amiodarone is a moderate CYP3A4 and CYP2C9 inhibitor	91
Azole Antifungals Fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole	Itraconazole, ketoconazole, posaconazole, and voriconazole are strong CYP3A4 inhibitors. Voricazole is also a CYP2C19 and CYP2C9 inhibitor. Fluconazole is a moderate CYP3A4 and potent CYP2C9 inhibitor	14, 17, 91, 92
Bile Acid Sequestrants Cholestyramine, colestipol	Decreased bioavailability of statins due to the drugs binding in the intestine	13
Calcium Channel Blockers Amlodipine, diltiazem, verapamil	Amlodipine is a CYP3A4 substrate. Diltiazem, and verapamil are CYP3A4 inhibitors. Diltiazem also inhibits P-glycoprotein-mediated transporters. Amlodipine might inhibit transport proteins that carry simvastatin into the liver for metabolism	91
Colchicine	Colchicine is a P-glycoprotein inhibitor and can itself cause myopathy	93
Cyclosporine	Cyclosporine is a CYP3A4 inhibitor and also inhibits P-glycoprotein, OATP1B1, and other transporters. Cyclosporine itself has been associated with myopathy and glucuronidation	91
Danazol	Danazol is a CYP3A4 inhibitor	91
Digoxin	Atorvastatin and simvastatin inhibit P-glycoprotein	47
Fibric Acid Derivatives	Gemfibrozil also inhibits hepatic glucuronidation of statins. Fenofibrate is a CYP2C9 inhibitor	71, 75, 76, 91
Fusidic acid	Cause is unclear: inhibition of CYP3A4 and inhibition of the glucuronidation pathway have been suggested	94, 95
Glyburide	Increased glyburide levels due to fluvastatin inhibition of CYP2C9	13
Grapefruit/Grapefruit Juice	Grapefruit juice inhibits CYP3A4 and P-glycoprotein	19, 20
Macrolide Antibiotics Clarithromycin, erythromycin	These macrolides are CYP3A4 inhibitors	96–98
Nefazodone	Nefazodone is strong CYP3A4 inhibitor	99, 100
Niacin	Increased risk for myopathy/rhabdomyolysis due to additive effects of both drugs	101
Phenytoin	Increased levels of fluvastatin due to competition for CYP2C9	13
Protease Inhibitors Atazanavir, boceprevir, darunavir, fosamprenavir, indinavir, lopinavir/ritonavir, nelfinavir, ritonavir, saquinavir, telaprevir, tipranavir	These antivirals are strong CYP3A4 inhibitors and many statins require CYP3A4 for their metabolism	84, 87, 102
Ranolazine	Ranolazine inhibits CYP3A4 and is a moderate P-glycoprotein inhibitor	65
Rifampin	Rifampin induces CYP450 enzymes but inhibits some non-CYP450 elimination pathways	13, 103
St John's wort	St John's wort is a CYP3A4 inducer	53
Telithromycin	Telithromycin is a strong CYP3A4 inhibitor	13, 104
Ticagrelor	Increased risk for myopathy/rhabdomyolysis due to decreased metabolism of simvastatin (and likely lovastatin)	105
Troglitazone	Troglitazone is a CYP3A4 inducer	106
Warfarin	Possibly due to decreased warfarin metabolism and displacement of warfarin from protein binding sites	70, 107

CYP = cytochrome P-450; OATP = organic anion transporting polypeptides.

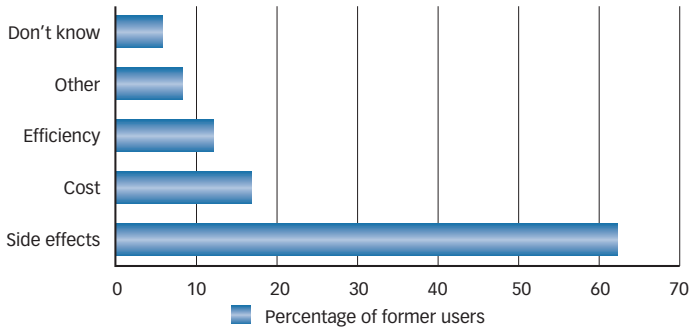
the SLCO1B1 gene may markedly increase plasma concentrations of simvastatin acid and result in an increased risk of myopathy.[36,40]

The membrane protein P-glycoprotein (P-gp),[13] an efflux protein located in the gastrointestinal tract, placenta, kidneys, brain, and liver, is believed to affect the bioavailability and elimination of statins, primarily in the acid form, and may therefore play a role in DDIs.[41–43] Studies of *in vitro* models have found that atorvastatin, simvastatin, and lovastatin are substrates for P-gp while pravastatin, fluvastatin and the acid form of pitavastatin do not show significant inhibition of P-gp.[41,44–46] Data from drug interaction studies involving statins and digoxin have suggested the involvement of P-gp.[47] Many drugs known to cause DDIs with statins are modulators of P-gp, and include diltiazem, verapamil, itraconazole, ketoconazole, and cyclosporine, as well as St John's wort and grapefruit juice. However, the role of P-gp in these specific DDIs is unclear.[41] Multidrug resistance associated proteins (MDR1 and MDP2) and breast cancer resistance protein (BRCP) may also be involved in the efflux of statins.[9]

Impact of Drug–Drug Interactions on Statin Usage

Many patients receiving statins are elderly, and/or have comorbid conditions such as diabetes, hypertension, and CHD. Treatment of patients at high risk for CVD invariably involves the prescription of multiple medications. As the clinical complexity of patients increases, so does the potential for DDIs. A high proportion of patients are co-prescribed a statin with potentially interacting drugs, and therefore the impact of polypharmacy on the safety profile of statins may be not be fully recognized.[48] It is also important to remember that polypharmacy involves not only prescribed medications but also over-the-counter medications, including vitamins, minerals, herbal remedies and foodstuffs such as grapefruit juice and fresh grapefruit. A recent study examined the concomitant exposure of patients to CYP3A4-metabolized statins and CYP3A4 inhibitors in the UK primary care population. In this analysis, which included a total of 364,574 patients, the majority (93 %) of the patients were prescribed

Figure 3: Reasons Cited for Switching or Stopping Statin Medication Use among Current and Former Statin Users Who Ever Switched or Stopped Taking a Statin Medication



Source: Cohen et al., 2012.[54]

CYP3A4-metabolized statins, most of whom received simvastatin (72 %) and atorvastatin (24 %). Almost one third of (30 %) of patients prescribed a CYP3A4-metabolized statin were also prescribed a CYP3A4 inhibitor (predominantly macrolide antibiotics, or calcium channel blockers).[49]

Many commonly used drugs are moderate-to-potent inhibitors of CYP3A4. These include calcium channel blockers, antifungals, antidepressants, antiretrovirals, immunosuppressants, and macrolide antibiotics.[50] Statin plasma levels may also be decreased as a result of DDIs; this has been reported in CYP inducers such as rifampicin[51] phenytoin[52] and St John's wort.[53] A summary of clinically significant statin DDIs is given in *Table 3*.

The Understanding statin use in America and gaps in education (USAGE) survey assessed the attitudes, beliefs and behavior of current and former statin users.[54] Nearly half of the 10,138 patients surveyed had switched or discontinued statin use, and amongst former statin users, 65 % cited side effects as the primary reason for discontinuation (see *Figure 3*). Muscle-related side effects were reported by 60 % and 25 % of former and current users, respectively. The average respondent used three prescription and/or non-prescription products with the potential to cause DDIs. Of the respondents, 84 % used at least one product with known DDI potential. Despite this, only 38 % of all respondents reported concern with potential DDIs.

The survey revealed important communication gaps regarding DDIs. Only 26 % of respondents spoke to their doctor about the possibility of DDIs. Of the respondents, 42 % who had concerns about DDIs but did not discuss them with their doctor stated that they relied on their pharmacist to identify potential DDIs. In fact, 57 % believed that the pharmacist was responsible for managing this issue, although a pharmacist may not be aware of their complete treatment regimen since patients may use more than one pharmacy. These findings highlight the need for discussion and education about DDIs within the clinical consultation.

Patient Populations at Risk of Drug–Drug Interactions

Certain subgroups of patients have an increased risk for DDIs compared to the general population, and include the elderly and those with comorbidities such as CVD and HIV.

Drug–Drug Interactions Risk in the Elderly

Elderly patients often have multiple medical conditions, such as hypertension, arthritis, heart disease, cancer, and diabetes, which require multiple medications. This raises the potential risk of DDIs and adverse drug reactions. In the US, people over 65 comprise approximately 13 % of the population but are responsible for around 30 % of all prescriptions written.[55] A US study that aimed to estimate the prevalence and patterns of medication use among older adults (including concurrent use) found that 29 % percent of the 3,005 surveyed used at least five prescription medications concurrently. Among prescription medication users, concurrent use of over-the-counter medications was 46 % and concurrent use of dietary supplements was 52 %.[56] In a recent study of concomitant exposure of patients to CYP3A4-metabolized statins and CYP3A4 inhibitors in the UK primary care population, DDI rates were highest in the subgroup aged 65 and over.[49]

Clinical evidence supports the use of statins in elderly patients despite the elevated risk of DDIs.[57] Two recent studies found that pitavastatin and pravastatin are safe and effective in elderly patients with primary hypercholesterolemia or combined dyslipidemia. In one (n=641), pitavastatin showed significantly greater lipid-lowering efficacy over 12 weeks.[58] The other (n=539) was a long term extension to 60 weeks but without an active comparator. Pitavastatin demonstrated long-term safety and efficacy in this patient population.[59]

Drug–Drug Interactions Risk in Patients with Cardiovascular Disease

Statin DDIs may occur with cardiovascular agents such as calcium channel blockers, antiarrhythmics, digoxin and warfarin (see *Table 2*). Calcium-channel blockers are frequently co-prescribed with statins since hypertension and chronic stable angina are a common comorbidity in patients with dyslipidemia. However, certain calcium channel blockers such as verapamil and diltiazem are weak or moderately potent CYP3A4 inhibitors[13] and have been shown to significantly increase serum concentrations of both lovastatin and simvastatin.[60–62] The FDA has introduced dose limitations on verapamil and diltiazem for these two statins.[24] Other statins, such as pitavastatin, have not been shown to significantly interact with calcium channel blockers. In a pharmacokinetics study in healthy volunteers, pitavastatin total (AUC) and peak (Cmax) exposure was only minimally increased by 10 % and 15 %, respectively.[63]

The anti-arrhythmic agent amiodarone is also a potent CYP34A inhibitor. A study of concomitant amiodarone therapy in statin-associated AEs, concluded that although the incidence is relatively rare, clinicians should be vigilant about muscle-related complaints in elderly patients on multiple medications who are being treated with a statin and amiodarone.[64] The dosage of simvastatin is limited when used in combination with amiodarone based on an FDA announcement.[25] The angina therapy ranozaline has also been found to increase plasma concentrations of simvastatin twofold.[65]

Statins have been shown to impact international normalized ratio (INR) when co-administered with warfarin. The interaction is particularly marked with simvastatin, and interactions have also been reported with fluvastatin.[66,67] Recent data suggest that a CYP2C9*3 polymorphism predicts an interaction between warfarin and simvastatin.[68] No DDIs between warfarin and pitavastatin have been demonstrated.[69] Steady-state INR during warfarin treatment did not change significantly when pitavastatin was added to the regimen, while a significant increase was observed when rosuvastatin was added.[70]

Fibrates are used as adjunctive therapy to many forms of hyperlipidemia in combination with statins. However, gemfibrozil increases the blood concentration of rosuvastatin approximately twofold[71] and the concomitant use of gemfibrozil and atorvastatin, lovastatin, pravastatin or simvastatin have been associated with reported cases of rhabdomyolysis.[72–74] The postulated mechanisms for this DDI include inhibition of glucuronidation[75,76] and inhibition of CYP2C8 and OATP1B1.[13] In contrast, fenofibrate has a minimal effect on the metabolic pathways of statins although it is a CYP2C9 inhibitor.[76]

Drug–Drug Interactions Risk in Patients Taking Protease Inhibitors

Protease inhibitors are prescription antiviral drugs targeting HIV or hepatitis C virus (HCV) and are used to treat infections associated with these viruses.[77,78] Antiretroviral therapy has dramatically increased survival for HIV-infected individuals. However, as this population lives longer, CHD has become an important comorbid condition. Furthermore, exposure to protease inhibitors in HIV infection is associated with an increased risk of dyslipidemia owing to increased triglyceride synthesis,[79] increased levels of LDL-C[80] and an increased risk of CHD.[81,82] Patients with HIV have a high risk of statin DDIs, due to the multiple medications often required for treatment.

Protease inhibitors are potent inhibitors of CYP3A4.[83] The simvastatin AUC increases 32-fold when co-administered with the combination of saquinavir/ritonavir, white atorvastatin increases approximately twofold.[83] Pravastatin can be used safely with most protease inhibitors[83] although it may be less effective as a result of induction of enzymes that metabolize pravastatin.[84] When administered with darunavir, however, pravastatin levels may increase up to fivefold[83] depending on polymorphisms within the SLCO1B1 drug transporter gene thereby making it difficult to predict whether a significant interaction will occur or not.[85]

The FDA recently released a communication regarding the risks of co-prescribing statins and protease inhibitors in cases of HIV and HCV infection.[86] Lovastatin, simvastatin, atorvastatin, and rosuvastatin have undergone labeling changes to reflect the risk for interactions with HIV and HCV protease inhibitors. Lovastatin and simvastatin are contraindicated for use with HIV protease inhibitors or HCV protease inhibitors, boceprevir and telaprevir. It is recommended by the FDA that co-administration of atorvastatin with tipranavir/ritonavir or telaprevir should be avoided. The recommended dose of atorvastatin is limited to 20 mg when co-administered with darunavir/ritonavir, fosamprenavir, fosamprenavir/ritonavir, or saquinavir/ritonavir. Caution is advised when co-administering atorvastatin with lopinavir/ritonavir and the dose of atorvastatin should be the lowest necessary. Doses of rosuvastatin should be limited to 10 mg when co-administered with the combinations lopinavir/ritonavir and atazanavir/ritonavir.[86] Pitavastatin in combination with lopinavir/ritonavir, darunavir/ritonavir, and atazanavir has shown no significant DDIs in healthy volunteers, and as such, there are no recommended dose limitations or restrictions when using pitavastatin in combination with HIV protease inhibitors.[9,86–89]

Management Strategies in the Treatment of Dyslipidemia to Reduce the Potential for Drug–Drug Interactions

The use of concomitant medications is widespread in patients with dyslipidemia and correct drug selection and dosing is crucial to avoid DDIs. Knowledge of statin pharmacokinetics can be employed to make better treatment choices. Recent study data indicate that many pharmacy clinical decision-support systems perform less than optimally with respect to identifying well-known DDIs, and that many important statin DDIs are not identified. There is a need for comprehensive pharmacy clinical decision-support software to alert users about clinically important DDIs.[90] Continued efforts should be made at educating clinicians about statin drug-interactions and the impact they have on patient side-effects, adherence, and clinical outcomes.

Summary and Concluding Remarks

The safety and tolerability of statins supports their use as first-line treatment for hyperlipidemia. However, patients who are receiving statin therapy are often taking multiple medications for comorbid conditions, and so are at increased risk of adverse effects because of altered drug metabolism via CYP and hepatic influx and efflux transporters. It is important for patients and clinicians to be aware of the potential for DDIs. Caution should be exercised in prescribing certain statins in combination with CYP3A4 inhibitors. Certain patient subgroups are more at risk of statin DDIs, notably patients with CVD and HIV infection, since some calcium channel blockers and antiretrovirals are CYP3A4 inhibitors. The elderly are also at high risk, due to the high incidence of polypharmacy within this patient population.

As the clinical complexity of patients at high cardiovascular risk and with multiple comorbidities increases, so does the potential for DDIs. Pitavastatin has a distinctive metabolic profile, as a result of which it is marginally metabolized by CYP enzymes, resulting in a reduced risk of DDIs. Its reduced potential for CYP-mediated DDIs has been studied in combination with a wide range of drug classes known to be CYP inhibitors and has been clinically evaluated in patient populations where multiple medications are used, including the elderly, those with high CV risk and patients with diabetes.

Knowledge of statin pharmacokinetics and their mechanisms of DDI allows the clinician to make better therapeutic choices, enabling an individual approach to lipid-lowering regimens based on the patient profile and concomitant medications. ■

1. Corsini A, Bellosta S, Baetta R, et al., New insights into the pharmacodynamic and pharmacokinetic properties of statins, *Pharmacol Ther,* 1999;84:413–28.
2. Baigent C, Blackwell L, Emberson J, et al., Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials, *Lancet*, 2010;376:1670–81.
3. Centers for Disease Control and Prevention, Vital signs: prevalence, treatment, and control of high levels of lowdensity lipoprotein cholesterol--United States, 1999-2002 and 2005-2008, MMWR Morb Mortal Wkly Rep, 60:109–14.
4. Davidson MH, Maki KC, Pearson TA, et al., Results of the National Cholesterol Education (NCEP) Program Evaluation ProjecT Utilizing Novel E-Technology (NEPTUNE) II survey and implications for treatment under the recent NCEP Writing Group recommendations, *Am J Cardiol*, 2005;96:556–63.
5. Ito MK, Dyslipidemia: management using optimal lipid-lowering therapy, *Ann Pharmacother,* 2012;46:1368–81.
6. Hakkarainen KM, Hedna K, Petzold M, et al., Percentage of patients with preventable adverse drug reactions and preventability of adverse drug reactions--a meta-analysis, PLoS One, 2012;7:e33236.
7. Thompson PD, Clarkson P, Karas RH, Statin-associated myopathy, JAMA, 2003;289:1681–90.
8. Staffa JA, Chang J, Green L, Cerivastatin and reports of fatal rhabdomyolysis, *N Engl J Med,* 2002;346:539–40.
9. Corsini A, Ceska R, Drug-drug interactions with statins: will pitavastatin overcome the statins' Achilles' heel?, *Curr Med Res Opin,* 2011;27:1551–62.
10. Kawai Y, Sato-Ishida R, Motoyama A, et al., Place of pitavastatin in the statin armamentarium: promising evidence for a role in diabetes mellitus, *Drug Des Devel Ther,* 2011;5:283–97.
11. Weber W (eds.), Pharmacogenetics, 2008, New York: Oxford University Press.
12. Guengerich FP, Cytochrome P-450 3A4: regulation and role in drug metabolism, *Annu Rev Pharmacol Toxicol,* 1999;39:1–17.
13. Neuvonen PJ, Niemi M, Backman JT, Drug interactions with lipid-lowering drugs: mechanisms and clinical relevance, *Clin Pharmacol Ther,* 2006;80:565–81.
14. Neuvonen PJ, Jalava KM, Itraconazole drastically increases plasma concentrations of lovastatin and lovastatin acid, *Clin Pharmacol Ther,* 1996;60:54–61.
15. Neuvonen PJ, Kantola T, Kivisto KT, Simvastatin but not pravastatin is very susceptible to interaction with the CYP3A4 inhibitor itraconazole, *Clin Pharmacol Ther,* 1998;63:332–41.
16. Cziraky MJ, Willey VJ, McKenney JM, et al., Statin safety: an assessment using an administrative claims database, *Am J Cardiol,* 2006;97:61C–8C.
17. Kantola T, Kivisto KT, Neuvonen PJ, Effect of itraconazole on the pharmacokinetics of atorvastatin, *Clin Pharmacol Ther,* 1998;64:58–65.
18. Martin J, Krum H, Cytochrome P450 drug interactions within the HMG-CoA reductase inhibitor class: are they clinically relevant?, *Drug Saf,* 2003;26:13–21.
19. Kantola T, Kivisto KT, Neuvonen PJ, Grapefruit juice greatly increases serum concentrations of lovastatin and lovastatin acid, *Clin Pharmacol Ther*, 1998;63:397–402.
20. Lown KS, Bailey DG, Fontana RJ, et al., Grapefruit juice increases felodipine oral availability in humans by decreasing intestinal CYP3A protein expression, *J Clin Invest,* 1997;99:2545–53.
21. Lilja JJ, Neuvonen M, Neuvonen PJ, Effects of regular consumption of grapefruit juice on the pharmacokinetics of simvastatin, *Br J Clin Pharmacol,* 2004;58:56–60.
22. FDA, FDA Consumer Update: Grapefruit juice and medicine may not mix. Available at: www.fda.gov/ForConsumers/ConsumerUpdates/ucm292276.htm
23. Bowman L, Armitage J, Bulbulia R, et al., Study of the effectiveness of additional reductions in cholesterol and homocysteine (SEARCH): characteristics of a randomized trial among 12064 myocardial infarction survivors, *Am Heart J,* 2007;154:815–23, 23 e1–6.
24. FDA, FDA Drug Safety Communication: New restrictions, contraindications, and dose limitations for Zocor (simvastatin) to reduce the risk of muscle injury. Available at: www.fda.gov/Drugs/DrugSafety/ucm256581.htm
25. FDA, FDA Drug Safety Communication: Revised dose limitation for Zocor (simvastatin) when taken with amiodarone. Available at: www.fda.gov/Drugs/DrugSafety/ucm283137.htm
26. FDA, FDA Drug Safety Communication: Important safety label changes to cholesterol-lowering statin drugs. Available at: www.fda.gov/Drugs/DrugSafety/ucm293101.htm
27. Olsson AG, McTaggart F, Raza A, Rosuvastatin: a highly effective new HMG-CoA reductase inhibitor, *Cardiovasc Drug Rev,* 2002;20:303–28.
28. White CM, A review of the pharmacologic and pharmacokinetic aspects of rosuvastatin, *J Clin Pharmacol,* 2002;42:963–70.
29. Ando H, Tsuruoka S, Yanagihara H, et al., Effects of grapefruit juice on the pharmacokinetics of pitavastatin and atorvastatin, *Br J Clin Pharmacol,* 2005;60:494–7.
30. Kurihara Y, Douzono T, Kawakita K, et al., A large-scale, long-term, prospective post-marketing surveillance of Pitavastatin (LIVALO tablet) - LIVALO Effectiveness and Safety (LIVES) study, *Jpn Pharmacol Ther,* 2008;36:709–31.
31. Hu MC, Cheung BMY, Tomlinson B, Safety of statins: an update, *Therapeutic Advances in Drug Safety,* 2012;3:133–44.
32. Ieiri I, Higuchi S, Sugiyama Y, Genetic polymorphisms of uptake (OATP1B1, 1B3) and efflux (MRP2, BCRP) transporters: implications for inter-individual differences in the pharmacokinetics and pharmacodynamics of statins and other clinically relevant drugs, *Expert Opin Drug Metab Toxicol,* 2009;5:703–29.
33. Kimoto E, Yoshida K, Balogh LM, et al., Characterization of organic anion transporting polypeptide (OATP) expression and its functional contribution to the uptake of substrates in human hepatocytes, *Mol Pharm,* 2012;(epub ahead of print).
34. Ho RH, Kim RB, Transporters and drug therapy: implications for drug disposition and disease, *Clin Pharmacol Ther,* 2005;78:260–77.
35. Hsiang B, Zhu Y, Wang Z, et al., A novel human hepatic organic anion transporting polypeptide (OATP2). Identification of a liver-specific human organic anion transporting polypeptide and identification of rat and human hydroxymethylglutaryl-CoA reductase inhibitor transporters, *J Biol Chem,* 1999;274:37161–8.
36. Kalliokoski A, Niemi M, Impact of OATP transporters on pharmacokinetics, *Br J Pharmacol,* 2009;158:693–705.
37. Olbricht C, Wanner C, Eisenhauer T, et al., Accumulation of lovastatin, but not pravastatin, in the blood of cyclosporine-treated kidney graft patients after multiple doses, *Clin Pharmacol Ther,* 1997;62:311–21.
38. Simonson SG, Raza A, Martin PD, et al., Rosuvastatin pharmacokinetics in heart transplant recipients administered an antirejection regimen including cyclosporine, *Clin Pharmacol Ther,* 2004;76:167–77.
39. Hasunuma TN, M; Yachi, T et al The drug-drug interactions of pitavastatin (NK-104), a novel HMG-CoA reductase inhibitor and cyclosporine, *J Clin Ther Med,* 2003;19:381.
40. Link E, Parish S, Armitage J, et al., SLCO1B1 variants and statin-induced myopathy--a genomewide study, *N Engl J Med,* 2008;359:789–99.
41. Holtzman CW, Wiggins BS, Spinler SA, Role of P-glycoprotein in statin drug interactions, *Pharmacotherapy*, 2006;26:1601–7.
42. Chen C, Mireles RJ, Campbell SD, et al., Differential interaction of 3-hydroxy-3-methylglutaryl-coa reductase inhibitors with ABCB1, ABCC2, and OATP1B1, *Drug Metab Dispos,* 2005;33:537–46.
43. Dorajoo R, Pereira BP, Yu Z, et al., Role of multi-drug resistance-associated protein-1 transporter in statin-induced myopathy, *Life Sci,* 2008;82:823–30.
44. Fujino H, Yamada I, Shimada S, et al., Metabolic fate of pitavastatin, a new inhibitor of HMG-CoA reductase--effect of cMOAT deficiency on hepatobiliary excretion in rats and of mdr1a/b gene disruption on tissue distribution in mice, *Drug Metab Pharmacokinet,* 2002;17:449–56.
45. Kajinami K, Takekoshi N, Saito Y, Pitavastatin: efficacy and safety profiles of a novel synthetic HMG-CoA reductase inhibitor, *Cardiovasc Drug Rev,* 2003;21:199–215.
46. Sakaeda T, Fujino H, Komoto C, et al., Effects of acid and lactone forms of eight HMG-CoA reductase inhibitors on CYP-mediated metabolism and MDR1-mediated transport, *Pharm Res,* 2006;23:506–12.
47. Boyd RA, Stern RH, Stewart BH, et al., Atorvastatin coadministration may increase digoxin concentrations by inhibition of intestinal P-glycoprotein-mediated secretion, *J Clin Pharmacol,* 2000;40:91–8.
48. P, Morris L, Kempf J, et al., The coprescription of contraindicated drugs with statins: continuing potential for increased risk of adverse events, *Am J Ther,* 2007;14:30–40.
49. Bakhai A, Rigney U, Hollis S, et al., Co-administration of statins with cytochrome P450 3A4 inhibitors in a UK primary care population, *Pharmacoepidemiol Drug Saf,* 2012;21:485–93.
50. Zhou S, Yung Chan S, Cher Goh B, et al., Mechanism-based inhibition of cytochrome P450 3A4 by therapeutic drugs, Clin Pharmacokinet, 2005;44:279–304.
51. Kyrklund C, Backman JT, Kivisto KT, et al., Rifampin greatly reduces plasma simvastatin and simvastatin acid concentrations, *Clin Pharmacol Ther,* 2000;68:592–7.
52. Murphy MJ, Dominiczak MH, Efficacy of statin therapy: possible effect of phenytoin, *Postgrad Med J,* 1999;75:359–60.
53. Sugimoto K, Ohmori M, Tsuruoka S, et al., Different effects of St John's wort on the pharmacokinetics of simvastatin and pravastatin, *Clin Pharmacol Ther,* 2001;70:518–24.
54. Cohen JD, Brinton EA, Ito MK, et al., Understanding Statin Use in America and Gaps in Patient Education (USAGE): An internet-based survey of 10,138 current and former statin users, *J Clin Lipidol,* 2012;*6*:208–15.
55. Williams CM, Using medications appropriately in older adults, *Am Fam Physician,* 2002;66:1917–24.
56. Qato DM, Alexander GC, Conti RM, et al., Use of prescription and over-the-counter medications and dietary supplements among older adults in the United States, *JAMA*, 2008;300:2867–78.
57. Maroo BP, Lavie CJ, Milani RV, Efficacy and safety of intensive statin therapy in the elderly, *Am J Geriatr Cardiol,* 2008;17:92–100.
58. Stender S, Budinski D, Gosho M, et al., Pitavastatin shows greater lipid-lowering efficacy over 12 weeks than pravastatin in elderly patients with primary hypercholesterolaemia or combined (mixed) dyslipidaemia, *Eur J Prev Cardiol,* 2012;(epub ahead of print).
59. Stender S, Budinski D, Hounslow N, Pitavastatin demonstrates long-term efficacy, safety and tolerability in elderly patients with primary hypercholesterolaemia or combined (mixed) dyslipidaemia, *Eur J Prev Cardiol,* 2012;(epub ahead of print).
60. Azie NE, Brater DC, Becker PA, et al., The interaction of diltiazem with lovastatin and pravastatin, *Clin Pharmacol Ther*, 1998;64:369–77.
61. Mousa O, Brater DC, Sunblad KJ, et al., The interaction of diltiazem with simvastatin, *Clin Pharmacol Ther,* 2000;67:267–74.
62. Tobert JA, Vega JM, Dobrinska M, et al., Calcium channel blocker-simvastatin interaction, *Clin Pharmacol Ther,* 1999;65:583–5.
63. Morgan RE, Campbell SE, Sponseller CA, et al., A drug-drug interaction study of steady-state pitavastatin and diltiazem in healthy adult volunteers, presented at American College of Clinical Pharmacy (ACCP) 2012, September 23–25, 2012, San Diego, CA, US, poster.
64. Alsheikh-Ali AA, Karas RH, Adverse events with concomitant amiodarone and statin therapy, Prev Cardiol, 2005;8:95–7.
65. Chaitman BR, Ranolazine for the treatment of chronic angina and potential use in other cardiovascular conditions, *Circulation*, 2006;113:2462–72.
66. Westergren T, Johansson P, Molden E, Probable warfarin-simvastatin interaction, *Ann Pharmacother,* 2007;41:1292–5.
67. Andrus MR, Oral anticoagulant drug interactions with statins: case report of fluvastatin and review of the literature, *Pharmacotherapy*, 2004;24:285–90.
68. Andersson ML, Eliasson E, Lindh JD, A clinically significant interaction between warfarin and simvastatin is unique to carriers of the CYP2C9*3 allele, *Pharmacogenomics*, 2012;13:757–62.
69. Inagaki Y, Hunt T, Arana B, et al., Drug-drug interaction study to assess the effects of multiple-dose pitavastatin on steady-state warfarin in healthy adult volunteers, *J Clin Pharmacol,* 2011;51:1302–9.
70. Yu CY, Campbell SE, Zhu B, et al., Effect of pitavastatin vs. rosuvastatin on international normalized ratio in healthy volunteers on steady-state warfarin, *Curr Med Res Opin*, 2012;28:187–94.
71. Schneck DW, Birmingham BK, Zalikowski JA, et al., The effect of gemfibrozil on the pharmacokinetics of rosuvastatin, *Clin Pharmacol Ther,* 2004;75:455–63.
72. Omar MA, Wilson JP, FDA adverse event reports on statin-associated rhabdomyolysis, *Ann Pharmacother,* 2002;36:288–95.
73. Pierce LR, Wysowski DK, Gross TP, Myopathy and rhabdomyolysis associated with lovastatin-gemfibrozil combination therapy, *JAMA*, 1990;264:71–5.
74. Duell PB, Connor WE, Illingworth DR, Rhabdomyolysis after taking atorvastatin with gemfibrozil, *Am J Cardiol,* 1998;81:368–9.
75. Prueksaritanont T, Zhao JJ, Ma B, et al., Mechanistic studies on metabolic interactions between gemfibrozil and statins, *J Pharmacol Exp Ther,* 2002;301:1042–51.
76. Prueksaritanont T, Tang C, Qiu Y, et al., Effects of fibrates on metabolism of statins in human hepatocytes, *Drug Metab Dispos,* 2002;30:1280–7.
77. Flexner C, HIV-protease inhibitors, *N Engl J Med,* 1998;338:1281–92.
78. Alkhouri N, Zein NN, Protease inhibitors: silver bullets for chronic hepatitis C infection?, *Cleve Clin J Med,* 2012;79:213–22.
79. Lenhard JM, Croom DK, Weiel JE, et al., HIV protease inhibitors stimulate hepatic triglyceride synthesis, *Arterioscler Thromb Vasc Biol,* 2000;20:2625–9.
80. Montes ML, Pulido F, Barros C, et al., Lipid disorders in antiretroviral-naive patients treated with lopinavir/ritonavir-based HAART: frequency, characterization and risk factors, *J Antimicrob Chemother,* 2005;55:800–4.
81. Friis-Moller N, Reiss P, Sabin CA, et al., Class of antiretroviral drugs and the risk of myocardial infarction, *N Engl J Med,* 2007;356:1723–35.
82. Grinspoon SK, Grunfeld C, Kotler DP, et al., State of the science conference: Initiative to decrease cardiovascular risk and increase quality of care for patients living with HIV/AIDS: executive summary, *Circulation*, 2008;118:198–210.
83. Fichtenbaum CJ, Gerber JG, Rosenkranz SL, et al., Pharmacokinetic interactions between protease inhibitors and statins in HIV seronegative volunteers: ACTG Study A5047, *AIDS*, 2002;16:569–77.
84. Aberg JA, Rosenkranz SL, Fichtenbaum CJ, et al., Pharmacokinetic interaction between nelfinavir and pravastatin in HIV-seronegative volunteers: ACTG Study A5108, *AIDS*, 2006;20:725–9.

85. Influence of SLCO1B1 polymorphisms on pharmacokinetic (PK) variability in the drug-drug interaction between darunavir/ritonavir (DRV/r) and pravastatin (PRA), 50th Interscience Conference on Antimicrobials and Chemotherapy, 2010.
86. FDA, FDA Drug Safety Communication: Interactions between certain HIV or hepatitis C drugs and cholesterol-lowering statin drugs can increase the risk of muscle injury. Available at: www.fda.gov/Drugs/DrugSafety/ucm293877.htm
87. Morgan RE, Campbell SE, Suehira K, et al., Effects of steady-state lopinavir/ritonavir on the pharmacokinetics of pitavastatin in healthy adult volunteers, *J Acquir Immune Defic Syndr,* 2012;60:158–64.
88. Yu CY, Campbell SE, Sponseller CA, et al., *Steady-state pharmacokinetic interactions of darunavir/ritonavir with pitavastatin in healthy adult volunteers. International AIDS Conference 2012,* July 22-27, 2012, Washington DC, US, poster.
89. Kowa, LIVALO (pitavastatin) Tablet [prescribing information], Montgomery, AL, US: Kowa Pharmaceuticals America, Inc, version 5.1, October 2012. Available at: www.kowapharma.com/documents/LIVALO_PI_CURRENT.pdf
90. Saverno KR, Hines LE, Warholak TL, et al., Ability of pharmacy clinical decision-support software to alert users about clinically important drug-drug interactions, *J Am Med Inform Assoc,* 2011;18:32–7.
91. Williams D, Feely J, Pharmacokinetic-pharmacodynamic drug interactions with HMG-CoA reductase inhibitors, *Clin Pharmacokinet,* 2002;41:343–70.
92. Mazzu AL, Lasseter KC, Shamblen EC, et al., Itraconazole alters the pharmacokinetics of atorvastatin to a greater extent than either cerivastatin or pravastatin, *Clin Pharmacol Ther,* 2000;68:391–400.
93. Tufan A, Dede DS, Cavus S, et al., Rhabdomyolysis in a patient treated with colchicine and atorvastatin, *Ann Pharmacother,* 2006;40:1466–9.
94. Magee CN, Medani SA, Leavey SF, et al., Severe rhabdomyolysis as a consequence of the interaction of fusidic acid and atorvastatin, *Am J Kidney Dis,* 2010;56:e11–5.
95. Burtenshaw AJ, Sellors G, Downing R, Presumed interaction of fusidic acid with simvastatin, 2008;63:656–8.
96. Kantola T, Kivisto KT, Neuvonen PJ, Erythromycin and verapamil considerably increase serum simvastatin and simvastatin acid concentrations, *Clin Pharmacol Ther,* 1998;64:177–82.
97. Jacobson TA, Comparative pharmacokinetic interaction profiles of pravastatin, simvastatin, and atorvastatin when coadministered with cytochrome P450 inhibitors, *Am J Cardiol,* 2004;94:1140–6.
98. Cenedella RJ, Beware of combining erythromycin with a statin, *J Am Osteopath Assoc,* 2003;103:117.
99. Skrabal MZ, Stading JA, Monaghan MS, Rhabdomyolysis associated with simvastatin-nefazodone therapy, *South Med J,* 2003;96:1034–5.
100. Thompson M, Samuels S, Rhabdomyolysis with simvastatin and nefazodone, *Am J Psychiatry,* 2002;159:1607.
101. Kosoglou T, Zhu Y, Statkevich P, et al., Assessment of potential pharmacokinetic interactions of ezetimibe/simvastatin and extended-release niacin tablets in healthy subjects, *Eur J Clin Pharmacol,* 2011;67:483–92.
102. Kiser JJ, Gerber JG, Predhomme JA, et al., Drug/Drug interaction between lopinavir/ritonavir and rosuvastatin in healthy volunteers, *J Acquir Immune Defic Syndr,* 2008;47:570–8.
103. Backman JT, Luurila H, Neuvonen M, et al., Rifampin markedly decreases and gemfibrozil increases the plasma concentrations of atorvastatin and its metabolites, *Clin Pharmacol Ther,* 2005;78:154–67.
104. Seithel A, Eberl S, Singer K, et al., The influence of macrolide antibiotics on the uptake of organic anions and drugs mediated by OATP1B1 and OATP1B3, *Drug Metab Dispos,* 2007;35:779–86.
105. Teng R, Mitchell PD, Butler KA, Pharmacokinetic interaction studies of co-administration of ticagrelor and atorvastatin or simvastatin in healthy volunteers, *Eur J Clin Pharmacol,* 2012;(epub ahead of print).
106. Lin JC, Ito MK, A drug interaction between troglitazone and simvastatin, *Diabetes Care,* 1999;22:2104–6.
107. Mackay JW, Fenech ME, Myint KS, Acute rhabdomyolysis caused by combination therapy with atorvastatin and warfarin, *Br J Hosp Med (Lond),* 2012;73:106–7.