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PERSPECTIVES IN CLINICAL PHARMACOLOGY

Drug interactions with lipid-lowering drugs: Mechanisms and clinical relevance

Lipid-lowering drugs, especially 3-hydroxy-3-methylglutaryl–coenzyme A inhibitors (statins), are widely used in the treatment and prevention of atherosclerotic disease. The benefits of statins are well documented. However, lipid-lowering drugs may cause myopathy, even rhabdomyolysis, the risk of which is increased by certain interactions. Simvastatin, lovastatin, and atorvastatin are metabolized by cytochrome P450 (CYP) 3A4 (simvastatin acid is also metabolized by CYP2C8); their plasma concentrations and risk of myotoxicity are greatly increased by strong inhibitors of CYP3A4 (eg, itraconazole and ritonavir). Weak or moderately potent CYP3A4 inhibitors (eg, verapamil and diltiazem) can be used cautiously with small doses of CYP3A4-dependent statins. Cerivastatin is metabolized by CYP2C8 and CYP3A4, and fluvastatin is metabolized by CYP2C9. The exposure to fluvastatin is increased by less than 2-fold by inhibitors of CYP2C9. Pravastatin, rosuvastatin, and pitavastatin are excreted mainly unchanged, and their plasma concentrations are not significantly increased by pure CYP3A4 inhibitors. Cyclosporine (INN, ciclosporin) inhibits CYP3A4, P-glycoprotein (multidrug resistance protein 1), organic anion transporting polypeptide 1B1 (OATP1B1), and some other hepatic uptake transporters. Gemfibrozil and its glucuronide inhibit CYP2C8 and OATP1B1. These effects of cyclosporine and gemfibrozil explain the increased plasma statin concentrations and, together with pharmacodynamic factors, the increased risk of myotoxicity when coadministered with statins. Inhibitors of OATP1B1 may decrease the benefit/risk ratio of statins by interfering with their entry into hepatocytes, the site of action. Lipid-lowering drugs can be involved also in other interactions, including those between enzyme inducers and CYP3A4 substrate statins, as well as those between gemfibrozil and CYP2C8 substrate antidiabetics. Knowledge of the pharmacokinetic and pharmacodynamic properties of lipid-lowering drugs and their interaction mechanisms helps to avoid adverse interactions, without compromising therapeutic benefits. (Clin Pharmacol Ther 2006;80:565-81.)

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Table I. Pharmacokinetic properties of statins

	Simvastatin	*Lovastatin*	*Atorvastatin*	*Fluvastatin*
Lactone prodrug	Yes	Yes	No	No
Lipophilicity of lactone or acid forms*	++++	++++	+++	+++
Absorption (%)	60-85	30	30	98
Bioavailability (%)	<5	5	12	30
Hepatic extraction (%)	≥80	≥70	70	≥70
Protein binding (%)	>95	>98	>98	>98
Half-life (h)	2-5	2-5	7-20	1-3
Metabolism†	+++	+++	+++	+++
Metabolizing CYP enzymes (of lactone or acid form)	3A4 2C8	3A4 2C8?	3A4 (2C8)	2C9
Substrate of OATP1B1‡	+	+	+	+
Substrate of BCRP‡	?	?	+	+
Substrate of MDR1‡	+, acid	+	+	?
Inhibitor of CYP3A4‡§	+	+	+	+
Inhibitor of CYP2C9‡	−	−	−	+
Inhibitor of MDR1‡§	+	+	+	−
Inhibitor of BCRP‡	+	?	+	+

A question mark indicates not known or uncertain, and parentheses indicate minor significance.
OATP, Organic anion transporting polypeptide; BCRP, breast cancer resistance protein; MDR, multidrug resistance protein (P-glycoprotein).
*Five plus signs indicate most lipophilic, and 1 plus sign indicates most hydrophilic.
†Three plus signs indicate extensively metabolized, and 1 plus sign indicates limited metabolism, eliminated mainly unchanged.
‡A plus sign indicates yes, and a minus sign indicates no.
§The lactone forms of statins have much lower 50% inhibitory concentration or inhibition constant values than their acid forms.[10,137]

Lipid-lowering drugs, particularly inhibitors of 3-hydroxy-3-methylglutaryl–coenzyme A (HMG-CoA) reductase (statins), are widely used to reduce the risk of cardiovascular events and death. In general, the currently used statins are well tolerated and have a good safety profile.[1,2] In addition, fibrates, cholesterol absorption inhibitors such as ezetimibe, and bile acid sequestrants are used as lipid-lowering therapeutics in certain clinical conditions.

It was noted already nearly 20 years ago that pharmacologically different drugs—for example, cyclosporine (INN, ciclosporin), erythromycin, and gemfibrozil—increase the risk of rhabdomyolysis when administered with lovastatin.[3-5] However, the mechanisms of statin interactions remained largely obscure until the roles of various cytochrome P450 (CYP) enzymes, above all, that of CYP3A4,[6-8] and of membrane transporters in the pharmacokinetics and interactions of different statins were recognized.[8-10]

Cerivastatin caused hundreds of cases of rhabdomyolysis before its withdrawal from the market in August 2001. Many of these cases occurred in patients using gemfibrozil and cerivastatin concomitantly.[11] Recognition of the pharmacokinetic component in the gemfibrozil-cerivastatin interaction has helped to reduce the risk of myotoxicity in lipid-lowering therapy. Muscle toxicity (myopathy) is a potential adverse effect of all statins and fibrates, but the most severe form of myotoxicity, rhabdomyolysis, is very rare with currently used statins.[2,12] High statin doses, as well as certain pharmacodynamic and pharmacokinetic drug interactions, particularly those leading to high statin concentrations in the peripheral blood and muscle cells, increase the risk of muscle toxicity. Although the effects of interacting drugs on the metabolism and transport of different statins have been studied extensively during recent years, the significance of some potential interaction mechanisms is still unclear.

In this review we summarize the mechanisms and clinical relevance of drug interactions involving lipid-lowering drugs, highlighting recent advances in understanding the pharmacokinetic mechanisms. In particular, the emerging status of membrane transporters in these drug-drug interactions is discussed. Beneficial interactions between different lipid-lowering agents are beyond the scope of this report.

PHARMACOKINETICS OF STATINS

Many interactions involving statins are based on a pharmacokinetic mechanism, and therefore knowledge about their pharmacokinetic characteristics is essential for understanding their interactions. The passive membrane permeability of statins increases along with their lipophilicity.[13,14] Thus lipophilic statin forms are more

Cerivastatin	*Pravastatin*	*Rosuvastatin*	*Pitavastatin*	*Reference*
No	No	No	No	
+++++	+	++	++++	10, 20, 137
>98	35	50	80	13, 25, 47, 48, 77
60	18	20	60	13, 25, 47, 48, 77
?	45	63	?	13, 25, 47, 48, 77
>99	50	90	96	13, 25, 47, 48, 77
1-3	1-3	20	10-13	13, 25, 47, 48, 77
+++	+	+	++	13, 25, 47, 48, 77
2C8 3A4	(3A4)	2C9 (2C19)	(2C9)	25, 43, 44, 47, 48, 77
+	+	+	+	19, 22, 26
+	+	+	+	84
+	+	−	+	10, 21-24
+	−	+	−	20, 137
−	−	(+)	−	20, 139
+	−	−	+	10, 20, 138
+	−	+	+	84

readily distributed into peripheral tissues than hydrophilic statins, such as pravastatin.[15] Simvastatin and lovastatin are administered as very lipophilic lactone prodrugs, whereas other statins are given as active acid forms (Table I). However, in the body significant amounts of most statins are converted to their lactone form,[16-19] which is more lipophilic than the corresponding acid form. Both acid and lactone forms can be important in statin interactions.[18-21]

The oral bioavailability of simvastatin and lovastatin is low (≤5%), largely as a result of their CYP3A-mediated first-pass metabolism in the intestinal wall and liver. The interplay of CYP3A4 and P-glycoprotein (ie, multidrug resistance protein 1 [MDR1], *ABCB1*) in the intestinal wall may contribute to the high presystemic extraction of these statins. The bioavailability of other statins ranges from 12% (atorvastatin) to more than 60% (pitavastatin) (Table I). The interindividual variation of the area under the plasma concentration–time curve (AUC) of different statins varies considerably; for example, the AUC of pravastatin ranges by more than 10-fold, even when studied in young healthy adults. At least simvastatin acid, lovastatin acid, cerivastatin, atorvastatin, and pitavastatin are substrates of MDR1.[10,21-23] Statins can also be substrates of other efflux or uptake transporters expressed in the intestine.[24] Accordingly, variable activity of CYP3A4 and transporter proteins, as well as the contents and pH of the gastrointestinal tract, can cause variability in the bioavailability of statins.[13,25]

Plasma protein binding (Table I) of the lipophilic statins is high (>95%) compared with that of rosuvastatin (90%) or pravastatin (50%).[13,25] However, displacement of statins from plasma proteins is not known to mediate clinically significant drug interactions.

The lipophilic statins are extensively metabolized, principally by CYP enzymes, whereas pravastatin, rosuvastatin, and pitavastatin are excreted mainly unchanged.[25] The elimination half-life of pravastatin, cerivastatin, fluvastatin, lovastatin, and simvastatin is short, which explains their better cholesterol-lowering efficacy when taken in the evening, because steroid synthesis is more active during the night. Atorvastatin and rosuvastatin have longer half-lives, about 10 and 20 hours, respectively. As a result of active metabolites of atorvastatin, its clinically relevant half-life (of HMG-CoA reductase inhibition) is similar to that of rosuvastatin.[16,25]

Hepatic transport mechanisms. The hydrophilic pravastatin and rosuvastatin have only a limited access to nonhepatic cells because of the slow passive diffusion of these statins across cell membranes. However, they also are avidly taken into hepatocytes, the site of statin action, by active uptake transporters, among which organic anion transporting polypeptide (OATP)

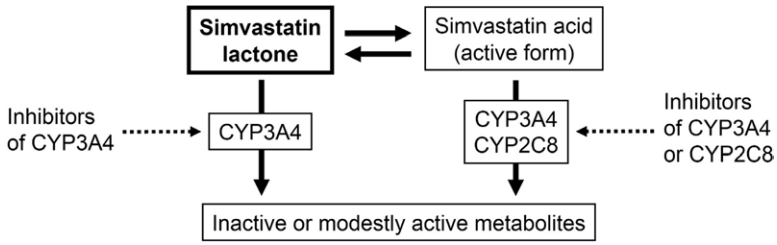

Fig 1. Metabolism of simvastatin lactone and acid by CYP enzymes.

1B1 (also known as OATP-C, OATP2, and LST-1) seems to be the most important (Table I).[9,22,26] Other hepatic uptake transporters that can transport rosuvastatin, for example, are OATP1B3, OATP2B1, OATP1A2, and sodium-dependent taurocholate cotransporting polypeptide (NTCP).[26] Accordingly, for pravastatin and rosuvastatin, the concentrations to cause a 50% reduction (IC_{50} values) in HMG-CoA reductase activity in nonhepatic cells are more than 100 times higher than in hepatocyte assays, whereas the IC_{50} values of lipophilic statins are of the same magnitude in both nonhepatic and hepatic cell-based assays.[27,28]

OATP1B1 facilitates the hepatic uptake of most statins, but its significance seems to be greatest for hydrophilic statins, such as pravastatin and rosuvastatin.[21,26,29] Given that all statins are cleared mainly by the liver, their active hepatic uptake, metabolism, and biliary excretion can be important mechanisms regulating their total clearance.[26,29] Efflux transporters localized on the canalicular membrane of the hepatocyte, such as MDR1, multidrug resistance associated protein 2 (MRP 2), breast cancer resistance protein (BCRP), and bile acid export pump (BSEP, *ABCB11*), are the final step in the transport of many drugs from the portal circulation into bile. Interference with the function of these hepatic uptake and efflux transporters could be a mechanism decreasing statin elimination.[21,29-31]

Pharmacogenetic factors—for example, polymorphisms of *SLCO1B1* (encoding OATP1B1) and *ABCC2* (encoding MRP2)—can cause intersubject variability in plasma statin levels.[32-40] Transporter polymorphisms may also explain interindividual differences in susceptibility to drug interactions. OATP1B1 is important not only in the elimination of many statins but also in their entry to the intracellular site of action in hepatocytes. Accordingly, low activity of OATP1B1 may decrease the cholesterol-lowering effect of statins (eg, pravastatin),[41,42] despite increased statin plasma concentrations and risk of muscle toxicity.

Metabolism of statins. CYP3A4 is important to the elimination of lovastatin, simvastatin, and atorvastatin. Lovastatin and simvastatin lactones are oxidized by CYP3A4 (and less by CYP3A5) in the intestinal wall and liver to several metabolites, or alternatively, the lactones are hydrolyzed by esterases and paraoxonases to their active open acids (lovastatin acid and simvastatin acid).[6,43] Simvastatin acid and, presumably, also lovastatin acid are further metabolized by CYP3A4 and CYP2C8 (Fig 1).[44] CYP3A4 is also important to the biotransformation of atorvastatin and its lactone.[16,19,45,46] The presystemic metabolism of atorvastatin is less significant than that of simvastatin or lovastatin. Cerivastatin is extensively metabolized by both CYP2C8 and CYP3A4.[47]

Fluvastatin, pravastatin, rosuvastatin, and pitavastatin are not significantly metabolized by CYP3A4.[25,48] Fluvastatin is biotransformed extensively by CYP2C9, whereas pravastatin, rosuvastatin, and pitavastatin are excreted, largely as parent compounds, into the feces via bile and into the urine. Pravastatin is partially degraded in the stomach and metabolized by non-CYP enzymes. About 10% of rosuvastatin is metabolized, mainly by CYP2C9.

The lactone forms of all statins are metabolized by CYP enzymes more rapidly than their acid forms.[21,49] In addition to oxidation by CYPs, statin acids can be converted to their lactone forms by a coenzyme A–dependent mechanism. In humans, unlike in rats and dogs, uridine diphosphate–glucuronosyltransferase (UGT)–mediated lactonization of statin acids seems to have only a minor contribution to their total clearance. In human liver microsomes the intrinsic clearance (Cl_{int}) of, for example, simvastatin acid by UGT-mediated metabolism (0.4 $\mu L \cdot min^{-1} \cdot mg^{-1}$ protein)[50] is much smaller than that by CYP-mediated metabolism (28 $\mu L \cdot min^{-1} \cdot mg^{-1}$ protein)[49] or the Cl_{int} of simvastatin lactone by CYP-mediated metabolism (1959 $\mu L \cdot min^{-1} \cdot mg^{-1}$ protein, mainly by CYP3A4).[49]

STATIN INTERACTIONS MEDIATED BY CYP ENZYMES

Effect of CYP3A4 inhibitors. CYP3A4 inhibitors reduce the presystemic metabolism of simvastatin and lovastatin more than the systemic metabolism of these drugs, increasing plasma concentrations (peak concentration and AUC > half-life) of both their lactone and acid forms but decreasing the formation of CYP3A4-dependent inactive (or less active) metabolites (Fig 1). Plasma HMG-CoA reductase inhibition increases somewhat less than the plasma concentration of simvastatin acid or lovastatin acid.[51,52] In addition, the further metabolism of these statin acids is reduced by CYP3A4 inhibitors.

Concomitant use of any potent inhibitor of CYP3A4 with simvastatin, lovastatin, or atorvastatin increases the exposure to these statins (Table II). The strong CYP3A4 inhibitors ritonavir, itraconazole, and ketoconazole can greatly increase, by up to about 20-fold, the AUC of lovastatin[7,53] and simvastatin,[45,51,54] as well as their active acid forms. Itraconazole, which probably has no significant effect on other drug-metabolizing CYP forms, has increased the AUC of atorvastatin by about 3-fold,[16,45,55] whereas the AUC values of cerivastatin,[17,55] fluvastatin,[53] pravastatin,[45,51,55] and rosuvastatin[56] are increased not at all, or by less than 1.5-fold, by itraconazole (Table II).

Certain macrolide antibiotics and calcium channel blockers are relatively potent CYP3A4 inhibitors at clinically relevant doses. Erythromycin, clarithromycin, and telithromycin have increased the AUC of simvastatin acid by about 4- to 12-fold, with the effect of clarithromycin and telithromycin being stronger than that of erythromycin.[45,57,58] Erythromycin and clarithromycin have increased the exposure to atorvastatin by about 1.5- to 4-fold,[59,60] whereas erythromycin has increased the AUC of cerivastatin somewhat less (Table II).[61] Clarithromycin has doubled the AUC of pravastatin, possibly by inhibiting membrane transporters involved in its pharmacokinetics,[45] but erythromycin has slightly decreased, if anything, the AUC of rosuvastatin.[62] Of the calcium channel–blocking agents, verapamil and diltiazem have increased, depending on their doses, the AUC of simvastatin acid and lovastatin acid by about 3- to 8-fold.[57,63-65] Mibefradil, which in combination with simvastatin caused several cases of rhabdomyolysis before its withdrawal from clinical use, increased the AUC of simvastatin acid by 5- to 10-fold[66] and that of atorvastatin by 3- to 4-fold,[45] without a significant effect on pravastatin AUC. It should be noted, however, that most of the currently used calcium channel blockers, except for diltiazem and verapamil, are not significant inhibitors of CYP3A in vivo in humans.

Considerable interindividual differences exist in the extent of CYP3A4 inhibitor–statin interactions, for example, as a result of the doses of inhibitors and statins used, as well as pharmacogenetic factors. Therefore some individuals may be particularly susceptible to the clinical consequences of these interactions. Inhibitors of CYP3A4 can also increase the cholesterol-lowering efficacy of the CYP3A4-dependent statins; for example, diltiazem increases the efficacy of simvastatin.[65,67] However, systemic use of any potent CYP3A4 inhibitor with simvastatin, lovastatin, or atorvastatin carries an increased risk of muscle toxicity, particularly if high statin doses are used. Cases of rhabdomyolysis have been reported with the combined use of simvastatin, lovastatin, or atorvastatin with inhibitors of CYP3A, such as mibefradil, ritonavir, cyclosporine, itraconazole, fluconazole, clarithromycin, erythromycin, nefazodone, danazol, amiodarone, diltiazem, and verapamil.[2,68-76]

In clinical trial participants receiving 20 to 80 mg of simvastatin daily, the incidence of myopathy was 10 times higher in those who also received verapamil (0.63% [4/635 patients]) than in those who did not receive verapamil (0.061% [13/21,224 patients]).[77] Myopathy occurs in about 1% of patients taking 40 or 80 mg simvastatin with verapamil or taking 80 mg simvastatin with diltiazem. In a trial with 80 mg simvastatin and amiodarone the incidence of myopathy was 6%.[77] The incidence of myopathy could be even higher if lovastatin or simvastatin is used (at usual doses) concomitantly with the most potent CYP3A4 inhibitors, such as itraconazole. Therefore their concomitant use should be avoided. On the other hand, weak or moderately potent CYP3A inhibitors, such as verapamil and diltiazem, can probably be used rather safely with lovastatin, simvastatin, and atorvastatin if the statin doses are low and the patients are carefully monitored.

It is reasonable to assume that the interaction of different CYP3A4-inhibiting drugs and chemicals with statins can be additive. Thus, for example, clarithromycin may increase the effect of verapamil and diltiazem on simvastatin or lovastatin. The interaction risk also increases if inhibitors of both CYP3A4 and OATP1B1 are coadministered with their joint substrates (eg, simvastatin).[78]

Selective inhibitors of CYP3A4 do not have a significant pharmacokinetic interaction with pravastatin, fluvastatin, rosuvastatin, or pitavastatin, because CYP3A4 has no appreciable role in their elimination.[25,45,51,53] Cyclosporine increases the plasma concentrations of pravastatin,

Table II. Effect of some CYP or membrane transporter inhibitors (fold increase) and inducers (percentage reduction) on AUC

	Simvastatin	*Lovastatin*	*Atorvastatin*	*Fluvastatin**
Fold increase of statin AUC by CYP3A4 inhibitors				
Itraconazole	5-20	5-20	2-4	≈
Erythromycin, clarithromycin	4-12	(4-12)	1.5-5	≈
Verapamil, diltiazem	3-8	3-8	?	(≈)
Fold increase of statin AUC by				
Cyclosporine	6-8	5-20	6-15	2-4
Gemfibrozil	2-3	2-3	<1.5	≈
Grapefruit juice	2-10	2-10	1-4	(≈)
Percentage decrease of statin AUC by potent inducers				
Rifampin, carbamazepine	70-95	(70-95)	60-90	50

Magnitude of effects is expressed as fold increase of the statin AUC by various inhibitors or as percentage reduction of the statin AUC by inducers. The doses of the inhibitors and inducers, as well as the pharmacogenetic factors, can affect the extent of interaction in an individual patient. An "approximately equal to" sign indicates practically unchanged, parentheses indicate estimation based on the pharmacokinetic properties of the statin, and a question mark indicates not known or estimated.
AUC, Area under plasma statin concentration–time curve.
*Inhibitors of CYP2C9 increase the AUC of fluvastatin and rosuvastatin by less than 2-fold.[94,95]

rosuvastatin, and pitavastatin, but these interactions are mediated by inhibition of OATP1B1 or other transporters and do not involve CYP3A4.[79-84] Of note is that many other drugs (eg, some human immunodeficiency virus protease inhibitors and clarithromycin) can inhibit, in addition to CYP enzymes, membrane transporters as well.[84]

Grapefruit juice can greatly increase the AUC of lovastatin and simvastatin, as well as their active acid forms,[52,85,86] by inhibiting their CYP3A4-mediated metabolism in the intestinal wall (Table II). Grapefruit juice can also markedly increase the AUC of atorvastatin and its lactone, unlike that of pravastatin or pitavastatin.[87-89] The extent of these interactions depends on the amount of grapefruit juice and on the time interval between grapefruit juice and statin intake. A glassful (200 mL) of grapefruit juice taken daily together with simvastatin increased the AUC of simvastatin acid by 3- to 4-fold and even by 6-fold in some subjects.[85] Daily consumption of large amounts of grapefruit juice can increase the AUC of simvastatin acid and lovastatin acid by even more than 10-fold.[52,86] On the other hand, a single glassful of grapefruit juice taken in the morning seems to have only minor effects on the pharmacokinetics of lovastatin or simvastatin taken in the evening.[90,91] However, because consumption of grapefruit juice with high doses of simvastatin or lovastatin may even cause rhabdomyolysis in some rare cases, care is recommended, particularly in the use of large amounts of grapefruit juice with the CYP3A4-dependent statins.[92,93]

Effect of CYP2C9 and CYP2C8 inhibitors. Potent inhibitors of CYP2C9 can increase plasma concentrations of fluvastatin. However, even high doses of fluconazole (400 mg on the first day, followed by 200 mg/d) increased the AUC of fluvastatin by less than 100%.[94] The AUC of rosuvastatin is only marginally increased by fluconazole.[95] The pharmacokinetics of other statins is not known to be affected by CYP2C9 inhibition.

CYP2C8 is crucial to the metabolism of cerivastatin,[96] and it can also contribute to the elimination of simvastatin acid and lovastatin acid.[44] Gemfibrozil and particularly its glucuronide metabolite inhibit CYP2C8 but not CYP3A4.[18,96-99] Gemfibrozil glucuronide is a potent, metabolism-based inhibitor and inactivator of CYP2C8.[98] Gemfibrozil considerably increases the AUC of cerivastatin (by about 6-fold) and its lactone, as well as the metabolite (M-1) formed by CYP3A4, but greatly decreases the AUC of the metabolite (M-23) formed by CYP2C8.[18] Gemfibrozil also markedly increases the AUC of active simvastatin acid[99] and lovastatin acid[100] but not of their parent lactones. These findings indicate a different interaction mechanism compared with that caused by the CYP3A4 inhibitors. Inhibition of OATP1B1-mediated hepatic uptake of statins can also be involved in the gemfibrozil-statin interactions (as discussed later in the "Effect of fibrates" section).

Effect of inducers. Rifampin (INN, rifampicin) and other potent inducers of CYP enzymes can greatly decrease the AUC of statins that are metabolized by CYP3A4. The mean AUC of simvastatin acid was reduced by 94% by rifampin[101] and by 82% by carbamazepine.[102] Because the pharmacokinetic profiles

Cerivastatin	*Pravastatin*	*Rosuvastatin**	*Pitavastatin*	*References*
<1.5	≈	≈	(≈)	7, 16, 17, 45, 51, 53, 55, 56
<1.5	≤2	≈	(≈)	45, 57, 60-62
?	≈	(≈)	(≈)	35, 57, 63
4	5-10	5-10	5	19, 79-83, 124-128
4-6	2	2	≤1.5	99, 100, 109-111
(<1.5)	≈	(≈)	≈	52, 85-90
?	30	?	?	48, 101-104

of simvastatin and lovastatin are similar, the effects of potent inducers on the AUC of lovastatin acid are likely to be of the same magnitude. Rifampin also markedly reduced the AUC of atorvastatin (by 80%) and its active metabolites.[103] However, rifampin has reduced the AUC of fluvastatin and pravastatin by about 50%[48] and 30%[104] only. In subjects taking potent enzyme inducers such as rifampin, the half-life of atorvastatin and its metabolites can be shortened by 60% to 90%.[103] Therefore in induced subjects taking atorvastatin in the evening instead of the morning may increase its cholesterol-lowering efficacy. Rifampin and carbamazepine also induce, in addition to CYP enzymes, many transporters, such as OATP1B1, MDR1, and MRP2. Increased activity of transporters is likely to explain the effect of inducers on pravastatin pharmacokinetics. Accordingly, potent inducers could also decrease the plasma concentrations of rosuvastatin and pitavastatin to some extent, although their metabolic clearance is minor.

The dose-response curve of statins is flat. Approximately two thirds of the maximum response can generally be expected with only one quarter of the highest dose.[105] Thus the clinical significance of enzyme induction can be limited, unless intensive lipid lowering is required. However, a case report suggests that the efficacy of simvastatin and atorvastatin may be reduced in some patients taking potent inducing drugs such as phenytoin.[106]

STATIN INTERACTIONS MEDIATED BY MEMBRANE TRANSPORTERS

OATP1B1 seems to be one of the most important membrane transporters that mediate the uptake of statins into the liver,[9,10,24,29] and certain drugs can affect its activity (Fig 2). In addition, many statins are substrates of other efflux or uptake transporters, expressed in the intestine, liver, or kidneys—for example, MDR1, MRP2, BCRP, OATP1B3, OATP2B1, and OAT3.[21,22,24,26,29] These transporters also may mediate drug interactions, but their significance as mediators of statin interactions needs further studies. Many inhibitors of CYP3A4, such as ritonavir, indinavir, saquinavir, clarithromycin, and cyclosporine, are also inhibitors of MDR1 or OATP1B1 (or both).[84,107] Of note, the combination of ritonavir and saquinavir greatly increases (by 30-fold) the AUC of simvastatin acid and moderately increases that of atorvastatin (by 3-fold).[54]

Effect of fibrates. In addition to inhibiting CYP2C8, gemfibrozil and its glucuronide can inhibit the OATP1B1-mediated hepatic uptake of statin acids (Fig 2).[18,96,97] According to a recent study, parent gemfibrozil can also inhibit OATP2B1 and NTCP.[26] Thus some of the gemfibrozil-statin interactions may be based on a dual mechanism: inhibition of hepatic uptake and CYP2C8-mediated metabolism. Daily use of gemfibrozil (1200 mg/d) increases the AUC of active simvastatin and lovastatin acids by 2- to 3-fold[99,100] and by even more in some subjects. Gemfibrozil does not

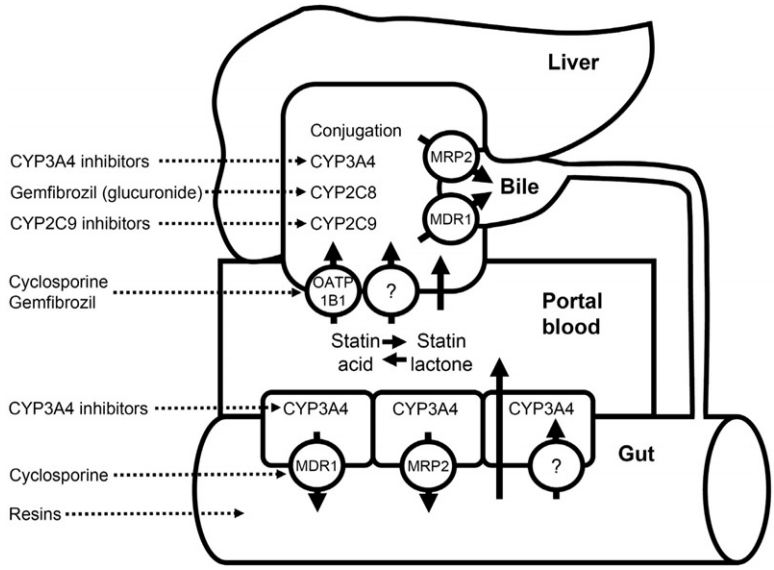

Fig 2. Sites of interactions affecting pharmacokinetics of statins. In addition to inhibitors, inducers can also change the activity of CYP enzymes and transporters. OATP, Organic anion transporting polypeptide; MDR1, multidrug resistance protein 1 (P-glycoprotein); MRP2, multidrug resistance associated protein 2. The *question marks* indicate other uptake transporters, (eg, OATP2B1 in the gut wall and OATP1B3, OATP2B1, and sodium-dependent taurocholate cotransporting polypeptide in the hepatocyte).

inhibit CYP3A4 enzyme,[18] and in contrast to the effect of CYP3A4 inhibitors, the AUC of the simvastatin or lovastatin lactones remains practically unchanged by gemfibrozil. Gemfibrozil greatly increases the AUC of cerivastatin (by about 6-fold) and its lactone but reduces the AUC of the CYP2C8-mediated metabolite.[18] Gemfibrozil also moderately or modestly increases the AUC values of atorvastatin and its active acid metabolites,[103] pravastatin,[108] rosuvastatin,[109] and pitavastatin[110] (Table II), suggesting a role for OATP1B1 in these interactions. However, according to one report, gemfibrozil does not affect the concentrations of fluvastatin.[111] The pharmacokinetics of fluvastatin is also unaffected by the *SLCO1B1* c.521T>C polymorphism, which is associated with a markedly increased AUC of pravastatin, rosuvastatin, and simvastatin acid.[36-38] These findings suggest a limited role of OATP1B1 in the pharmacokinetics of fluvastatin in vivo, although it is a substrate for OATP1B1 in vitro.[112] The extent of gemfibrozil-statin interaction can depend on the relative importance of OATP1B1 (or other rate-limiting hepatic uptake transporters) and CYP2C8 in the pharmacokinetics of the statin in question. On the other hand, neither fenofibrate nor bezafibrate has increased the AUC of simvastatin, lovastatin, pravastatin, rosuvastatin, or pitavastatin,[100,110,113-115] which indicates that a pharmacokinetic interaction with statins is not a group effect of the fibrates. In humans the significance of inhibition of UGT-mediated lactonization of statins by gemfibrozil,[116,117] though theoretically interesting, seems to be of limited quantitative importance in the gemfibrozil-statin interactions, because of the small contribution of glucuronidation to the total clearance of statins.[49,50]

The rate of rhabdomyolysis during cerivastatin monotherapy was 10 to 100 times higher than with the other statins, and gemfibrozil greatly increased the risk.[11,12] The number of rhabdomyolysis cases reported to the US Food and Drug Administration with the gemfibrozil-cerivastatin combination was 533, for an estimated rate of 4600 cases per 1 million prescriptions dispensed.[118] With the combination of fenofibrate and cerivastatin, 14 cases of rhabdomyolysis were reported, for an estimated 140 cases per 1 million prescriptions.[118] A higher incidence was also seen with other statins combined with gemfibrozil (57 cases, or 8.6 cases per 1 million prescriptions) than with statin-fenofibrate combinations (2 cases, or 0.58 cases per 1 million prescriptions). Gemfibrozil has a greater susceptibility than other fibrates to cause myotoxicity also in monotherapy.[12,119] Thus, on the basis of both pharmacokinetic and epidemiologic data, the adverse inter-

action potential of statins with gemfibrozil is considerably greater than that with other fibrates studied. The risks involved in the concomitant use of gemfibrozil with fluvastatin and pravastatin may be lower than those with simvastatin.

Effect of cyclosporine. The risk of lipid disorders and cardiovascular disease is high in transplant patients, and therefore patients receiving cyclosporine immunosuppression often require lipid-lowering drugs. Cyclosporine is a potent inhibitor of several membrane transporters, including OATP1B1, NTCP, OATP2B1, OATP1B3, MRP2, and MDR1, as well as of CYP3A4.[26,84,107,120-124] These properties of cyclosporine can probably explain its effects on various statins, although the exact role of individual transporters in the pharmacokinetics of different statins is not yet clear. Cyclosporine has increased the AUC of statins by 2- to 25-fold (Table II).[19,79-83,124-130] The plasma concentrations of pravastatin and rosuvastatin also are much higher (about 10-fold) in transplant patients taking cyclosporine than in control patients. Of the statins, fluvastatin seems to be the least sensitive to the effects of cyclosporine; cyclosporine increased fluvastatin concentrations by only 2- to 4-fold.[81] However, there are considerable interindividual differences in the extent of cyclosporine-statin interactions.

The effects of cyclosporine on many statins are characterized by a great increase in the peak plasma concentration and AUC of the statin, without a significant effect on its terminal half-life.[80,128] This interaction profile could indicate an increased bioavailability by inhibition of intestinal efflux transporters, such as MDR1, by cyclosporine (Fig 2). If the increased AUC of statins is a result of decreased systemic clearance by inhibition of hepatic uptake (eg, OATP1B1) or biliary efflux (or both), a corresponding reduction in the volume of distribution would explain the unchanged half-life. An alternative explanation is that cyclosporine inhibits hepatic uptake mechanisms that are important only during the absorption phase of statins when statin concentrations in portal blood are high, as well as that other uptake mechanisms (not inhibited by cyclosporine) are more important during the elimination phase when statin concentrations in systemic circulation are much lower. A reduced hepatic uptake of statins would also explain their limited lipid-lowering effect, despite increased plasma concentrations, in cyclosporine-treated patients.[80,129,130]

Numerous cases of rhabdomyolysis have occurred during concomitant use of cyclosporine and different statins, with the exception of fluvastatin.[81,131-133] One study reported a 0.15% incidence of myopathy with lovastatin monotherapy, which increased to 2%, 5%, and 28% in patients receiving niacin, gemfibrozil, and gemfibrozil plus cyclosporine, respectively.[134] Despite the increased risk of myopathy with concomitant use of cyclosporine and regular doses of statins, their combined use is rather safe when small doses of statins are used and the patients are carefully monitored.[7,135,136]

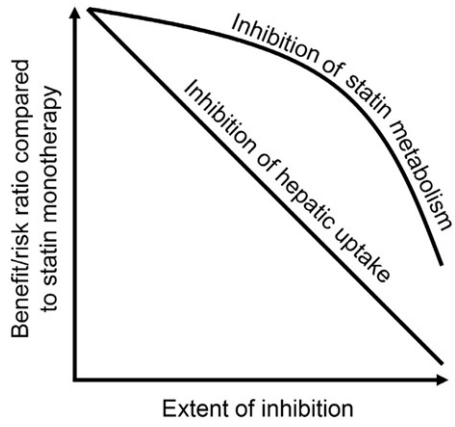

Fig 3. Theoretic relationships between benefit/risk ratio of statin treatment and extent of inhibition of statin metabolism or hepatic uptake.

Inhibitors of hepatic uptake transporters may increase the plasma concentrations of "transporter-dependent" statins by decreasing both their plasma clearance and volume of distribution. Furthermore, because the entry of statins into their intracellular site of action is reduced, the inhibition of HMG-CoA reductase in hepatocytes can be limited despite the elevated statin concentrations in plasma. Thus their cholesterol-lowering effect in relation to their (elevated) concentrations in plasma may be smaller than in monotherapy.[80,129,130] Accordingly, the benefit (cholesterol-lowering effect)/risk (myotoxicity) ratio of OATP1B1-dependent statins can be reduced along with inhibition of their hepatic uptake. The clinical significance of the interactions caused by inhibition of hepatic uptake may be greater than those mediated by the inhibition of CYP enzymes only, because in the latter case both the therapeutic effect and risk myotoxicity can be expected to increase along with moderately elevated plasma statin concentrations (Fig 3). However, further studies are needed to evaluate the benefit/risk ratio in patients concomitantly taking statins and inhibitors of OATP1B1.

OTHER INTERACTIONS OF LIPID-LOWERING DRUGS

Effect of statins on other drugs. In vitro, many statins (lactone or acid form [or both]) inhibit CYP enzymes, such as CYP3A4, CYP2C9, and CYP2C8, or transporters, such as MDR1 and OATP1B1.[10,20,137-140] However, the significance of these properties in the observed or suspected effects of statins on other drugs is unclear.

Most statins, including rosuvastatin, have been reported to slightly increase the anticoagulant effect of warfarin, requiring warfarin dosage reduction. The exact mechanisms of these interactions are unknown.[141,142] Among statins, only fluvastatin inhibits CYP2C9, the main enzyme mediating the metabolism of *S*-warfarin, at concentrations equaling its typical plasma concentrations.[20,139] Accordingly, fluvastatin could slightly increase (by about 10%-30%) the plasma concentrations of CYP2C9 substrate drugs, such as phenytoin and glyburide (INN, glibenclamide), as suggested by some pharmacokinetic data with CYP2C9 substrates.[48] Inhibition of the partially CYP3A4-mediated metabolism of *R*-warfarin might explain the effects of lovastatin, simvastatin, and atorvastatin on warfarin, but other mechanisms can be more important to the increased effect of anticoagulants. Close monitoring of the international normalized ratio is recommended when any statin is added to or withdrawn from oral anticoagulant therapy.

In experimental studies in humans, atorvastatin but not pravastatin has decreased the inhibitory effect of clopidogrel on platelet aggregation.[143] It has been suggested that atorvastatin reduces the effects of clopidogrel by inhibiting the CYP3A-dependent formation of its active metabolite, because clopidogrel itself is an inactive prodrug, metabolized mainly by CYP3A4 and CYP3A5 isozymes.[144] However, the clinical importance of the atorvastatin-clopidogrel interaction is unclear, and studies designed to resolve this question are needed before final conclusions can be drawn.

The clearance of the CYP3A4 substrate midazolam administered intravenously has been 30% smaller in patients receiving concurrent atorvastatin therapy than in control patients.[145] In another study atorvastatin slightly increased the AUC of terfenadine (by 35%), another well-known CYP3A4 substrate.[146]

High doses of some statins (eg, simvastatin and atorvastatin) can slightly increase the plasma concentrations of digoxin (up to 20%), possibly by inhibiting its MDR1-mediated efflux.[77,147] The clinical significance of these statin-digoxin interactions is limited. Statins may slightly reduce the blood concentrations of cyclosporine, but in general, these changes have been inconsistent and clinically insignificant.[81,130]

Effect of gemfibrozil on other drugs. Gemfibrozil can substantially affect the pharmacokinetics of other drugs, in addition to statins, by its inhibitory effects on CYP2C8 and OATP1B1. In particular, the interaction with the oral antidiabetic repaglinide can be clinically significant. Gemfibrozil, unlike the other fibrates (fenofibrate and bezafibrate), has increased the AUC of repaglinide by 8-fold, leading to a considerably increased and prolonged blood glucose–lowering effect.[148,149] Of note, simultaneous administration of gemfibrozil and itraconazole caused an almost 20-fold increase in the AUC of repaglinide. Repaglinide, like cerivastatin, is a substrate of CYP2C8, and the same polymorphism (c.521T>C) of the *SLCO1B1* gene (encoding OATP1B1) that affects the pharmacokinetics of many statins[32-39] also affects the pharmacokinetics of repaglinide.[150]

Gemfibrozil can increase the plasma concentrations of other CYP2C8 substrate drugs as well. For example, the AUCs of the antidiabetic agents rosiglitazone and pioglitazone were increased by over 2-fold and 3-fold, respectively, by gemfibrozil, and the AUC of loperamide was increased by about 4-fold by gemfibrozil.[151-153] However, gemfibrozil did not increase the plasma concentrations of zopiclone,[154] suggesting that CYP2C8 does not significantly contribute to its metabolism. Moreover, gemfibrozil, which in vitro, unlike in vivo (as a result of gemfibrozil glucuronide), is a more potent inhibitor of CYP2C9 than of CYP2C8,[96-98,155] has had only limited effects on the pharmacokinetics of CYP2C9 substrate drugs, including glimepiride, nateglinide, and warfarin, in humans.[156-158]

Ezetimibe, nicotinic acid, and resins. Ezetimibe inhibits the intestinal uptake of dietary and biliary cholesterol. Cyclosporine can greatly increase the exposure to ezetimibe (by 3- to 12-fold in patients with reduced renal function), whereas gemfibrozil and fenofibrate only moderately increase the AUC of ezetimibe (by 1.5- to 2-fold).[159-162] In contrast to these findings, cholestyramine (INN, colestiramine) can decrease the bioavailability of ezetimibe (by 50%), and therefore these drugs should be administered several hours apart.[159] There seem to be no clinically significant pharmacokinetic interactions between ezetimibe and statins. Some cases of myopathy reported during the combined use of ezetimibe or nicotinic acid and statins are probably of pharmacodynamic origin.[163,164] Given that ezetimibe can increase the blood levels of cyclosporine, and vice versa, care is warranted in their combined use.[159,165]

Plasma concentrations of the statins and fibrates are considerably reduced by their simultaneous ingestion with cholestyramine or colestipol but probably not with colesevelam.[166,167] An interval of 2 to 3 hours between the ingestion of systemically absorbed drugs and potentially interacting resins is recommended.

CONCLUSION

Both pharmacokinetic and pharmacodynamic interactions can be involved in the increased risk of myotoxicity observed with different lipid-lowering drugs. It is particularly important to avoid concomitant use of potent inhibitors of CYP3A4 (eg, ritonavir, ketoconazole, and itraconazole) and high doses of lovastatin, simvastatin, and atorvastatin, the metabolism of which depends on CYP3A4, because high plasma concentrations of lipophilic statins increase the risk of muscle toxicity. Weak or moderately potent CYP3A4 inhibitors (eg, verapamil and diltiazem) can be used carefully with small doses of these statins. Grapefruit juice consumption should be avoided or limited when one is taking simvastatin, lovastatin, or atorvastatin. When cyclosporine is used, careful dosing is recommended for all statins. Gemfibrozil, but not other fibrates, may increase plasma levels of most statins. Cyclosporine and gemfibrozil inhibit membrane transporters (eg, OATP1B1 by both and MDR1 by cyclosporine) and CYP enzymes (CYP3A4 by cyclosporine and CYP2C8 by gemfibrozil glucuronide). Their pharmacokinetic interaction potential, together with pharmacodynamic effects of gemfibrozil, explains the increased risk of myotoxicity with coadministration of statins. Inhibitors of hepatic uptake transporters may decrease the benefit/risk ratio of statins by increasing their plasma concentrations and interfering with their entry into hepatocytes, the site of their therapeutic action. Lipid-lowering drugs can also be involved in other potentially harmful interactions—for example, gemfibrozil with some oral antidiabetic drugs, as well as statins and gemfibrozil with oral anticoagulants. However, most of the clinically significant drug-drug interactions of lipid-lowering drugs can be avoided by correct selection and dosing of the drugs.

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