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Drug Interactions of Lipid-Altering Drugs

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Abstract

The use of lipid-altering drugs has been shown to reduce the progression of atherosclerotic lesions and reduce the risk of atherosclerotic events (such as myocardial infarction and stroke). In general, these lipid-altering drugs are well tolerated but there is the potential for drug interactions. For example, HMG-CoA reductase inhibitors may interact with macrolides, azalides, azole antifungals and cyclosporin. Resins (such as cholestyramine and colestipol) may impair the absorption of many concurrent medications. Fibrates have potential drug interactions with warfarin, furosemide (frusemide), oral hypoglycaemics and probenecid. Nicotinic acid (niacin) may have potential drug interactions with high dose aspirin (acetylsalicylic acid), uricosuric agents (such as sulfapyrazone) and alcohol (ethanol). Finally, probucol may have potential drug interactions with antidysrhythmics, tricyclic antidepressants and phenothiazines. In addition, lipid-altering drugs, used in combination, may have the potential for drug interactions, enhancing some of the risks of adverse effects, such as myositis and hepatotoxicity. Therefore, in order to use lipid-altering drugs in the most effective, and safest manner, it is important for the clinician to have an understanding of the mechanisms of potential drug interactions, which drug interactions may theoretically occur, and specifically, which specific drug interactions have already been described.

Atherosclerotic cardiovascular disease is the single most common cause of morbidity and mortality in most developed nations. Dyslipidaemia is an important risk factor for the development of atherosclerotic lesions. It has now been conclusively demonstrated that reducing low density lipoprotein cholesterol (LDLC) blood levels through diet and/or lipid-altering drugs will reduce atherosclerotic progression and atherosclerotic events (i.e. myocardial infarction and stroke).

Many patients with dyslipidaemia may be receiving drug treatment for other medical illnesses. Therefore, it is important for the clinician to understand potential drug interactions prior to prescribing lipid-altering drugs, prior to changing lipid-altering drugs (perhaps even within the same class), or prior to combining two or more lipid-altering drugs. This article provides practical guidelines with respect to potential drug interactions with lipid-altering drugs.

1. HMG-CoA Reductase Inhibitors

3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors decrease total cholesterol, LDLC and fasting very low density lipoprotein cholesterol (VLDLC) [triglyceride] blood levels. High density lipoprotein cholesterol (HDLC) blood levels may be slightly to moderately increased. Drugs in this class are often referred to as 'statins'. A summary of some clinical pharmacological characteristics of this class of agents is shown in table I.

1.1 Mechanism of Action and Metabolism

After gastrointestinal absorption, all of the currently approved HMG-CoA reductase inhibitors competitively inhibit HMG-CoA reductase during first pass metabolism through the liver. As the result of the inhibition of this important enzyme, cholesterol synthesis is reduced. Furthermore, the use of HMG-CoA reductase inhibitors results in an upregulation of the LDL receptors, increasing LDLC clearance and thereby further contributing to the lipid lowering effects of these agents.

As with most drugs, drug interactions with the use of HMG-CoA reductase inhibitors may occur, or may theoretically occur, due to factors that influence pharmacokinetic properties (such as alterations in absorption, distribution, biotransformation and elimination). Although definitive, comparative studies demonstrating safety differences among the different HMG-CoA reductase in-

hibitors are lacking, particularly with regard to drug interactions, HMG-CoA reductase inhibitors may differ in their potential for drug interactions, based upon their differences in pharmacological properties (table I).

All HMG-CoA reductase inhibitors are mainly metabolised in the liver, where they undergo extensive first-pass extraction. Some have metabolites that also have HMG-CoA reductase inhibitor activity. Although their urinary excretion may often be minor, some HMG-CoA reductase inhibitor blood concentrations may double in patients with severe renal insufficiency (creatinine clearance <30 ml/min).[2] Therefore, if HMG-CoA reductase inhibitors are to be used in patients with severe renal dysfunction, they should be started at low dosages and the patient should be monitored routinely for muscle and hepatic enzyme level elevations. Since myositis, which may rarely result in rhabdomyolysis, is correlated with higher HMG-CoA blood concentrations, symptoms of myalgia should be followed-up by determination of possible increases in creatine phosphokinase blood levels. A possible exception would include HMG-CoA reductase inhibitors with very limited renal excretion such as atorvastatin, which is not influenced by renal disease (atorvastatin and its metabolites, after hepatic and extrahepatic metabolism, are eliminated primarily in the bile, with less than 2% recovered in urine after oral administration).[3] Atorvastatin, therefore, requires no adjustment in dosage in patients with renal dysfunction. However, definitive, confirmatory clinical trials demonstrating the safety of atorvastatin in patients with severe renal dysfunction, or end-stage renal disease are lacking.

With regard to absorption, HMG-CoA reductase inhibitors may exhibit variability in their uptake if taken with food, and once absorbed may also vary in the degree to which they are bound to plasma proteins. Furthermore, some HMG-CoA reductase inhibitors may have greater hydrophilicity, which may result in lower rates of uptake in peripheral tissues and decreased diffusion across the blood-brain barrier. Finally, not all HMG-CoA

Table I. Examples of some biochemical/pharmacological characteristics of HMG-CoA reductase inhibitors

Order of generation	Generic name	Derivation	Metabolic enzymes	Lipophilicity	Protein binding (%)	$t_{1/2}$ (h)	Relative HMG-CoA reductase inhibition potency/mg (*in vitro*)[b]	Hepatic first-pass extraction (%)	Active metabolites (n)	Renal excretion (%)	Increased plasma concentrations in patients >60 years[1]
First	Lovastatin	Fungal fermentation	CYP 3A4	+	80	2-3	2	40-70	Yes (3)	30	Unknown
First	Pravastatin	Fungal fermentation	Hydroxylase[a]	–	50	1-2	2	50-70	Yes (2)	60	Not increased
Second	Simvastatin	Semi-synthetic	CYP 3A4	+	90	2-3	4	50-80	Yes (3)	13	Increased
Third	Fluvastatin	Synthetic (racemic)	CYP 2C9	±	98	0.5-3	1	40-70	No	<6	Unknown
Fourth	Atorvastatin	Synthetic (pure enantiomer)	CYP 3A4	+	98	13-16	8	20-30	Yes (2)	<2	Increased
Fourth	Cerivastatin	Synthetic (pure enantiomer)	CYP 3A4, CYP 2C8	+	99	2-3	100	50-60	Yes (2)	24	Not increased

a The enzyme system responsible for the metabolism of pravastatin is unknown.

b These numbers represent very generalised estimates of relative HMG-CoA reductase inhibition on a mg per mg basis, based upon the starting dosage. Because the increase in HMG-CoA reductase inhibitor activity for these drugs is not linear with respect to lipid lowering, such relativity does not apply to doses beyond the starting dosages. Finally, the clinical efficacy of actual lipid-lowering in patients by these drugs should be based upon trials of their use at the marketed dosages, rather than the mg per mg potency of the HMG-CoA reductase inhibition.

CYP = cytochrome P450; **HMG-CoA** = 3-hydroxy-3-methylglutaryl coenzyme A; $t_{1/2}$ = half-life; + = lipophilic; – = not lipophilic; ± = not predominantly lipophilic or predominantly hydrophilic.

Table II. Examples of non–lipid-altering drug relationships with the CYP3A3/4 mixed function oxidase system[5-7]a

Inhibitors	
Antidepressants	Fluoxetine, fluvoxamine, sertraline, nefazodone
Azoles	Fluconazole (large doses), itraconazole, ketoconazole, clotrimazole
Food	Grapefruit juice (naringenin)
Macrolides	Clarithromycin, erythromycin
Miscellaneous	Cimetidine, cyclosporin, danazol, diltiazem, ethinylestradiol, gestodene, indinavir, metronidazole, mibefradil, omeprazole, quinidine, quinine, ritonavir, tacrolimus, verapamil, zafirlukast
Substrates	
Antiarrhythmics	Amiodarone, digoxin, disopyramide, lidocaine (lignocaine), propafenone, quinidine
Anticonvulsants	Carbamazepine, ethosuximide
Antidepressants	Amitriptyline, doxepin, imipramine, sertraline
Antihistamines	Astemizole, fexofenadine, loratadine, terfenadine
Benzodiazepines	Alprazolam, diazepam, midazolam, triazolam
Calcium antagonists	Diltiazem, felodipine, nifedipine, verapamil
Cancer chemotherapy	Cyclophosphamide, docetaxel, paclitaxel, tamoxifen, vinca-alkaloids
Immunosuppressive drugs	Corticosteroids, cyclophosphamide, cyclosporin, dapsone, tacrolimus
Miscellaneous	Paracetamol (acetaminophen), cisapride, codeine, dextromethorphan, enalapril, ergotamine, erythromycin, estrogens, flutamide, pimozide, omeprazole, oral contraceptives, tretinoin (retinoic acid), ritonavir, saquinavir, theophylline, warfarin
Inducers	
Anticonvulsants	Carbamazepine, phenobarbital (phenobarbitone), phenytoin, primidone
Antituberculous agents	Isoniazid, rifabutin, rifampicin (rifampin)
Miscellaneous	Dexamethasone, glutethimide, griseofulvin, phenylbutazone, troglitazone

a For most of the listed drugs, no validated controlled clinical reports have confirmed drug interactions. However, theoretical possibilities exist. Therefore, clinicians should be aware of potential drug interactions when combinations of drugs are given that are metabolised by the same enzyme system.

CYP = cytochrome P450.

reductase inhibitors appear to be metabolised by the same hepatic enzyme system (table I).

With regard to biotransformation, HMG-CoA reductase inhibitors are metabolised to active or inactive by-products through enzymes in the liver.[4] The major enzyme systems involved in phase 1 drug metabolism (oxidative, reduction and hydrolysis reactions) is the cytochrome P450 (CYP) mixed function oxidase system, which is mainly present in the liver, but may also be present in other organs, such as the intestine. The CYP mixed oxidase system is a source of patient-to-patient variability in drug metabolism, which may explain specific toxic interactions of drugs. More than 20 different P450 mono-oxygenases have been described in humans, with the majority of drug metabolism occurring through 3 distinct gene families of CYP1, CYP2 and CYP3.

Drugs metabolised through the CYP system may be characterised as inhibitors, substrates, or inducers. The addition of a drug that is solely an inhibitor of a specific enzyme system may potentially result in toxic concentrations of concurrent drugs that are substrates for that same enzyme system. Alternatively, in patients already treated with drugs that are substrates for a specific enzyme system, the addition of a drug that is also a substrate for this same enzyme system may result in competitive inhibition of the common enzyme system. If the metabolic capacity of that enzyme system is exceeded, the blood concentrations of all substrate drugs have the potential to be increased with attendant risks of increased drug toxicity.

With specific regard to HMG-CoA reductase inhibitors, table I lists the CYP mixed function oxidase systems thought to be responsible for their metabolism. The interclass differences in metabolism may indicate interclass differences in the risk for drug interactions. For example, some drugs that are metabolised by, or affect the activity of the CYP3A4 mixed function oxidase enzyme should be used with caution in combination with HMG-CoA reductase inhibitors that are also metabolised by, or that may affect, this same enzyme (table II).[5-7]

Patient-to-patient variances in the metabolism through these enzyme systems can occur through genetic and environmental differences, and through the use of concurrent drugs that may affect the ac-

tivity of these enzymes. But, from a practical standpoint, the main problem with determining whether these chemical/pharmacological differences are clinically relevant is the lack of definitive, confirmatory and comparative trials demonstrating the degree of toxicity differences among the currently marketed HMG-CoA reductase inhibitors.

Many of the reports of drug interactions, or reports of lack of drug interactions, have been isolated, unconfirmed case reports, or studies of small patient populations. Further confusing this issue is the fact that drugs, including HMG-CoA reductase inhibitors, have differing degrees of metabolism through the CYP mixed function oxidase system, and have differing activity of their subsequent metabolites. It is also likely they have other differing pharmacological metabolic properties. These factors make it difficult to predict definitively whether or not adverse drug interactions may, or may not occur.

It is not enough to know whether the drugs are inhibitors, substrates, or inducers of the CYP mixed function oxidase system. This is because the degree that inhibitors impair the CYP enzyme system, and the degree that substrates may competitively inhibit the CYP system has yet to be established for most drugs. Also, few comparative data exist that make it possible to rank 1 drug against another based on their effects upon specific CYP enzyme systems. Therefore, it is currently impossible, for example, to state with certainty whether lovastatin/simvastatin has any more, or any less, potential for drug interactions than atorvastatin, when used concurrently with other drugs that are also metabolised by, or that may affect the activity of, the CYP3A4 mixed function oxidase enzyme.

Another practical example of the hazards of predicting potential drug interactions by theoretical concepts alone might be cimetidine, which is a known inhibitor of the CYP3A4 mixed function oxidase system. However, in many years of clinical use, cimetidine has demonstrated no clinically significant drug interactions when used in combination with HMG-CoA reductase inhibitors, despite the fact that all of them are metabolised by the CYP3A4 mixed oxidase system. In fact, despite the widespread use of HMG-CoA reductase inhibitors, and despite numerous other drugs metabolised by the same enzyme system, relatively few drug interactions have been reported in clinical practice. This suggests that even if interactions may theoretically occur, they typically do not result in toxicity unless the HMG-CoA inhibitor is used in combination with drugs having very potent effects on the same P450 mixed oxidase system.

For example, in contrast to cimetidine, mibefradil is a strong inhibitor of the CYP3A4 enzyme. Included in its reported drug interactions was simvastatin, which resulted in reports of rhabdomyolysis when mibefradil was used in combination with high dose simvastatin – resulting in over a 4-fold increase in simvastatin blood concentrations. Due to potential such drug interactions such as this mibefradil has been withdrawn.[8]

In summary, the clinician should be aware of theoretical drug interactions prior to prescribing HMG-CoA reductase inhibitors, to changing HMG-CoA reductase inhibitors, or to the addition of other drugs to the regimens of patients currently treated with HMG-CoA reductase inhibitors. But most importantly, from a clinical standpoint, clinicians should be especially aware of those interactions that are well known, or have been reported to occur.

1.2 Drug Interactions

Table III lists some of the most important potential drug interactions with HMG-CoA reductase inhibitors that may be of clinical significance.[9-11]

Some of the HMG-CoA reductase inhibitors are metabolised by the CYP3A4 enzyme (atorvastatin, cerivastatin, lovastatin and simvastatin). Therefore, the use of the combination of HMG-CoA reductase inhibitors metabolised by the CYP3A4, and some other drugs metabolised by, or affecting the activity of this same enzyme, may increase the risk of myopathy and rhabdomyolysis (table II).

In general, studies of the effect of HMG-CoA reductase inhibitors upon warfarin have demon-

Table III. Some of the most clinically relevant potential drug interactions with HMG-CoA reductase inhibitors[11]a

Concomitant administration of non–lipid-altering drugs
Macrolides (erythromycin, clarithromycin)
Azalides (azithromycin)b
Azole antifungals (itraconazole, ketoconazole)
Anticoagulants (warfarin)
Cyclosporin
Mibefradil
?Nefazodone[9]
Concomitantly administered lipid-altering drugs (excluding lipid blood level effects)
Resins (cholestyramine, colestipol)
Fibrates (gemfibrozil, clofibrate, fenofibrate)
?Nicotinic acid (niacin)c

a Many of the drugs listed as potentially interacting with HMG-CoA reductase inhibitors have been reported to do so only through isolated case reports, or small clinical trials. Although individual HMG-CoA reductase inhibitors may theoretically have less potential for drug interactions, based on differing pharmacological properties, clinical trials demonstrating safety differences among the HMG-CoA reductase inhibitors, with regard to drug interactions, are lacking.

b Azithromycin is an azalide that may not inhibit hepatic enzymes as does erythromycin, but has been suggested to have the potential to result in rhabdomyolysis when used in combination with HMG-CoA reductase inhibitors metabolised by the cytochrome P450 mixed function oxidase system.[10]

c Some controlled clinical trials of the combination of an HMG-CoA reductase inhibitor and nicotinic acid have not demonstrated increased risk of significant myopathy.

? = Undetermined clinical significance.

strated either no effect,[3,12-15] or a small increase in the prothrombin time with simvastatin and possibly lovastatin.[13,16] However, if HMG-CoA reductase inhibitors are to be used in combination with warfarin, it may be wise to determine prothrombin time before initiating therapy and then weekly for 2 weeks and then periodically afterwards.

β-Adrenergic blockers may modify hepatic blood flow, as well as alter the vascular resistance of splanchnic vessels. As a result, the first-pass elimination may be changed, affecting the hepatic metabolism of HMG-CoA reductase inhibitors. The effect is probably small and the clinical significance of this potential effect is unknown.[17]

A review of the literature reveals no other confirmed increased toxicity with the use of HMG-CoA reductase inhibitors with calcium antagonists, with the exception of mibefradil. As noted in section 1.1, this agent is a potent inhibitor of CYP3A4 and was reported to interact with simvastatin, resulting in myopathy and rhabdomyolysis. This example illustrates how potential drug interactions may differ among drugs of the same class, depending on the route of metabolism. For example, fluvastatin and pravastatin are not significantly metabolised by the CYP3A4 enzyme. Therefore, the mibefradil package insert, prior to the drug's withdrawal, stated that *'no specific dose adjustment of fluvastatin or pravastatin is recommended with coadministration'* with mibefradil.[8,18] And because cerivastatin has significant metabolism by additional hepatic enzymes other than the CYP3A4, the concurrent use of mibefradil with cerivastatin may not have the same risk of myopathy as with simvastatin. However, clinical trials comparing the toxicity differences of the combined use of HMG-CoA reductase inhibitors and mibefradil were lacking, and a definitive statement regarding safety differences cannot be made.

Table IV lists US package insert information regarding clinically significant drug interactions with selected drugs.[3,10,12-16]

1.3 Concomitant Administration of Lipid-Altering Drugs

HMG-CoA reductase inhibitors in combination with resins have been shown to result in significant potentiation of lipid lowering effects. No adverse drug interactions have been described with this combination, except that resins may impair the absorption of HMG-CoA reductase inhibitors.[19] However, the clinical significance of this potential drug interaction, with regard to the endpoint of lipid lowering is unclear. In fact, the combination of resins and HMG-CoA reductase inhibitors greatly enhances the lipid-lowering effects of each. Nonetheless, it is still generally recommended that HMG-CoA reductase inhibitors be taken 1 hour before, or at least 4 hours after the use of resins.

The use of the fibrate gemfibrozil with some of the HMG-CoA reductase inhibitors has been re-

ported to result in myopathy and rhabdomyolysis.[11] Due to this potential severe drug interaction, this combination is generally not recommended, unless the potential benefits of this combination outweighs the potential risks. Table V lists some practical guidelines for potential use of this combination.

Uncontrolled studies have reported that combined use of HMG-CoA reductase inhibitors and nicotinic acid (niacin) may cause myopathy and rhabdomyolysis, but only rarely.[11] The mechanism is unknown. Due to the lack of repeated, definitive, confirmatory clinical trials designed to determine the precise risk of this lipid-altering drug combination, not enough information is available to date to recommend for or against the use of this combination. Therefore, it should be left up to the clinician to determine whether the potential benefits of HMG-CoA reductase inhibitors with nicotinic acid, exceed the remote increased risk of myopathy. Packet inserts for pravastatin and fluvastatin, as well as controlled studies, suggest that when used in combination with nicotinic acid, myopathy was not observed.[12,15,20,21] Although the package insert of simvastatin implies a potential drug interaction, a controlled trial of low dose immediate release nicotinic acid and low dose simvastatin did not demonstrate significant change in creatine phosphokinase blood levels, or myopathy with concurrent use.[22] Similarly, in a controlled trial, fluvastatin combined with nicotinic acid was proven to be well tolerated.[23]

1.4 Special Issues

1.4.1 Lovastatin/Simvastatin/Atorvastatin

Lovastatin, simvastatin and atorvastatin[3,13,16] are metabolised through the CYP3A4 mixed function oxidase system. These HMG-CoA reductase inhibitors should be used with caution with some other concomitantly administered non–lipid-alter-

Table IV. HMG-CoA reductase inhibitor package insert information regarding clinically significant drug interactions with selected drugs in the US[a]

HMG-CoA reductase inhibitor	Warfarin	Digoxin (digitalis)	Cyclosporin	Macrolides (i.e. erythromycin, clarithromycin)[b]	Azoles (i.e. itraconazole, ketoconazole)	Calcium antagonists[c]	Antidepressants[d]
Lovastatin	U	–	+	+	+	–	–
Simvastatin	+	U	+	+	+	–	–
Atorvastatin	–	+	+	+	+	–	–
Pravastatin	–	–	U	–	–	–	–
Fluvastatin[e]	–	–	U	U	U	–	–
Cerivastatin[f]	–	–	+	+	+	–	–

a Although the combination of HMG-CoA reductase inhibitors with some of these drugs may alter drug blood concentrations, table IV lists only drug interactions that may be of clinical significance. Some of the interactions are theoretical. In most cases, definitive, confirmatory clinical trials are lacking.

b Also includes the related azalide antibacterials, such as azithromycin.[10]

c Mibefradil is a calcium antagonist that has the potential to result in severe toxicity with certain HMG-CoA reductase inhibitors. However, most studies have suggested that other calcium antagonists are well tolerated when used in combination with HMG-CoA reductase inhibitors.

d Nefazodone and other similar selective serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitors (SSRIs) may inhibit the cytochrome P450 (CYP) 3A4 mixed-function oxidase system. However, despite multiple clinical trials of HMG-CoA reductase inhibitors that did not exclude these drugs, and despite the widespread use of both HMG-CoA reductase inhibitors and SSRIs, the reported toxicity of this combination is extremely rare.

e Fluvastatin is not thought to be metabolised through the cytochrome CYP3A4 mixed function oxidase system. Therefore, even though the package insert reports potential drug interactions, some reports, such as those concerning the concomitant use of fluvastatin and erythromycin, have demonstrated no significant pharmacokinetic interactions.

f Since it is significantly metabolised by both CYP3A4 and CYP2C8 (see table I), it is possible that cerivastatin blood concentrations may be less influenced by drugs that impair metabolism through CYP3A4, as compared to other HMG-CoA reductase inhibitors that are more exclusively metabolised by this one enzyme.

+ = reported, or suspected potential drug interactions; **–** = no reported, or doubtful drug interactions; **U** = unable to determine, or conflicting studies.

Table V. Guidelines for potential use of HMG-CoA reductase inhibitors with fibrates

Due to the potential severe adverse effects of the combined treatment of HMG-CoA reductase inhibitors with fibrates, it is generally recommended that this combination be avoided in these instances
• By physicians who are not well acquainted with the potential risks of such therapy
• In patients with significant pretreatment liver, muscle or renal dysfunction
• In patients with significant pretreatment elevations in liver, or muscle enzyme levels, i.e. greater than 3 times normal
• In patients with known elevations in muscle or liver enzyme levels with HMG-CoA reductase inhibitors or fibrates alone
• In patients who do not have readily available access to a physician should clinical or laboratory evidence of myalgias occur
• In patients unwilling to comply with the level of clinical and laboratory monitoring required with such combination therapy
• In patients who are receiving numerous other medications
• In patients receiving any drug known to impair the cytochrome P450 3A4 mixed function oxidase system

ing drugs that also are metabolised by, or that affect the activity of this same hepatic enzyme system (table II). Such combinations may increase the risk of myopathy and rhabdomyolysis.

Information regarding simvastatin is illustrative of how potential drug interactions may occur and how they should be managed. Simvastatin is supplied as tablets at a dose of between 5 and 80mg. As noted before, the higher the blood concentration of HMG-CoA reductase inhibitors, the higher the risk of potential toxicities, such as myopathy and rhabdomyolysis. Therefore, the greatest risk of toxicity occurs when the highest dosage of HMG-CoA reductase inhibitors are used, particularly when they are used in combination with drugs that impair the CYP450 mixed function oxidase system responsible for their metabolism.

In a study of the efficacy and safety of simvastatin 80 mg/day in patients with hypercholesterolaemia,[24] 2 of 314 patients (0.6%) receiving the 80 mg/day dosage developed myopathy, defined as muscle pain accompanied by an increase in creatine kinase levels >10 times the upper limit of normal. Both patients had higher drug concentrations than expected. One of them had been treated with nefazodone, metronidazole and clarithromycin 28 days before developing myopathy. Due to the fact that all 3 of these concomitant drugs impair the same CYP450 enzyme (CYP3A4) responsible for the metabolism of simvastatin, it was concluded that this drug interaction may have accounted for the unexpected elevations in simvastatin blood concentrations and the resultant toxicity.

As the result of the concern of toxicity that may occur with the highest approved dose of simavastatin, the package insert recommends that for patients taking concomitant drugs known to have potential drug interactions (such as cyclosporin), the dose of simvastatin should not exceed 10 mg/day.

This example emphasises principles that relate to other HMG-CoA reductase inhibitors. Firstly, as a class HMG-CoA reductase inhibitors are generally well tolerated, with few adverse effects. Second, even when administered to patients receiving no other agents, all HMG-CoA reductase inhibitors have the potential for adverse effects, such as muscle and liver toxicity. Finally, if taken with drugs that have the theoretical potential for drug interactions, toxicity is rarely reported unless the HMG-CoA reductase inhibitor is administered at high doses either with a concurrent drug that acts as a clinically significant inhibitor of the same enzyme system responsible for the metabolism of the specific HMG-CoA reductase inhibitor in question or with multiple concurrent drugs that act as substrates for this enzyme. In these instances, it is best to limit the HMG-CoA reductase inhibitor to low dosages, or use a HMG-CoA reductase inhibitor that may have less potential for interacting with the concurrent drug or drugs in question and closely monitor for liver or muscle toxicity.

Although conflicting reports exist, it has also been suggested that lovastatin and simvastatin may slightly prolong prothrombin time in patients treated with warfarin-like anticoagulants.[25-31] Therefore, the package inserts recommend that prothrombin time be obtained prior to the addition of any HMG-CoA reductase inhibitor to patients already treated with warfarin.[13,16] Afterwards,

frequent measurement of prothrombin time should be done to ensure that no clinically significant alteration of prothrombin time occurs. Once a stable prothrombin time has been achieved, then periodic prothrombin time monitoring should be done as is usually recommended for those patients treated with warfarin alone. A similar recommendation for close monitoring of prothrombin time is made for patients receiving warfarin in whom the lovastatin or simvastatin dosage is changed.

In addition, the addition of simvastatin or atorvastatin to patients taking digoxin may result in a slight elevation in digoxin blood concentrations. Therefore, the package inserts recommend that routine monitoring of digoxin blood concentrations should be performed when simvastatin or atorvastatin is added, or if the dosage is changed, in patients treated with digoxin.[3,16]

Atorvastatin has also been shown to increase estrogen blood levels when taken with oral estrogen-containing contraceptives.[3]

With regard to lipid-altering drugs, the use of fibrates (such as gemfibrozil) has been reported to result in myopathy and rhabdomyolysis in some patients when used in combination with some HMG-CoA reductase inhibitors.[11]

1.4.2 Pravastatin

Pravastatin is hydrophilic and may not be metabolised through the CYP mixed function oxidase system. Therefore, it may not have the same potential for myopathy and rhabdomyolysis, as might occur with the combination of non–lipid-altering drugs and HMG-CoA reductase inhibitors that are metabolised by this enzyme. In addition, the use of pravastatin has been shown not to alter plasma protein binding of warfarin and no change in anticoagulation was produced by this combination.[12] Finally, pravastatin blood concentrations may be increased with concurrent use of cyclosporin. However, no clinically significant elevations of cyclosporin blood concentrations have been conclusively demonstrated.[32] In fact, it has been suggested that pravastatin has the lowest propensity to cause myopathy in cyclosporin-treated patients among the currently available HMG-CoA reductase inhibitors.[33]

With regard to lipid-altering drugs, the use of gemfibrozil and pravastatin has been shown in a randomised trial to not result in severe myopathy during the 12 weeks of the study.[34] Although this combination was found to be effective in improving the lipid profile of selected patients with combined hyperlipidaemia, the authors concluded 'However, since myopathy at a low incidence or after long term therapy cannot be excluded, the routine use of combination therapy is not advisable'. Furthermore, the package insert[12] states 'The use of fibrates alone may occasionally be associated with myopathy. The combined use of pravastatin and fibrates should be avoided unless the benefit of further alterations in lipid levels is likely to outweigh the increased risk of this drug combination.' Nonetheless, due to the presence of a clinical trial[34] demonstrating safety in the use of pravastatin and gemfibrozil, if fibrates are to be used in combination with HMG-CoA reductase inhibitors, pravastatin maybe among the safest to use. The theoretical basis favouring pravastatin over other HMG-CoA reductase inhibitors is unclear, since a specific drug interaction with fibrates and HMG-CoA reductase inhibitors is unknown.

1.4.3 Fluvastatin

Fluvastatin[15] is partially metabolised through the CYP2C9 mixed function oxidase system. Perhaps due to this and other pharmacological differences, the potential drug interactions of fluvastatin may differ from other HMG-CoA reductase inhibitors. For example, some studies suggest that due to its metabolism by the CYP2C9 enzyme, shorter half-life and no circulating metabolites, fluvastatin metabolism may be less effected by the concurrent use of drug metabolised by the CYP3A4 enzyme, such as cyclosporin, than other HMG-CoA reductase inhibitors.[35] Also, due to increased absorption of fluvastatin in the presence of reduced gastric acidity, fluvastatin is the only currently marketed HMG-CoA reductase inhibitor in which the package insert[15] describes a significant increase in fluvastatin blood concentrations with the

Table VI. Some of the most common drugs described to have decreased absorption with resins (cholestyramine, colestipol)[39-41]a

Parecetamol (acetaminophen)	Penicillin
Amiodarone	Phenobarbital (phenobarbitone)
β-Blockers	Phenylbutazone
Corticosteroids	Sulphonylurea oral antihyperglycaemics
Digitalis glycosides	Tetracycline
Fat-soluble vitamins	Thiazide diuretics
Fibric acid derivatives	Thyroid hormones
Methotrexate	Warfarin
Nonsteroidal anti-inflammatory drugs	

a Resins may decrease the absorption of many drugs. Therefore, it is recommended in the package insert that all drugs be given 1 hour before, or 4 or more hours after, administration of resin.

concurrent use of cimetidine, ranitidine and omeprazole. The package insert also indicates that fluvastatin may alter digoxin metabolism. But studies have suggested that this drug interaction between fluvastatin and digoxin are not clinically relevant.[36] Administration of fluvastatin to patients treated with rifampicin (rifampin) results in a significant increase in rifampicin clearance.[15] Also, at least 1 report suggests no effects of the administration of erythromycin on fluvastatin steady-state pharmacokinetics.[37] With regard to fibrates (such as gemfibrozil), the combination with fluvastatin has shown no significant differences in blood concentrations of either drug when used concomitantly.[38]

1.4.4 Cerivastatin

Cerivastatin[14] is partially metabolised through the CYP3A4 mixed function oxidase system, as well as other hepatic enzymes. Therefore, it is possible that cerivastatin may not have the same risk of drug interactions when used with non–lipid-altering drugs, as might occur with other HMG-CoA reductase inhibitors whose metabolism is more directly dependent upon the CYP3A4 mixed function oxidase system. Nevertheless, until confirmatory studies are available, this HMG-CoA reductase inhibitor should be used with caution with some concurrently administered non–lipid-altering drugs that also are metabolised by, or that affect, the activity of this hepatic enzyme system (table II). The clinical significance of the use of cerivastatin with other lipid-altering drugs await results of large, long term, definitive clinical trials and/or specific studies.

2. Resins

2.1 Mechanism of Action and Metabolism

Cholesterol is the precursor for hepatic bile acid synthesis. After a meal, bile acids are secreted into the intestines and then reabsorbed and returned to the liver (enterohepatic circulation). Resins are polymers that combine with and bind bile acids to form an insoluble complex which is excreted in the faeces. As they bind to bile acids, they decrease bile acid reabsorption in the intestine. Thus, more cholesterol is required for hepatic *de novo* synthesis to compensate for the lost bile acids, and cholesterol blood levels are thus reduced. Furthermore, LDLC receptor activity is subsequently increased. Thus, LDLC blood levels are reduced through increased utilisation of cholesterol for bile acid formation, as well as through the increased LDLC clearance from the blood.

2.2 Drug Interactions

The most clinically relevant drug interaction with resins is the impairment of absorption of concomitantly prescribed medications. Resins are well known to decrease the absorption of drugs such as those listed in table VI.[39-41] Furthermore, fat digestion may be impaired, with malabsorption of fat-soluble vitamins such as A, D and K. Therefore, it is recommended that any medication given concurrently with resins should be taken at least 1 hour before, or 4 hours after the intake of resins.[39,40]

2.3 Concomitant Administration of Lipid-Altering Drugs

Due to the potential for impaired absorption, it is recommended that other lipid-altering drugs being taken in combination with resins be administered at least 1 hour before, or 4 hours after the intake of the resins.

2.4 Special Issues

If drug blood concentrations (such as digoxin), or the effect of drugs (such as the prothrombin time in patients on warfarin), can be measured, then it is prudent to monitor these levels closely and frequently when medications are given in combination with resins. After dosages have been stabilised for an appropriate period of time, less frequent monitoring may be required.

3. Fibrates: Gemfibrozil, Fenofibrate, Bezafibrate, Clofibrate

3.1 Mechanism of Action and Metabolism

The mechanism of action of fibrates has not been completely characterised. However, they are thought to lower fasting triglyceride blood levels by decreasing peripheral lipolysis via a decrease of the release of free fatty acids from peripheral adipose tissue and an increase of lipoprotein lipase activity. HDLC blood levels are often increased as well, due to the inverse relationship with hypertriglyceridaemia. Total cholesterol and LDLC may be decreased, or increased with the use of fibrates.

Gemfibrozil is well absorbed from the intestine and undergoes enterohepatic recirculation. Gemfibrozil is metabolised by the liver into metabolites, one of which possesses pharmacological activity. These metabolites are primarily excreted by the kidney.[42] Fenofibrate a has similar safety profile as gemfibrozil, but may have considerably more efficacy than gemfibrozil in lowering triglyceride and LDLC blood levels.

3.2 Drug Interactions

Clofibrate, gemfibrozil, fenofibrate and most fibrates are avidly bound to serum proteins and may displace acidic drugs such as phenytoin or tolbutamide from their binding sites. Caution should be exercised when adding fibrates to either of these drugs, or other highly protein-bound drugs. For example, the hypoglycaemic effect of tolbutamide has been reported to increase when clofibrate is given concurrently.[43,44]

Table VII. Some of the most clinically relevant potential drug interactions with fibrates (gemfibrozil, fenofibrate, bezafibrate, clofibrate)[41,42,46][a]

	Comments
Concomitantly administered non–lipid-altering drugs	
Warfarin	May increase prothrombin time
Furosemide (frusemide)	May cause myalgias and marked diuresis when clofibrate is given to patients with nephrotic syndrome
Oral hypoglycaemic drugs (sulphonylureas, biguanides)	Clofibrate may increase the hypoglycaemic effects
Rifampicin (rifampin)	Rifampicin may decrease clofibrate blood levels
Probenecid	Probenecid may increase clofibrate concentrations
Concomitant administration of lipid-altering drugs (excluding lipid blood level effects)	
HMG-CoA reductase inhibitors[b]	May result in myopathy and rhabdomyolysis
Resins	Resins may decrease the absorption of fibrates

a Definitive, confirmatory clinical trials to determine the precise risk of potential drug interactions with fibrates are largely lacking. It is unknown whether or not drug interactions described with clofibrate can be generalised to other fibrates.

b See table V.

Similarly, caution should be exercised when anticoagulants, i.e. warfarin, are given with fibrates.[45] Prothrombin time must be monitored closely, and some suggest that the dosage of warfarin be reduced by as much as 50 to 75% if fibrates are to be added. Afterwards, frequent measurements of prothrombin time is recommended until dosage has stabilised.

Some of the most clinically relevant potential drug interactions with fibrates are listed in table VII.

3.3 Concomitant Administration of Lipid-Altering Drugs

This issue has been addressed in the discussion on HMG-CoA reductase inhibitors (see sections 1.3 and 1.4). However, the use of HMG-CoA reductase inhibitors alone has been shown to have a small risk of myopathy in susceptible patients.[3,12-16] The concomitant use of some HMG-CoA reductase inhibitors with fibrates has resulted in reports of

severe myopathy, with secondary kidney failure (rhabdomyolysis). Patients who are most susceptible to the rhabdomyolysis from the use of HMG-CoA reductase inhibitors and fibrates appear to be patients on many other concurrent medications, such as immunosuppressive agents, antibacterials, corticosteroids etc, renal insufficiency and known myopathy with HMG-CoA reductase inhibitors or fibrates alone. (See table V.)[41,46]

Rhabdomyolysis has occurred with combined gemfibrozil and lovastatin therapy as early as 3 weeks after initiation of combined therapy, as well as after several months.[47-50] In patients at high atherosclerotic cardiovascular risk, who have had an unsatisfactory lipid response to either drug alone, the possible benefit of combined therapy with lovastatin (or other HMG-CoA reductase inhibitors) and gemfibrozil may outweigh the risks of severe myopathy, rhabdomyolysis and acute renal failure. However, there is no assurance that periodic monitoring of creatine kinase levels will prevent the occurrence of severe myopathy and subsequent rhabdomyolysis. Table V outlines some monitoring guidelines if this combination is to be used.

3.4 Special Issues

Due to the concerns of increased noncardiovascular mortality in animal and human studies and because of the relative lack of data demonstrating reduction in atherosclerotic events, clofibrate is no longer generally prescribed in most countries.

4. Nicotinic Acid (Niacin)

4.1 Mechanism of Action and Metabolism

Nicotinic acid is a B vitamin that decreases both LDLC and triglyceride levels and increases HDLC blood levels. Nicotinic acid also lowers elevated lipoprotein (a) blood levels, which is thought to be an important independent, or contributory atherosclerotic risk factor in some patients. The mechanism by which nicotinic acid exerts these effects is not entirely understood, but may involve several actions, including a decrease in esterification of hepatic triglycerides and inhibition of lipolysis with decreased free fatty acid release from adipose tissue.

Table VIII. Some of the most clinically relevant drug interactions with nicotinic acid (niacin)[41]

Concomitant administration of non–lipid-altering drugs
High dose aspirin (acetylsalicyclic acid)
Uricosuric agents (sulfinpyrazone)
?Nicotine patch[a]
Diabetes mellitus treatments[b]
Alcohol (ethanol)
Concomitant administration of lipid-altering drugs (excluding lipid blood level effects)
?HMG-CoA reductase inhibitors[a]
Resins

a Clinical significance has not been confirmed by definitive, controlled, repeated clinical trials.[22,52]

b Nicotinic acid may result in an increase in glucose blood levels, and thus require intensified diabetes mellitus treatments, such as more aggressive dietary efforts, or increase in dosage of oral hypoglycaemic drugs and/or insulin.

? = Undetermined clinical significance.

Nicotinic acid is rapidly absorbed from the intestine and is metabolised in the liver to metabolites that are excreted in the urine.[42]

4.2 Drug Interactions

Nicotinic acid may potentiate the effects of ganglionic blocking agents and vasoactive drugs, resulting in postural hypotension. Nicotinic acid, in combination with clonidine, may exacerbate orthostatic hypotension.[11]

Concomitant administration of high dose aspirin (acetylsalicylic acid) with nicotinic acid may decrease the metabolic clearance of nicotinic acid. The clinical relevance of this finding is unclear. Aspirin may also exacerbate, or potentiate nicotinic acid-induced gastritis and hyperuricaemia.[51] (table VIII).[22,41,52]

Concomitantly administered alcohol (ethanol) or hot drinks with nicotinic acid may increase the adverse effects of flushing and pruritus, and should be avoided at the time of drug ingestion.

Nicotinic acid may also worsen underlying conditions, which may require an increase in medications used to treat that condition. For example, in

susceptible patients, nicotinic acid may produce a predictable, dose-related increase in glucose blood levels, requiring adjustment of antidiabetic treatments such as more aggressive dietary efforts, or an increased need for higher dosages of oral hypoglycaemic/antihyperglycaemic agents or insulin.

Finally, one of the most common and severe systemic adverse effects of nicotinic acid is liver toxicity. Therefore, concurrent use of this agent with significant amounts of alcohol, or other drugs and substances with known liver toxicity, could possibly potentiate liver dysfunction.

4.3 Concomitant Administration of Lipid-Altering Drugs

Rare cases of rhabdomyolysis have been associated with the simultaneous administration of nicotinic acid and other lipid-altering drugs, such as with HMG-CoA reductase inhibitors.[53,54]Physicians should understand the potential risks and benefits of the use of nicotinic acid with HMG-CoA reductase inhibitors and patients should be monitored carefully for signs and symptoms of myalgias, particularly during the initial months of therapy, or during any periods of upward dosage titration of either drug. Periodic serum creatine phosphokinase determinations should be considered. However, it should be noted that the package inserts of pravastatin and fluvastatin cite studies suggesting that, when used in combination with nicotinic acid, myopathy was not observed.[20,21] In addition, while the package insert for simvastatin implies a potential drug interaction, a controlled trial of nicotinic acid and low dose simvastatin did not demonstrate significant changes in creatine phosphokinase blood levels or myopathy with concurrent use.[22] Similarly, a controlled trial of fluvastatin with nicotinic acid has proven to be well tolerated with combined use.[23]

4.4 Special Issues

Although high dose aspirin may decrease nicotinic acid metabolism, low dose aspirin is often recommended to be taken before nicotinic acid to decrease many of the most common and least tolerated adverse effects of nicotinic acid, including flushing, warmth and paraesthesias and burning to the skin. This benefit is thought to be due to aspirin's suppression of nicotinic acid–induced prostacyclin release from the endothelium. Some patients with a history of gastritis, peptic ulcer disease and haemorrhagic stroke may be at an increased risk for complications of aspirin treatment. In addition, if the risks of long term aspirin treatment (such as potentiation of the gastritis effects of nicotinic acid, with, or without gastrointestinal bleeding) outweigh the benefit of reducing nicotinic acid-induced flushing, the aspirin dose may be reduced to antithrombotic doses, such as 81mg of enteric coated aspirin per day.[55] Alternatively, aspirin may be discontinued altogether, if necessary, after 2 to 4 months once flushing has decreased, or is no longer occurring.

5. Fish Oils

5.1 Mechanism of Action and Metabolism

Omega-3 fatty acids are polyunsaturated fatty acids abundant in cold-water marine fish such as mackerel, herring, sardines and salmon. The omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) found in these fish oils have been shown to reduce VLDL synthesis in the liver with a reduction in triglyceride blood levels.[11]

As with other fatty acids and other lipids and lipoproteins, the liver plays a central role in omega-3 fatty acid metabolism.

5.2 Interactions

Omega-3 fatty acids are precursors to prostaglandin. Therefore, fish oil consumption usually decreases platelet aggregation and, theoretically, may increase the risk of haemorrhage. However, significant bleeding has not been reported in the many clinical trials of fish oil therapy.[11] Nevertheless, fish oils, as with any other antiplatelet or anticoagulant drug, should be used with caution in patients at high risk for haemorrhagic stroke, such

Table IX. Some of the most clinically relevant potential drug interactions with fish oils[56]

Concomitant administration of non–lipid-altering drugs
Anticoagulants[a]
Aspirin (acetylsalicyclic acid)[a]
Diabetes mellitus treatments[b]
Concomitant administration of lipid-altering drugs (excluding lipid blood level effects)
Resins[c]

a The clinical significance of any potential adverse drug interaction with fish oils and anticoagulants or aspirin are yet to be proven by definitive, confirmatory clinical trials. In fact, in patients at risk for thrombosis, the antithrombotic properties of fish oils may, conceivably, be beneficial.

b At worst, fish oils may cause a transient increase in glucose blood levels, and thus may require adjustment of diabetes mellitus treatments, such as more aggressive dietary efforts, or increase in dosage of oral hypoglycaemic drugs and/or insulin for a few weeks. However, most studies have demonstrated no significant effect of fish oils, rich in omega-3 fatty acids, on glucose blood level control.

c Theoretical interaction.

as in those patients with very poorly controlled high blood pressure (table IX). Alternatively, it is possible that a decrease in platelet aggregation may be advantageous in decreasing the risk of acute thrombotic events (myocardial infarction and most cases of thrombotic stroke).

A transient increase in glucose blood levels in patients with diabetes mellitus or glucose intolerance has been sometimes described as an adverse effect of fish oil treatment.[11] But most trials have demonstrated no significant effects upon blood glucose levels.

Although there may be no specific drug interactions with fish oils, the use of other drugs that impede thrombosis may enhance the possibility of bleeding. Some studies have suggested that aspirin may not affect bleeding time in patients treated with fish oils given concomitantly.[56] Nonetheless, for high risk patients, it may be reasonable to clinically monitor them for symptoms of bleeding.

5.3 Concomitant Administration of Lipid-Altering Drugs

No significant, definitive adverse drug interactions have been reported with the use of fish oils and other simultaneously administered lipid-altering drugs. Furthermore, specific fish oil preparations high in EPA and DHA may be very effective in lowering triglyceride blood levels and in fact, may often be as efficacious as the use of fibrates. For this reason, the use of fish oils may be an acceptable alternative to fibrates, particularly if the use of a HMG-CoA reductase inhibitor is being considered.

5.4 Special Issues

In some patients, fish oils may cause diarrhoea. If this is of sufficient severity, absorption of other drugs may be decreased.

6. Probucol

6.1 Mechanism of Action and Metabolism

Probucol lowers LDLC and HDLC blood levels and has been shown to be the most potent and consistent antioxidant drug available, with antioxidant effects greater than vitamin E at doses as high as 800 IU/day.[57]

Probucol's mechanism of action has not been definitively characterised. However, its effect may be due to an increased rate of LDLC catabolism. Increased excretion of fecal bile acids, a final metabolic pathway for the elimination of cholesterol from the body, has been observed. As a result, diarrhoea may occur and may potentially decrease the absorption of other concomitantly administered drugs.

Probucol is not readily absorbed. Its main elimination is through the bile and faeces. However, it is very lipid soluble and once steady state is reached, it may remain in adipose tissue for more than 6 months.

6.2 Drug Interactions

As noted before, probucol is highly lipophilic and its absorption may be dramatically increased when administered with a high-fat meal.[41]

The most potentially serious drug interactions are related to the prolongation of the QT interval on the electrocardiogram (ECG). Therefore, it is

recommended than an ECG should be done prior to starting treatment with this agent and repeated at appropriate intervals during treatment. If an abnormally long QT interval is observed, then discontinuation of probucol should be considered. Furthermore, patients should be monitored for palpitations, or syncopal episodes that might suggest cardiac dysrhythmias.

With concomitant use of probucol and any drug with the potential to increase the QT interval, the greatest risk for toxicity occurs upon initiation, or an increase in the dose of either drug. Drugs of special concern in patients treated with probucol include tricyclic antidepressants, class I and III antiarrhythmics and phenothiazines. Furthermore, any drug that may cause hypokalaemia or hypomagnesaemia, severe bradycardia (β-blockers) or that may affect the AV node (digoxin) may place the patient at risk if used in combination with probucol.

Some of the most clinically relevant potential drug interactions with probucol are listed in table X.

6.3 Concomitant Administration of Lipid-Altering Drugs

No significant drug interactions have been reported with the use of probucol and other concurrently administered lipid-altering drugs. However, patients may experience a laxative like effect, due to the cholinergic effects of probucol. This may be a therapeutic advantage in those patients who experience constipation with resin lipid-lowering agents, but may constitute a risk of malabsorption for other concomitantly administered drugs.

6.4 Special Issues

Although probucol may have some lipid-altering benefits, its use does have some drawbacks such as reductions in HDLC blood levels (although the clinical significance of this is unclear). However, due to the lack of clinical trial efficacy in reducing atherosclerotic disease, probucol is no longer marketed in the US and its use is limited to a few remaining countries.

Table X. Some of the most clinically relevant potential drug interactions with probucol[41]

Concomitant administration of non–lipid-altering drugs
May further worsen high density lipoprotein cholesterol blood levels
Androgens
Progestin
May have the potential to increase the risk of cardiac dysrhythmias
β-Blockers
Group 1a antidysrhythmic agents (quinidine, procainamide, disopyramide)
Digoxin
Tricyclic antidepressants
Phenothiazines
Concomitant administration of lipid-altering drugs (excluding lipid blood level effects)
Resins

7. Alcohol (Ethanol)

Alcohol may not generally be considered a 'drug' by the general public. As a result, the patient may not list it as a medication prior to the clinician's consideration of prescribing lipid-altering drugs. Therefore, it is important to specifically inquire as to the use of alcohol in all patients prior to prescribing lipid-altering drugs because even mild to moderate alcohol consumption may have adverse effects upon blood lipid levels (such as increasing triglycerides), as well as a toxic effect to body tissues (such as gastritis, hepatic enzyme elevation, cardiac toxicity, myositis, etc.) in susceptible individuals. Furthermore, low to moderate, or intermittent alcohol ingestion may inhibit some drug metabolising enzymes. This may potentially increase the risk of myopathy or liver toxicity when used in combination with drugs such as HMG-CoA reductase inhibitors. Conversely, heavy, long term consumption of alcohol may result in hepatic enzyme induction which has the potential to accelerate drug metabolism and thus reduce the lipid-altering effects of simultaneously administered agents.

Table XI provides examples of potential drug interactions of alcohol consumption with lipid-altering drugs.

Table XI. Some of the most clinically relevant potential lipid-altering drug interactions with alcohol (ethanol)

Metabolic effects	Hyperuricaemia may occur, or be exacerbated when alcohol is used in addition to nicotinic acid (niacin)
	The flushing effects of nicotinic acid may occur, or be exacerbated, if taken concurrently with alcohol
Cardiac toxicity	In susceptible patients, alcohol may be a cardiac toxin. Therefore, the cardiac dysrhythmic effects of nicotinic acid, and possibly probucol may occur, or be exacerbated, particularly if the alcohol consumption is heavy, and of long duration
Gastrointestinal	Signs, and symptoms of gastritis may be worsened if alcohol is taken concurrently with nicotinic acid. For patients who have gastritis with other lipid-altering drugs, alcohol has the potential to worsen gastritis symptoms
Liver toxicity	The risk for elevations in liver enzymes, with or without toxic hepatitis, may be increased if alcohol is taken concurrently with nicotinic acid, HMG-CoA reductase inhibitors, or fibrates
Myositis	The risk for myositis may be increased in patients who consume intermittent, mild/moderate alcohol

8. Conclusion

Prior to prescribing lipid-altering drugs, prior to changing lipid-altering drugs (perhaps even within the same class), or prior to combining two or more lipid-altering drugs, it is important for the clinician to understand potential drug interactions. Although the risks for potential drug interactions may be exceeded by the benefits of treatment with certain combinations of drugs, having knowledge of potential drug interactions can alert the physician as to how best to avoid adverse effects and how best to monitor their patients.

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