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Overcoming challenges with statin therapy

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Because statins markedly reduce cardiovascular risk, poor persistence with them is an important clinical problem. If statins were stopped for valid reasons, there may be no opportunity for improvement. However, there are many invalid reasons why patients stop medication, often for symptoms that, although not causally related, are listed in package inserts. Physicians also stop statin therapy for invalid reasons. Several consensus statements, from the Canadian Cardiology Society,[1] the European Atherosclerosis Society,[2] and the National Lipid Association,[3] have reviewed aspects of the adverse effects of statins from various perspectives. In this narrative review, we discuss approaches to helping patients continue needed therapy with statins, based on experience with >50 000 patients attending our vascular prevention clinics over many years and from the perspective of clinical pharmacology, including pharmacokinetic and pharmacogenomic factors that impair persistence by worsening causally related effects of statins.

Importance of Helping Patients Continue to Take Statins

Adherence markedly affects outcomes in high-risk patients. In a recent study of guideline-based treatment in peripheral vascular disease,[4] patients adhering to all 4 therapies had a nearly 40% reduction in major cardiovascular events and a 45% reduction in adverse limb events. Inhibitors of hydroxymethylglutaryl–coenzyme A reductase (statins) markedly reduce cardiovascular risk, particularly in high-risk patients. In a large meta-analysis of clinical trials, each 1-mmol/L reduction of low-density lipoprotein (LDL) cholesterol reduced cardiovascular events by just over 20%[5]; importantly, this benefit was independent of the baseline LDL cholesterol. The authors concluded that "reduction of LDL cholesterol by 2 to 3 mmol/L would reduce occlusive vascular events by about 40% to 50%." Stopping a medication that reduces risk by half is equivalent to doubling risk; it is, therefore, an important problem that so many patients stop statins. Evidence now supports statin treatment in primary prevention,[6] and recent revision of guidelines on treatment of cholesterol[7] will result in statin treatment of many more patients,[8] so persistence with statin therapy is an issue that is increasing in importance. In discussion with patients who believe they are having adverse effects of statins, it is important to evaluate the likelihood that the symptoms are caused by statins or attributable to some other cause. A history of probably causal adverse effects (myalgia, cramps, weakness), particularly with repeat occurrence of adverse effects after re-trial of statin following a drug holiday or after a recent increase in dose or potency of statin, will be convincing evidence that the statin is causing the adverse effect; this may be supported by increased blood levels of creatine kinase. Less convincing will a history of symptoms attributed to statin that are unlikely to be causally related, as described later, particularly when the new symptoms arose after a long period of well-tolerated statin.

Problems With Persistence

In real-world practice, as opposed to clinical trials, persistence drops off rapidly; after 3 years, <40% of patients persist in taking statins for primary prevention,[9] and for secondary prevention, only 45% are persistent at 3 years.[10] This is the case all over the world.[11,12] Even in high-risk patients such as diabetics, persistence is only ≈50% at 2 years.[13] Haukka et al,[14] in a nationwide study in Finland, observed a 5% decrease in mortality from coronary heart disease for every 10% increase in persistence with statins. In Italy, a study of >19 000 patients showed that the 41% of patients with high adherence had a 40% reduction in risk of cardiovascular events, compared with those who had low adherence.[15]

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Persistence, Putative Adverse Effects, Health Beliefs, and Package Inserts

If nonpersistence were unavoidable—for example, if patients stopped statins for good reason or if physicians discontinued statins for good reason, such as causally related adverse effects—there might be little reason to try to improve on it. However, there are many reasons why patients and physicians mistakenly stop these medications. There are probably only 2 important causally related adverse effects of statins—myopathy and impairment of insulin resistance—and as discussed later, both are probably related to impaired mitochondrial function and are treatable or avoidable in most cases. Yet, as shown in Table 1, adapted from a study by Zhang et al,[16] most patients stop statins for other reasons, and most patients who stopped them because of adverse effects attributed to statins were able to continue them when rechallenged.

Why Patients Mistakenly Stop Statins

One important reason for patient discontinuation of statins is that too often package inserts provide misleading information. They commonly list not just causally related adverse effects of statins but also mythical adverse effects and, in too many cases, simply all symptoms known to humankind,[17] whether they were caused by the medication, cancer, a flulike illness, a hangover, or any other cause. Patients read such lists and often stop their medication when they have a symptom they find on the list. Perhaps the worst word on such lists is "dizziness," a word that has so many meanings it is worse than useless. There are drugs, such as α-blockers and tricyclic antidepressants, that can cause postural hypotension, but there is probably no drug that causes vertigo. Busy physicians who respond to patients' concerns by simply changing medications (rather than discussing the issue of causality) merely feed into the patients' belief that the symptoms were causally related to the drug. In some patients, this may result in long lists of drugs that "cause" adverse effects, most of which are not causally related. What is needed is useful information about causality—such as a table showing the frequency of symptoms on active drug versus placebo. Such lists make it obvious that, in most cases, common symptoms such as fatigue, headache, nausea, diarrhea, constipation, and so on are just as common when taking placebo as when taking active drug.

In extreme cases, it may be useful to carry out a blinded "n-of-1" crossover study to determine the likelihood of causality.[17] This may seem difficult to carry out, but we have used it in clinical practice. Unfortunately, some patients convinced of causality may not accept a negative result.

Why Physicians Mistakenly Discontinue Statins

Reasons why physicians inappropriately discontinue or limit the dose of statins include commonly held myths about statin adverse effects including hepatotoxicity, nephrotoxicity, cognitive decline, cataracts, and intracerebral hemorrhage (ICH). In some cases, this may be driven by concern about litigation, when guidelines specify, for example, monitoring of liver function.

Although rare cases of true hepatotoxicity may exist,[1] statins probably do not cause hepatotoxicity, as stated in the 2013 International Atherosclerosis Society guideline.[18] Fluc-

Table 1. Reasons for Discontinuation of Statins

Reasons for Discontinuation of Statins Among Patients With a Statin-Attributed Event	Percent of Patients
No longer necessary, ineffective, change requested by insurance	16
Inadequate coverage by insurance, too expensive, switch to another drug, rejected by patient	4.8
Adverse events attributed to statins	11.9
Myalgia or myopathy	4.71
Other musculoskeletal problems (cramps, arthralgia, extremity pain, other)	2.54
General medical (asthenia, pain fatigue, other)	2.31
Hepatobiliary	2.1
Gastrointestinal	1.6
Nervous system and psychiatric disorders (memory, other)	0.82
Immune, vascular, cardiac disorders	0.86
Injury, poisoning, skin, reproductive, respiratory, thoracic, mediastinal, ear/labyrinth	0.4
Blood/lymphatic, renal/urinary, eye, metabolism/nutrition	0.08

Based on data from 107 835 patients in routine care from Zhang et al.[16]

tuations in blood levels of transaminase enzymes that are often blamed on statins ("transaminitis") are more likely to be caused by fatty liver or by release of enzymes from muscle in patients with statin myopathy.[19,20] In the Heart Protection Study, in which >20 000 high-risk patients were randomized to simvastatin 40 mg versus placebo and were followed for 5 years, hepatotoxicity was undetectable.[21] Athyros et al[22] compared patients with and without abnormal liver function tests in the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) study. They found that liver function tests actually improved among patients given statins, whereas they worsened in patients not given statins. Further, the cardiovascular benefit of statins was greater among patients with abnormal liver function tests than among patients with normal liver function tests at baseline. Their conclusion[22] was that "Statin treatment is safe and can improve liver tests and reduce cardiovascular morbidity in patients with mild-to-moderately abnormal liver tests that are potentially attributable to non-alcoholic fatty liver disease." Guidelines regarding monitoring of liver function in patients taking statins should be revised accordingly.

The myth of ICH from statins[23] arose mainly from the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial[24] and resulted from intention-to-treat analyses that did not take into account the high rate of crossover of patients from placebo to active therapy or the high dropout rate. Patients in that study were randomized to atorvastatin 80 mg daily versus placebo, so patients taking atorvastatin had much lower levels of LDL cholesterol. However, patients with ICH in that study did not have lower levels of LDL; a more likely interpretation of the reason for the observed increased risk of ICH is that they stopped their antihypertensive medication when they went off their study medication.[25] Recent studies from a stroke registry,[26] a population-based study,[27] a meta-analysis,[28] and studies in patients treated with thrombolysis[29–31] confirmed that low levels of LDL cholesterol or statins do not increase the risk of ICH. Statins also probably do not cause cataracts.[32]

Despite anecdotes and 2 suggestive small studies,[33,34] statins probably do not cause cognitive decline. There was no association of statins with dementia in the Cardiovascular Health Study,[35] the Ginkgo Evaluation of Memory Study,[36] or the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study.[37] In the Rotterdam Study, statins reduced the occurrence of dementia.[38] There are good reasons to think that therapies that reduce the risk of stroke should also reduce the risk of dementia.[39] Indeed, a meta-analysis showed in 2013 that statins reduced the risk of dementia.[40]

There may be a difference between dementia and reversible cognitive dysfunction attributed by some patients to statin therapy; however, the burden of the evidence suggests that statins probably do not impair cognitive function.[41–44] While it seems unlikely that reversible cognitive impairment would be causally related to statin, a blinded n-of-1 crossover trial (described later) may be helpful in establishing whether a patient's complaint is truly related to statin therapy. Unfortunately, patients convinced of adverse effects that are probably not causal are extremely difficult to persuade otherwise.

There is no doubt that rhabdomyolysis from statin myopathy can cause renal failure. This is particularly a problem when statins that are metabolized during absorption by intestinal cytochrome P450 (CYP)3A4 are coprescribed with drugs that inhibit that mechanism[45] or, as discussed later, when patients taking such statins consume grapefruit. However, independent of rhabdomyolysis, the myth of nephrotoxicity from statins probably arose from reports of proteinuria after initiation of statins, particularly rosuvastatin.[46] Such reports were based on dipstick assessment of proteinuria and were probably not caused by nephrotoxicity but rather by changes in tubular secretion of low-molecular-weight proteins.[47] It is possible that increases in serum creatine released from damaged muscle may cause a falsely low estimated glomerular filtration rate, when calculated from serum creatinine. It is now clear that statins actually slow the decline in renal function[48–51] or improve renal function.[52]

Statin Myopathy

The most common causally related adverse effect of statins is myopathy. Even without myopathic symptoms, simvastatin 40 mg daily impaired adaptation to exercise training and muscle mitochondrial content in participants with metabolic syndrome.[53] In real-world practice, myalgias and cramps are more common than estimated from clinical trials; in a cardiology clinic in the Netherlands, one-third of patients reported such problems.[54] Bruckert et al[55] reported in a study of 7924 outpatients taking high-dose statins that 38% had limitation of even moderate exertion by muscle pain. Rosenbaum et al[56] reported that among 1074 patients taking statins, 62% complained of stiffness, 67% of cramps, and 50% of weakness or a loss of strength during exertion; 42% of patients had major disruption to their everyday life. However, weakness and wasting are less common (≈1%), and rhabdomyolysis is rare (≈0.1%).[57]

Mechanisms of Statin Myopathy

Vaklavas et al[58] reviewed molecular mechanisms for statin myopathy. One possibility discussed in their review was protein modification. Statins can affect protein prenylation, an important posttranslational modification of membrane-bound proteins, and can adversely affect synthesis of selenoprotein

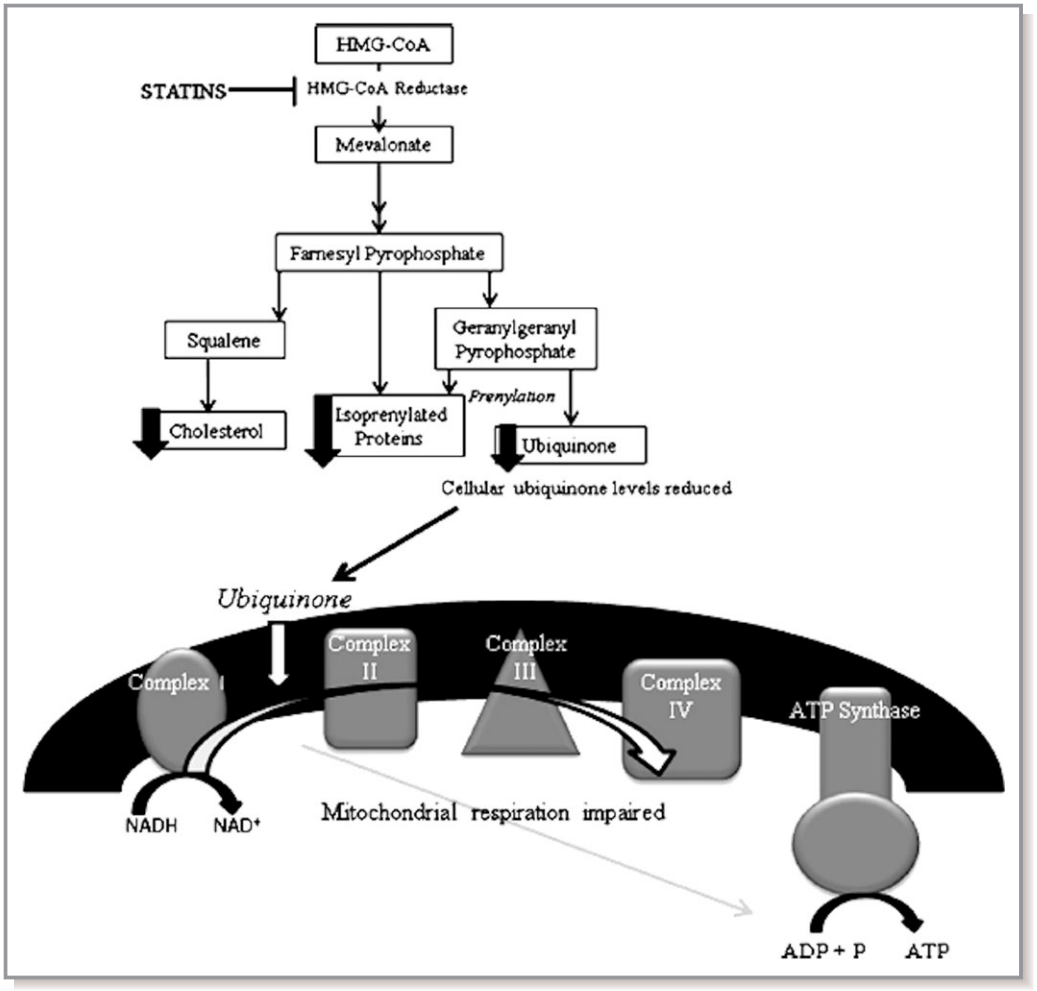

Figure 1. Illustration of the proposed theory explaining statin myopathy as related to cellular ubiquinone depletion. Statins inhibit hydroxy-methylglutaryl-coenzyme A (HMG-CoA) reductase, leading to reduced production of mevalonate pathway metabolites, including ubiquinone or CoQ10. Ubiquinone is an essential coenzyme in the process of mitochondrial respiration, facilitating the transfer of electrons between complex I and II of the respiratory chain. Consequently, depletion of ubiquinone may impair mitochondrial respiration and cellular energy production within skeletal muscle. ADP indicates adenosine diphosphate; ATP, adenosine triphosphate; NAD1, nicotinamide adenine dinucleotide (reduced form); NADH, nicotinamide adenine dinucleotide (oxidized form); P, phosphate. Reproduced by permission of the publisher from Parker et al.[64]

and dolichols, which are involved in the process of protein glycosylation.

Phillips and Haas[59] have argued that lipid lowering per se may cause statin myopathy, but an alternative and more likely explanation is that inhibition of HMG-CoA reductase reduces formation of isoprenoids farnesyl pyrophosphate and geranylgeranyl pyrophosphate, resulting in reduced prenylation of small GTPase proteins involved in cell growth and maintenance[60]; this also results in decreased formation of ubiquinone (Coenzyme Q10 [CoQ10]). Much of statin myopathy may be caused by depletion of muscle levels of ubiquinone (CoQ10) and resultant impairment of mitochondrial function[61–63] (Figure 1).[64] Mechanisms were reviewed by Needham and Mastaglia[60] and by the European Atherosclerosis Society Consensus Panel.[2] Vladutiu found that muscle levels of CoQ10 in patients with statin myopathy were 3 to 4 SDs below normal.[65] This effect is directly related to potency of statins, although lipophilicity may aggravate the problem, with a theoretical advantage of the more hydrophilic rosuvastatin and pravastatin. Brewer[66] reported that for a given reduction in LDL cholesterol, rosuvastatin increased plasma levels of creatine kinase less than other statins.

Factors That Increase Adverse Effects by Increasing Exposure to Statins

There are a number of mechanisms that affect drug exposure in individual patients; these are integral to and associated

with risk of adverse events that exhibit dose dependence (notably myopathy). They include pharmacokinetic interactions, and pharmacogenomic factors that result in higher levels of statins in the blood and in hepatic and muscle tissue.

Pharmacokinetic Interactions

Drugs

Two main classes of drug interactions will account for most of the important interactions of statins with other drugs: drugs that affect CYP3A4/5 and drugs that affect transport proteins. An additional mechanism, affected by gemfibrozil, is glucuronidation.[67] Tables 2 and 3 summarize statin metabolism and interactions.[68–75] For reasons discussed later, simvastatin and lovastatin are particularly susceptible to huge drug interactions. Indeed, in considering the clinical relevance of polymorphisms of *SLCO1B1* affecting statins, the Clinical Pharmacogenomics Implementation Consortium restricted its concerns to simvastatin.[67]

Grapefruit Juice

The effect of grapefruit on drug metabolism was first described by our group in 1989[76] and further elucidated in 1991.[77] The discovery was serendipitous; we used grapefruit to mask the flavor of ethanol in a study of interaction between ethanol and felodipine.[76,78] Almost immediately, drug manufacturers sought to downplay the magnitude and importance of this interaction, and this may possibly account for the important underestimation of this problem. Contrary to the statement by Egan and Colman,[79] large quantities of grapefruit are not required to have an important effect on drug metabolism. Grapefruit juice, probably mainly through the effect of cyanocoumarins, is a suicide inhibitor of gut wall CYP3A4; only a single glass of grapefruit juice[80] or a single fruit daily[81] is required to have the effect, and it persists for >24 hours, so it is not safe to take the drug in the evening if the grapefruit is taken in the morning, as is so often stated. This is a particular problem with drugs that have low bioavailability caused by inactivation during absorption by intestinal CYP3A4. Because simvastatin and lovastatin are only 5% bioavailable as a result of this mechanism, grapefruit and other inhibitors of CYP3A4 have the theoretical potential to increase blood levels 20-fold, and indeed grapefruit increases the area under the curve of the levels of both simvastatin[80] and lovastatin[82] by 15-fold. Atorvastatin area under the curve only doubles with grapefruit,[83] and pravastatin and rosuvastatin are not affected.[83,84]

Although pharmacists will often detect potential drug interactions, grocers seldom inquire about medication history when dispensing grapefruit.[85] For this reason, a case report from Germany illustrates why particular caution is needed with simvastatin and lovastatin. A woman taking 80 mg of simvastatin daily developed rhabdomyolysis 4 days after beginning to consume one grapefruit daily.[81]

Insulin Resistance/Aggravation of Diabetes

In the past several years, it has become evident that statins increase the risk of incident diabetes, by ≈9% to 28%.[86–89] For this reason, among others, we tend to use low-moderate doses of statins in combination with ezetimibe. Because statins and ezetimibe affect different mechanisms, they are synergistic: 10 mg of atorvastatin with 10 mg of ezetimibe lowers the LDL to the same extent as 80 mg of atorvastatin[90] but, in our experience, with fewer adverse effects. It seems likely from meta-analyses that most of the benefit of statins is the result of the reduction in LDL cholesterol.[91] Putative benefits such as lowering of C-reactive protein are unlikely to be important, since Mendelian randomization studies[92,93] and some large clinical trials[94,95] indicate that lowering of C-reactive protein is probably not important in vascular prevention. The results of the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) trial[96] support this approach.

Table 2. Summary of Relevant Pharmacokinetic Determinants of Disposition for Selected HMG-CoA Reductase Inhibitors[68–75]

	Oral Bioavailability	Metabolism	Transport	Effect of SLCO1B1 Variants on Drug Exposure
Atorvastatin	12–14%	CYP3A4/5	ABCB1, ABCC2, SLCO1B1	↑52–144%
Fluvastatin	19–29%	CYP2C8/9/19	SLCO1B1, SLC15A1	↑13–19% (NS)
Lovastatin	<5%	CYP3A4/5	ABCB1, ABCC2, SLCO1B1	NA
Pravastatin	18%	Sulfation	SLCO2B1, SLCO1B1, ABCB1/11, ABCG2, ABCC2, SLC22A6/8	↑39–111%
Rosuvastatin	20%	CYP2C9,2C19	ABCB11, SLCO1B1, SLCO2B1	↑6–117%
Simvastatin	<5%	CYP3A4/5	ABCB1, ABCC2, SLCO1B1	↑23–221%

Table 3. Major Pharmacokinetic Interactions and Magnitude of Effect[68–75]

Disposition Pathway	HMG-CoA Reductase Inhibitor	Reported Change in Area Under the Curve With Interacting Agent	Important Interacting Agents
CYP3A4/5±OATP1B1	Atorvastatin	+50% to 500%	Amiodarone, clarithromycin, diltiazem, grapefruit juice, itraconazole, ketoconazole, protease inhibitors
	Lovastatin	+200% to 2000%	
	Simvastatin	+200% to 2000%	
CYP2C8/9/19	Fluvastatin	+84% to 400%	Cyclosporine, fluconazole
	Rosuvastatin	NS	
OATP1B1	Atorvastatin	Minimal	Gemfibrozil
	Lovastatin	+100% to 200%	
	Simvastatin	+100% to 200%	
	Pravastatin	+100%	
	Rosuvastatin	+100%	
MDR1+OATP1B1+other transporters	Atorvastatin	+500% to 1400%	Cyclosporine
	Fluvastatin	+100% to 300%	
	Lovastatin	+400% to 2000%	
	Pravastatin	+400% to 1000%	
	Rosuvastatin	+400% to 1000%	
	Simvastatin	+500% to 700%	
Inducers of CYP3A4+MDR1±other transporters	Atorvastatin	−60% to 90%	Rifampin, carbamazepine
	Fluvastatin	−50%	
	Lovastatin	NA	
	Pravastatin	−30%	
	Rosuvastatin	NS	
	Simvastatin	−70% to 95%	

Despite the increase in incident diabetes, the cardiovascular risk reduction with statins is of similar magnitude in diabetics to that in nondiabetics,[87,88] and because diabetics are at high risk of cardiovascular events, they should be treated with statins.[97] What is less well known is that supplementation with L-carnitine can prevent the adverse effects of statins on diabetes[98,99] and insulin resistance.[100] Further, in diabetics taking statins, supplementation with L-carnitine improves the effect of the statin on LDL cholesterol, high-density lipoprotein cholesterol, lipoprotein(a), and LDL particle size.[98] L-Carnitine is required for entry of fatty acids into mitochondria and thus has a central role in energy metabolism and mitochondrial function.[101] All of the foregoing therefore supports the hypothesis that the adverse effects of statins may be largely caused by mitochondrial dysfunction.

Genetic Predisposition

It is likely that patients who develop statin myopathy are predisposed genetically.[62,65,102] There appear to be 2 main mechanisms by which patients may be genetically predisposed to statin myopathy. One is pharmacogenomic—mutations affecting absorption, metabolism, transport, and removal of statins that result in higher blood levels and higher tissue levels of statins.[84] Another is mutations affecting mitochondrial function[62,65,102]; the latter could affect either mitochondrial genes[103] or somatic genes affecting mitochondrial function.[104] A third category is disorders of muscle metabolism independent of mitochondrial function, including a polymorphism of glycine amidinotransferase that encodes the rate-limiting enzyme in creatine synthesis.[105] Other mechanisms include genetic variants affecting glucose metabolism, synthesis of CoQ10, lactic acid metabolism, and sensitivity to pain. Table 4[65,102,106] summarizes the genes involved.

In the pharmacogenomic category, a polymorphism of SCLO1B1, which encodes organic anion transport protein B1, was shown to be associated with statin myopathy in a genome-wide association study.[107] Because several statins are metabolized to inactive forms during absorption in the intestinal wall by CYP3A4, as discussed later, it can be expected that

Table 4. Genetic Predisposition to Statin Adverse Effects[65,102,106]

Pharmacogenomic mechanisms that increase blood and tissue levels of statins
Absorption
SCLO1B1, which encodes organic anion transport protein B1 (OATPB1)
Metabolism (cytochrome P450, subfamily genes)
CYP2C8
CYP2D6
Intestinal wall first-pass metabolism (during absorption)
CYP3A4/5
Distribution (tissue levels of drug in muscle)
Uptake transporters
OATP2B1 (human organic anion transporting polypeptide 2B1)
Efflux transporters
Multidrug resistance–associated proteins (ATP binding cassette subfamily C genes)
ABCC1 (MRP1)
ABCC4 (MRP4)
ABCC5 (MRP5)
Mitochondrial dysfunction
COQ2—CoQ10 deficiency
CPT2 carnitine-palmitoyl transferase deficiency II
Other mechanisms affecting muscle function
ATP2B1—calcium-transporting ATPase
DMPK—encodes plasma membrane calcium-transporting ATPase 1
PYGM—glycogen phosphorylase, muscle
AMPD1—adenosine monophosphate deaminase 1
SLC16A4—lactic acid (monocarboxylic acid) transporter
GATM—glycine amidinotransferase creatine synthesis
Other mechanisms
AGTR1—angiotensin receptor 1
NOS3—nitric oxide synthase 3
HTR3B—5-hydroxytryptamine receptor 3b (individual variations in pain perception)
HTR7—5-hydroxytryptamine receptor 7 (individual variations in pain perception)
APOE—apolipoprotein E (reduced compliance in E4 carriers)

polymorphisms or copy number variants of CYP3A4 might also affect blood levels of statins. With regard to tissue levels of drugs, and in particular muscle levels of statins, Knauer et al[108] found that the uptake transporter human organic anion transporting polypeptide 2B1 and the efflux transporters, multidrug resistance–associated protein 1, 4, and 5, are expressed on the sarcolemmal membrane of human skeletal muscle fibers and that atorvastatin and rosuvastatin are substrates of these transporters. Thus, variants of these transport proteins might also predispose to statin myopathy.

Approaches to Minimizing Adverse Effects of Statins

The main causally related adverse effects of statins, myopathy and aggravation of insulin resistance, can be minimized by several maneuvers. First, in patients who experience myopathic symptoms and in patients with insulin resistance and/or diabetes, it may be useful to limit or reduce the dose of statin, with the addition of ezetimibe, bile acid sequestrants, niacin, and/or fibrates, to maintain the LDL-lowering effect. Ezetimibe, which blocks absorption of cholesterol at the intestinal lining, is synergistic with statins. Concerns about possible adverse effects of ezetimibe on atherosclerosis were probably misplaced and were based on measurement of carotid intima-media thickness, which is not atherosclerosis.[109–111] The IMPROVE-IT[96] showed a reduction of cardiovascular events with ezetimibe among patients with acute coronary syndromes, and the Plaque Regression With Cholesterol Absorption Inhibitor or Synthesis Inhibitor Evaluated by Intravascular Ultrasound (PRECISE-IVUS)[112] showed regression of coronary plaque with ezetimibe added to atorvastatin.

Possible Treatments Worth Considering

It may useful to give supplements of CoQ10.[1,113] However, the doses required may need to be higher than in most of the clinical trials (200–400 mg twice a day, or perhaps more), as illustrated in the case report that follows. Although it is commonly stated that the effects of CoQ10 supplementation are contradictory and unproved[114] and a meta-analysis indicated that it is not beneficial,[115] the authors of the meta-analysis concluded that "Larger, well-designed trials are necessary to confirm the findings from this meta-analysis." There may be problems with small trials, including patients who do not have true statin myopathy. A related meta-analysis[116] concluded that statins do lower levels of CoQ10 in plasma.

Higher doses of ubiquinone such as 300 mg twice daily are more effective in improving muscle fatigue.[117,118] The negative trial of Bookstaver et al[119] used only 60 mg twice daily. Fedacko et al[120] found a significant improvement of statin myopathy with CoQ10 200 mg daily in a factorial designed trial in which selenium was not efficacious. Ubiquinone does improve mitochondrial function in an animal model of statin myopathy.[121]

Table 5. Approaches to Minimizing Adverse Effects of Statins

For the present
1 Reduce the dose of statin, alternate daily dosing of statin, or switch to weaker statin
2 Add ezetimibe, bile acid sequestrants, niacin, fibrates, proprotein convertase subtilisin/kexin 9 antagonists/antibodies
Possible treatments worth considering
1 Supplement with Coenzyme Q10 200 to 400 mg twice daily
2 Supplement with L-carnitine 500 to 1000 mg twice daily
In future
1 Squalene synthase inhibitors?
2 Other new therapies in development

It may also be useful to add supplements of L-carnitine (500–1000 mg twice a day).[122,123] In diabetics taking simvastatin, L-carnitine not only prevented the rise of blood sugar but improved the effect of statin on LDL cholesterol, high-density lipoprotein cholesterol, lipoprotein(a), and LDL particle size.[98,99] L-Carnitine was effective in an animal model of statin myopathy.[124] However, effects of L-carnitine on production of trimethylamine-N-oxide by intestinal bacteria[125] may limit the usefulness of L-carnitine supplements for this purpose; this will require further study. The issues have recently been reviewed.[126] Table 5 summarizes approaches to minimizing adverse effects of statins.

Switching Statins, Low-Dose and/or Alternate-Day Statins

The truly causal adverse effects of statins are probably related to efficacy in inhibition of HMG-CoA reductase and therefore entirely attributable to intensity of statin therapy. Switching statins probably will not help reduce adverse effects except when weaker statins or lower doses of statins are used. A useful maneuver may be alternate-day low-dose statin in combination with ezetimibe. A case report illustrates this.

Case Report

The patient was a 63-year-old physician with a mitochondrial disorder (multiple lipomatosis) and moderately severe statin myopathy. He had severe nocturnal leg cramps that abated during drug holidays from statins and recurred reproducibly on reinitiation of statins; they were only partly relieved with CoQ10 150 mg daily. He had proximal muscle weakness in the hip girdle, and creatine kinase levels were repeatedly elevated to 4 to 5 times the upper normal limit for the laboratory, despite reducing his dose of rosuvastatin to 5 mg daily in combination with ezetimibe. Because of these difficulties, he stopped statin therapy despite a coronary calcium score of 300 and a family history of premature cardiovascular death. At that time, his carotid total plaque area (a strong predictor of cardiovascular risk[127–129]) was only 20 mm^2, so he felt somewhat reassured about the safety of stopping statin, while continuing ezetimibe. However, by April 2009, his plaque area had progressed to 29 mm^2, a matter of concern since Spence et al reported in 2002[127] that plaque progression was associated with a doubling of risk. (This was the basis for developing a new approach to managing atherosclerosis, "treating arteries instead of treating risk factors,"[130] which markedly reduced risk among high-risk patients.[131]) Because of the plaque progression, he began taking rosuvastatin 5 mg on alternate days with an increased dose of CoQ10 (200 mg daily). As shown in Figure 2,[130] the plaque area regressed in just over 3 months to 19 mm^2. In later years he continued ezetimibe 10 mg daily and a Mediterranean diet, but his myopathic symptoms and high creatine kinase levels persisted. He therefore reduced the dose of rosuvastatin to 2.5 mg on alternate days, and increased the dose of CoQ10 to 400 mg twice daily to tolerate it, but the plaque regression persisted; in August 2015, the plaque area was only 15 mm^2.

What Is to Be Done With Patients Who Are Entirely Intolerant of Statins?

Some patients, particularly those with mitochondrial disorders, are entirely unable to tolerate even small doses of statins. For such patients, continuation of ezetimibe, addition of fibrates, perhaps slow-release niacin preparations if tolerated, and strict adherence to a Mediterranean or perhaps vegan diet may be indicated.

Antibodies to proprotein convertase subtilisin/kexin 9[132] are recently available on the market, and offer a substitute or add-on to low-dose statins for patients with myopathy or diabetes. Unfortunately, their high cost may limit their usefulness.[133]

In the future, the problem of statin adverse effects may be solved by the availability of new alternatives such as inhibitors of cholesterol ester transfer protein[134] or siRNA silencing[135] or other approaches to blocking proprotein convertase subtilisin/kexin 9, and other new therapies in development.[136–138] Inhibitors of squalene synthase[139] should increase levels of CoQ10 by shunting, but it appears that this class of drug may not reach the market.

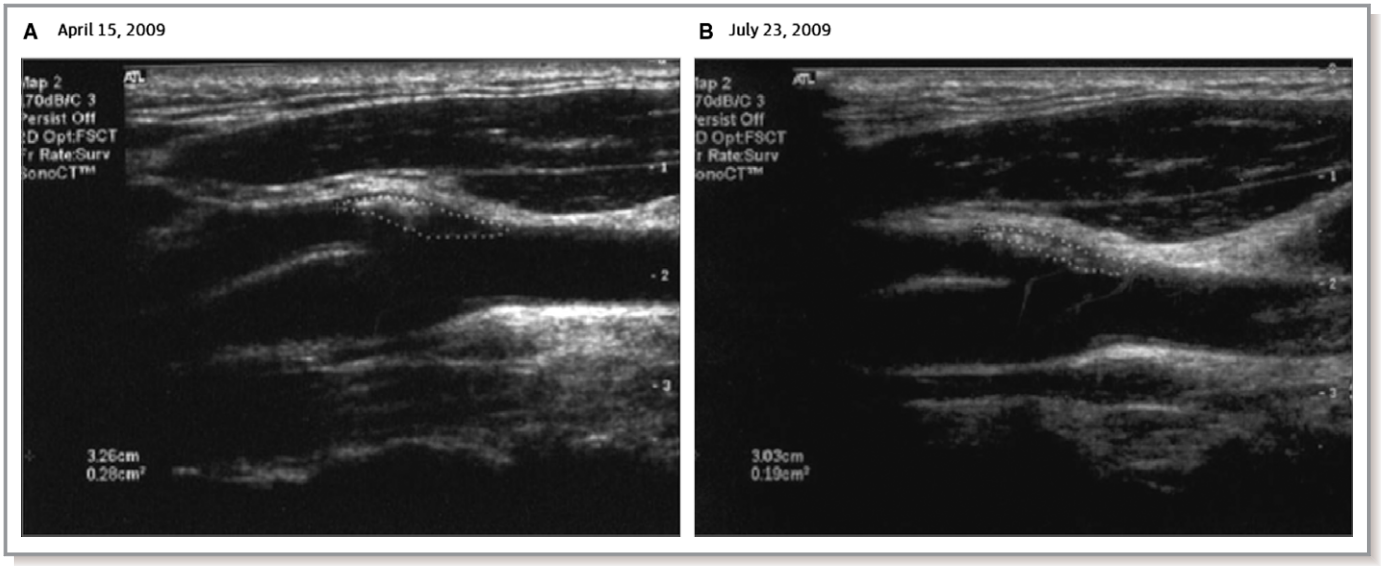

Figure 2. Plaque regression with alternate-day statin and daily ezetimibe. A, A soft plaque is shown at the origin of the right external carotid in a 63-year-old man using ezetimibe alone, having stopped statin because of statin myopathy. His plaque area had progressed from 20 mm^2 6 months earlier, to 28 mm^2. B, After adding back rosuvastatin 5 mg daily with CoQ10 200 mg daily to prevent myalgias, the plaque area regressed to 0.19 mm^2 in just over 3 months. The plaque had also become denser, with regression of the soft plaque and more calcification. Reproduced by permission of the publisher from Spence and Hackam.[130]

Conclusion

Poor persistence with statin therapy is an important and common problem that can be mitigated. Many common reasons for stopping statins are invalid. Pharmacists need to provide better information to patients receiving statins, and physicians need to be better able to help their high-risk patients persist with therapy.

The main causally related adverse effect of statins is impaired insulin resistance, with a risk of diabetes and myopathy. Both of these problems are probably largely caused by impaired mitochondrial function, from depletion of ubiquinone. Although new therapies to lower LDL cholesterol are in development, statins will still be needed for some time, and statin adverse effects can be minimized by several maneuvers.

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