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Statin Adverse Effects: A Review of the Literature and Evidence for a Mitochondrial Mechanism

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Abstract

HMG-CoA reductase inhibitors (statins) are a widely used class of drug, and like all medications have potential for adverse effects (AEs). Here we review the statin AE literature, first focusing on muscle AEs as the most reported problem both in the literature and by patients. Evidence regarding the statin muscle AE mechanism, dose effect, drug interactions, and genetic predisposition is examined. We hypothesize, and provide evidence, that the demonstrated mitochondrial mechanisms for muscle AEs have implications to other nonmuscle AEs in patients treated with statins. In meta-analyses of randomized controlled trials (RCTs), muscle AEs are more frequent with statins than with placebo. A number of manifestations of muscle AEs have been reported, with rhabdomyolysis the most feared. AEs are dose dependent, and risk is amplified by drug interactions that functionally increase statin potency, often through inhibition of the cytochrome P450 (CYP)3A4 system. An array of additional risk factors for statin AEs are those that amplify (or reflect) mitochondrial or metabolic vulnerability, such as metabolic syndrome factors, thyroid disease, and genetic mutations linked to mitochondrial dysfunction. Converging evidence supports a mitochondrial foundation for muscle AEs associated with statins, and both theoretical and empirical considerations suggest that mitochondrial dysfunction may also underlie many non-muscle statin AEs. Evidence from RCTs and studies of other designs indicates existence of additional statin-associated AEs, such as cognitive loss, neuropathy, pancreatic and hepatic dysfunction, and sexual dysfunction. Physician awareness of statin AEs is reportedly low even for the AEs most widely reported by patients. Awareness and vigilance for AEs should be maintained to enable informed treatment decisions, treatment modification if appropriate, improved quality of patient care, and reduced patient morbidity.

Introduction

HMG-CoA reductase inhibitors (statins) have been the best selling prescription drug class in the US and include atorvastatin, the best-selling prescription drug in the world – indeed in history.[1-3] These drugs are perceived to have a favorable safety profile[4-6] and have well documented benefits to cardiovascular disease in many groups, including persons who are younger and older, male and female, at moderate and high cardiovascular risk. In addition, benefits have been objectively shown to exceed risks on average for both total mortality and total morbidity (indexed by serious adverse events), specifically in clinical-trial equivalent middle-aged men who are at high cardiovascular risk.[7-9] Although many people treated with statins do well, no drug is without potential for adverse effects (AEs). There is need for

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awareness of risks as well as benefits of all drugs, particularly those that, like statins, are used on a wide scale where even uncommon effects can translate to significant public health impact.

Statins inhibit the enzyme HMG-CoA reductase, at a stage early in the mevalonate pathway.[10] This pathway generates a range of other products in addition to cholesterol, such as coenzyme Q10, heme-A, and isoprenylated proteins,[10] which have pivotal roles in cell biology and human physiology and potential relevance to benefits as well as risks of statins.[11-13] Additionally, cholesterol itself is not merely a final product (with its own range of vital roles) but also an intermediate to a suite of additional products of fundamental relevance to health and well-being, such as sex steroids, corticosteroids, bile acids and vitamin D, several of which have been shown to be affected with statin administration.[14, 15] The biochemical influences of statins extend well beyond the lipid profile and its constituents (low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C], and triglycerides), and even beyond the direct products of the mevalonate pathway, to include a wide swath of products and functions modified through these as well as nonmevalonate effects of statins, ranging from nitric oxide and inflammatory markers[16] to polyunsaturated fatty acids,[17] among many others.

This report reviews evidence related to statin induction of AEs and evidence for a dose-response relationship, and describes reported drug interactions. Muscle AEs are emphasized as they are the best recognized AEs of statins (liver AEs are perhaps second most recognized), and the AEs on which much of the information on mechanism, drug interactions, and dose-response has been obtained – information that, as we show, has relevance to other statin AEs.[18, 19] Statins lead to dose-dependent reductions in coenzyme Q10,[20-22] a key mitochondrial antioxidant and electron transport carrier that serves to help bypass existing mitochondrial respiratory chain defects.[23-25] We review convergent evidence supporting a role for mitochondrial predispositions and mechanisms for statin muscle AEs. We seek to place other statin AEs in the context this evidence provides, proposing that mitochondrial dysfunction may underlie additional AEs reported on statins.

Muscle Adverse Effects (AEs)

Myositis and Myalgia

The best recognized and most commonly reported AEs of statins are muscle AEs,[26, 27] and include muscle pain, fatigue and weakness as well as rhabdomyolysis. While individual randomized controlled trials (RCTs) often fail to show an excess of muscle problems or symptoms, meta-analysis of randomized double-blind, placebo-controlled trials have shown increased myositis in patients receiving statins relative to placebo (odds ratio [OR] 2.56, 95% CI 1.12-5.85), with myositis there defined as creatinine kinase (CK) > 10 times the upper limit of normal with myalgia.[28]

In contrast to myositis, myalgia was not increased on average based on meta-analysis of RCTs that compared statins to placebo (relative risk [RR] 1.09, 95% CI 0.97-1.23).[28] However, this does not necessarily mean that statins do not cause myalgia, and this point seems not to be uniformly appreciated. Rather, evidence has shown that statins reduce pain and improve walking distance in many individuals (for instance, but not confined to, persons with peripheral arterial disease),[29] an effect that may arise through improved blood flow deriving from endothelial function benefits in persons with endothelial dysfunction.[30] An overall null effect of statins on muscle pain in clinical trials may therefore indicate that, in the samples selected for these trials, statins caused muscle pain in approximately as many people as they relieved it.

In support of this view, triangulating evidence suggest that statins have a causal role in myalgia as well as muscle weakness in some people. For instance: A double-blind, placebo-controlled,

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crossover biopsy study showed partially reversible mitochondrial myopathy in persons reporting non-CK-elevating or minimally CK-elevating muscle symptoms on statins.[31] In a family in which multiple members experienced statin-associated non-CK elevating muscle pain, objective investigation affirmed myopathic findings.[32] Prior muscle symptoms on statins or other cholesterol drugs represent a predictor for future symptoms with statin rechallenge and may signal elevated risk for rhabdomyolysis on statins.[33-36] Patients who experienced muscle symptoms on statins (typically with normal or slightly elevated levels of CK), that reverse with discontinuation, most often re-experienced muscle symptoms if rechallenged with an equivalent or higher expected potency statin based on calculated potency equivalencies; in contrast, those rechallenged with a lower potency statin re-experience problems significantly less frequently, $p<0.01$).[37] These data support the view that muscle symptoms arising on statins and reversing with discontinuation are in many individual cases causally statin-associated, whether or not on average an increase in muscle symptoms occurs with statins.

This observation underscores a critically important point relevant to drug AEs in general, which merits emphasis and has relevance to other reported statin AEs. A significant increase in rates of a problem on drug vs placebo in RCTs supports a causal link between that drug and that AE, in some persons. However, absence of an average significant increase in a problem, or even presence of a significant average reduction in a problem, does not preclude causal occurrence of that problem in some individuals. Illustrating this point are the recognized occurrence of 'paradoxical' increases in blood pressure (BP) in some people with use of medicines designed to lower BP in most people, and 'paradoxical' increases in anxiety or aggression in some people who are given drugs designed to produce the opposite effect.[38-45]

In the case of statins, a potential basis for opposing effects occurring in muscle and in other organs can be identified. Evidence supports the proposition that antioxidant effects of statins underlie (or contribute to) many fundamental statin benefits – including benefits to flow and oxygen delivery[46-48] and inflammation.[49, 50] These effects may participate in improved walking distance in patients on statins, including benefits to muscle/walking in persons with and without peripheral artery disease.[29] Yet a subset of people reproducibly exhibit increases in markers of oxidation on statins,[51] and the occurrence of this increase has been tied to muscle pain on statins.[52, 53]

RCTs are important for evaluating average effects that may have relevance to use of a drug for treatment in a group overall. However, AEs are important to an individual even if they do not occur on average, and non-RCT data, including case-based data, have recognized importance in AE assessments.[54-57] Bearing this in mind, Table I shows a range of additional muscle problems that have been reported on statins beyond the classical 'myalgia' and 'myositis.'[17, 29, 51, 58-78]

Persistent Muscle Effects

Muscle effects arising on statins do not uniformly resolve fully with statin discontinuation.[155] Crossover biopsy studies show a partially reversible mitochondrial myopathy in persons presenting with recurrent muscle pain on statins.[31] Statins elevate the respiratory exchange ratio and do so even in asymptomatic persons, while persons who have been symptomatic on statins show an elevated off-statin respiratory exchange ratio.[156-158] This altered cell respiratory function in persons with AEs may represent a cause (predisposing to statin myopathy) and/or a consequence of statin myopathy; the relative contributions of each awaits prospective study.

A range of cases have now been reported in which statin use has "uncovered" previously clinically silent or clinically tolerated conditions, ranging from McArdle disease[159, 160] to myotonic dystrophy[159] to acid maltase deficiency[161] to possible Kennedy disease.[159] Statins

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have also exacerbated known muscle conditions, such as myasthenia gravis.[78] In the case of mitochondrial myopathies, the relative degree to which statins have unmasked vs induced disease may not always be clear.[159, 162]

Rhabdomyolysis

Rhabdomyolysis is among the best-recognized and most feared complications of statins; it occurs when muscle damage is severe, leading to a marked elevation of CK (e.g. in excess of 10 times the upper limit of normal) often accompanied by evidence of renal dysfunction and occasionally renal failure and death.[81, 94, 163-166] Over 900 unique PubMed citations (as of January 2009) pair the keywords 'rhabdomyolysis' with terms referring to statins, i.e. 'statins', 'HMG', or each generic statin name individually. However, the recognition of rhabdomyolysis as a statin complication does not rest on randomized trial data, which even on meta-analysis do not support a significant increase (e.g. OR 1.59, 95% CI 0.54-4.70).[28]

A case report has suggested that misinterpretation of evidence-based medicine from RCTs on statin rhabdomyolysis may have fatal consequences – and perhaps has had.[81] Underscoring the limitations of clinical trials for AE identification, cerivastatin was withdrawn from the market due to excess risk of rhabdomyolysis, although no cases of rhabdomyolysis occurred on cerivastatin in a meta-analysis of randomized trials.[28] In contrast, observational studies of real-world use reported that rhabdomyolysis occurred with substantially higher frequency on cerivastatin than other statins,[167, 168] particularly for cerivastatin in combination with fibrates (and specifically gemfibrozil).[168] This was true for postmarketing surveillance data[169] and for claims data.[168] Illustrative of this, in one study, claims data rates per 10,000 person-years of treatment were 0.44 for simvastatin, atorvastatin or pravastatin alone (95% CI 0.20-0.84); 5.34 for cerivastatin (95% CI 1.46-13.68); 2.82 for fibrates (95% CI 0.58-8.24); and 0 for no lipid therapy (95% CI 0-0.48). With a modest number of total rhabdomyolysis cases, the difference approached but did not quite reach significance (p=0.056). Rates rose to 5.98 for statin (non-cerivastatin) combined with a fibrate (95% CI 0.72-216.0), and 1035 for cerivastatin-fibrate combinations (95% CI 389-2117).[168]

Emphasizing that figures for a larger group need not apply to subgroups within that group, per year of therapy the number needed to treat, to see one case of rhabdomyolysis was 22,727 for statin (monotherapy) overall, but 484 for older patients with diabetes mellitus treated with combined statin and fibrate, and 9.7 to 12.7 for patients who received cerivastatin plus fibrate.[168] (As reviewed below, much of the excess in cases is attributable to high potency resulting specifically from gemfibrozil-cerivastatin interaction effects.[170, 171])

In the setting of statin rhabdomyolysis, other organs may also be severely affected. Renal failure is well recognized and is a consequence of the rhabdomyolysis, but concurrent heart,[96, 109, 110] pancreas,[96, 105] liver,[96, 106-108, 172] bone marrow,[96, 173, 174] respiratory,[96, 98] and CNS toxicity[96, 112] – or all of the above[96] – are also reported.

Dose Response

A range of sources support a dose relation for statin AEs (Table II[37, 167, 170, 171, 175-184]), although there may exist AEs that are not dose dependent. Meta-analyses of RCTs comparing lower vs higher potency statins are of greatest relevance among the clinical trial data because these examine *similar* patients (within the same study) placed on drugs of different potencies.[176, 178] Results of these meta-analyses have supported more total AEs with statin vs placebo[175] (although this may not be equally true in all settings), more total AEs with intensive vs nonintensive statin use,[176] and more AEs leading to dropouts with intensive vs nonintensive statin use.[176] (Dropout rates are not, however, necessarily greater for lower intensity statin use

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vs placebo in clinical trial samples.[28]) In addition, CK elevations and liver function test (LFT elevations) occur more frequently with higher dose vs lower dose statins.[176, 178]

Rechallenge data also support dose-related effects. This study design examines muscle symptom recurrence in persons with prior statin AEs. Patients rechallenged with same-or-higher potency statins (relative to the potency of the statin on which problems originally arose) usually re-experienced the problem, and did so significantly more frequently than those rechallenged with lower potency statins.[37] Examination of rechallenge data provides a highly efficient study design because at-risk patients are selected for, and by comparing subjects to themselves, erosion of power arising from cross-subject variability is reduced.

Although some investigators promote very low LDL-C targets, proposing that lower is better and no LDL-C is too low,[191-193] the US FDA has stated that "all statins… should be prescribed at the lowest dose that achieves the goals of therapy (e.g. target LDL-C level)."[180] Intensive statin treatment in RCTs does not improve mortality, even in patients with heart disease, relative to less intensive treatment (although it may do so in the setting of acute coronary syndrome).[194] Moreover, intensive treatment comes at the cost of an increased risk of adverse outcomes.[176, 194]

Drug Interactions

Fibrates, particularly gemfibrozil, amplify the risk of rhabdomyolysis on statins (most powerfully for cerivastatin[170, 171]), and are present in many statin rhabdomyolysis reports,[82, 99, 105, 109, 195-221] likely due to their effect of impeding statin metabolism and perhaps their additional lipid-modifying effects. (Other cholesterol-lowering drugs have also been implicated in muscle toxicity[222] and in statin rhabdomyolysis cases, although less frequently.[223-225]) However, lipid-lowering drugs are not the sole drug class that may increase risk of statin rhabdomyolysis and other statin AEs (see Table III,[105 155, 169-171, 179, 195-199, 202, 210, 223-233]).

Drug interactions arise when drugs inhibit metabolic pathways of statins, compete for metabolism with statins, or cause similar or interacting toxicity. Additionally, apparent interactions may arise when drugs serve as markers for existing problems that signal vulnerability to statin AEs.

Several widely used statins – atorvastatin, simvastatin, and lovastatin (and previously cerivastatin, now off the market) – are metabolized by the cytochrome P450 (CYP)3A4 pathway.[318] (Simvastatin acid is also metabolized by CYP2C8; fluvastatin is primarily metabolized by the CYP2C9 pathway, while pravastatin and rosuvastatin are not metabolized by these systems.[318]) Concurrent administration of statins with CYP3A4 inhibitors may raise statin concentrations and risk of toxicity, including rhabdomyolysis.[185] The CYP3A4 pathway is inhibited by a variety of agents including cyclosporin, erythromycin, azole antifungals, and antiretrovirals such as ritonavir.[318, 319] (Antiretrovirals may also cause lipids to rise, thus creating both the need for lipid therapy and the setting in which it is more toxic.[302]) Some agents, such as calcium channel blockers, are considered weaker CYP3A4 inhibitors and appear to increase statin rhabdomyolysis risk, perhaps to a lower degree.[186, 318, 320] However, interaction effects vary dramatically among statins as well as among subjects for a single statin. Regarding the former, increases in simvastatin concentrations may be several times greater than in atorvastatin concentrations with concurrent CYP3A4 inhibitors.[321] Regarding the latter, one study of 12 subjects showed more than tenfold interindividual variation in the extent of interaction between simvastatin and both erythromycin and verapamil as indexed by these drugs' effect on simvastatin concentration.[322] Of note, in a large study using administrative

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claims data, statin-associated muscle disorders including rhabdomyolysis were six-fold elevated in persons on concurrent CYP3A4 inhibitors.[167]

Grapefruit juice and perhaps pomegranate juice inhibit CYP3A4 and have been presumptively linked to statin rhabdomyolysis.[230, 323] (Combined rosuvastatin-ezetimibe therapy was involved in the report involving pomegranate juice.[230]) Although some urge caution only with consumption of greater than a quart of grapefruit juice a day,[94, 324, 325] far smaller quantities of grapefruit juice can pose a potential risk in vulnerable subjects: less than a cup daily of grapefruit juice for three days, consumed prior to subjects' simvastatin dose, reportedly increased simvastatin concentrations by four-fold on average (range: ~two-fold to nine-fold, $p<0.01$).[326]

The CYP3A pathway has a prominent role in drug metabolism in liver and intestine[327] and approximately half of prescription drugs are metabolized by CYP3A4.[328] For this reason polypharmacy may lead to competition for a common metabolic pathway. This competition may increase statin concentrations and the risk of dose-related statin AEs.

Individuals may differ in their response to individual statins, in terms of both efficacy and tolerability, due to pharmacogenomic differences, including those that affect statin hepatic uptake, clearance, and CYP pathways.[329-332] Differences in these pathways may also lead to differential vulnerability to drug interactions.

Fibrates have special relevance to statin AEs, and as noted above, gemfibrozil, in particular, interferes with statin metabolism (an effect that was found to be singularly powerful in combination with cerivastatin[170, 171]). Additionally, fibrates themselves may be linked to rhabdomyolysis.[168] Finally, fibrates may serve as markers for a population at risk for statin AEs – persons with high triglycerides and impaired fatty acid oxidation (those most likely to receive fibrates) may also be at amplified risk of statin AEs.[94, 155, 333]

Risk Factors for Adverse Effects

In addition to dose and drug interactions, a multitude of other factors have been associated with an increased risk of statin AEs. Reported risk factors and corresponding citations are delineated in Table IV.[36, 37, 51, 52, 94, 163, 176, 178, 180, 186, 191, 192, 283-288, 300, 325, 334-340]

Most risk factors depicted can be viewed as sharing one or both of two primary mediating pathways: increased statin exposure (e.g. dose, drug interactions, genetic variants or other factors that affect clearance or hepatic uptake) or mitochondrial derangement or vulnerability (with factors producing mitochondrial problems or serving as a marker for existing ones). Reduced concentrations of coenzyme Q10 are particularly a problem in the setting of existing mitochondrial dysfunction because ample coenzyme Q10 can bypass a range of respiratory chain defects,[23-25] fostering adequate ATP production and improving the redox state. Additionally, toxicity of certain interacting drugs may be mediated through mitochondrial mechanisms (as Table III shows), and mitochondrial-relevant genetic defects have been disproportionately found in patients who experience statin myopathy (reviewed below), strongly supporting mitochondrial vulnerability. Metabolic syndrome factors, particularly hypertension, are linked to increased risk of statin AEs; and these factors, including obesity, hypertriglyceridemia, hyperglycemia and particularly hypertension, have been linked to mitochondrial dysfunction and mitochondrial DNA defects.[377]

Mitochondrial Effects

While a medley of potential mechanisms may cause or contribute to statin AEs (and these merit more full review in another venue), mitochondrial mechanisms have been repeatedly

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implicated in muscle AEs. Mitochondrial defects predispose to problems on statins (as shown in the second to last entry of Table IV, 'Genetic mutations associated with mitochondrial dysfunction'). Additionally, statins predispose to mitochondrial defects (Table V,[22 31, 32, 112, 155, 158, 162, 397, 406-414]) – in all users and, to a greater degree, in vulnerable individuals. Dose-dependent reductions in coenzyme Q10[20-22] can reduce cell energy, promote oxidation, [362, 415] promote apoptosis, and unmask silent mitochondrial defects.[23-25, 362, 415-418] The mevalonate pathway, which statins inhibit, also produces heme-A, which has it own central involvement in mitochondrial electron transport.[419]

Statins reduce[20-22] and coenzyme Q10 supplementation increases[420-422] serum coenzyme Q10 levels. The ability to demonstrate tissue changes in coenzyme Q10 with administration of either agent is more variable; however, irrespective of changes in tissue coenzyme Q10 levels, changes in tissue mitochondrial and respiratory function clearly occur (improved with coenzyme Q10, impaired with statins).[25, 156-158, 407, 423] Indeed, a range of study types have shown mitochondrial and metabolic predispositions to statin AE vulnerability, and mitochondrial and metabolic effects of statins in animals[317, 347, 424-428] as well as humans, with mitochondrial effects in humans arising in all users or selectively in those who express AEs (**Tables V and VI**).

Non-muscle Statin Adverse Effects

Muscle is highly aerobically dependent and selectively vulnerable to mitochondrial pathology.[430] But given the evidence for mitochondrial vulnerability and pathology related to statin AEs, it merits note that other organs – including brain, liver, heart and kidney – can be affected by mitochondrial pathology as well,[430] and we suggest mitochondrial mechanisms may also be involved in a range of nonmuscle statin AEs. The occurrence of failure of other organs in concert with rhabdomyolysis is noteworthy in this regard, and multiple organ injury or failure has been reported in the context of statin rhabdomyolysis.[81, 91, 96, 98, 100, 105, 107-109, 112, 431]

Cognitive problems are second only to muscle problems among patient reports of statin AEs.[432] Brain tissue shares with muscle tissue a high mitochondrial vulnerability as both are postmitotic tissue with high metabolic demand.[433-437] Muscle has a very high dynamic range of demand; and the brain, while reflecting only about 2-4% of (nonobese) body mass, accounts for approximately 20% of oxygen[438] and 50% of glucose utilization.[439] Muscle and brain are the organs most classically affected in mitochondrial disease (mitochondrial myopathy and encephalomyopathy are classical manifestations of respiratory chain diseases). For instance, mitochondrial encephalomyopathy resulting from heritable coenzyme Q10 deficiency classically produces fatigue, muscle symptoms, and cognitive problems,[440] although the cases referred for analysis are often relatively severe.[429, 441] Gastrointestinal[26] and neurological symptoms,[432, 442] psychiatric symptoms,[443-446] sleep problems,[444, 447] glucose elevations,[182] and a range of other symptoms reported on statins also arise in mitochondrial dysfunction.[379, 448-457]

Table VII,[28 31, 108, 172, 178, 181, 458-481] shows those AEs for which there is RCT support in some subject groups (and provides, in some cases, additional non-RCT evidence). Randomized trials have recognized limitations for AE detection, due in part to selection considerations.[482] Even among RCTs, studies that differ in selection criteria are expected to differ in expression of, and power for, AE occurrence due to effect modification. (This issue is not specific to statins, but is germane to assessment of risks and benefits for all drugs.)

When the average effect (of drug on outcome) is harmful in RCTs, then it can be concluded that adverse consequences to that outcome occur in at least some individuals. However, when

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average effects are *not* harmful, AEs to that outcome are *not* on that basis excluded. Recall that randomized trials seek to determine the overall or average impact of a drug on an outcome (in the selected sample), in order to assess whether the drug may be used to benefit that outcome *on average*. It is worth re-emphasizing that harms in an individual are important even if benefits occur on average.

Case reports coupled with triangulating evidence can represent an important source of evidence regarding occurrence of specific AEs, and case reports and case series are reportedly the primary grounds upon which label changes with drugs occur.[54-57] For identification of AEs *in an individual*, the experience of the individual is the most relevant since average effects need not apply to an individual, whether average effects are determined by RCT or observational designs. Table VIII,[15 369, 444, 538-560] characterizes reported AEs that do not have identified RCT support.

Effect modification – leading to statins producing different effects on the same outcome in different individuals – is recognized in the context of statin (and other lipid-lowering drug) effects on lipids,[881, 882] and has previously been discussed in relation to statin muscle effects (benefits to walking occur in some,[29] while detriments occur in others[113]). As Table VII shows, a similar theme pervades other statin effects, with statins reported to benefit and worsen proteinuria and to benefit and worsen arrhythmia, cardiac function, and an array of other outcomes. We speculate that a common source of effect modification underlies many of these reported benefits and harms – with statin-induced antioxidant effects and improved flow benefiting many organs in some individuals; and statin-induced pro-oxidant effects and mitochondrial dysfunction adversely affecting a range of organs and outcomes in other individuals. Indeed, even RCT evidence has differed for the same outcome in different subject groups, generally along the lines this proposition predicts.

Prevention, Treatment, and Recovery of Statin Adverse Effects

Observational and limited randomized trial data variably suggest partial (though incomplete) benefit of coenzyme Q10 supplementation to muscle symptoms; and to other AEs of statins (observational data).[883-886] Additional studies are required to better understand the role of coenzyme Q10 supplementation in prevention and mitigation of statin AEs. It merits note that preparations of coenzyme Q10 vary widely in their bioavailability.[887]

Randomized trial evidence has little to offer in understanding recovery profiles for statin AEs, although some evidence is beginning to emerge. While one study reported uniform recovery of statin muscle AEs,[888] a larger statin myopathy clinic including more objective data noted that recovery is often incomplete when objective measures are used.[889] Other evidence supports this, noting for muscle AEs that "variable persistent symptoms occurred in 68% of patients despite cessation of therapy."[155] Incomplete resolution in some subjects has been reported for other AEs. Thus, in an analysis of data, presented in the *Australian Adverse Drug Reaction Bulletin*, it was noted that "Statin-associated peripheral neuropathy may persist for months or years after withdrawal of the statin… In two ADRAC (Adverse Drug Reactions Advisory Committee) cases of persistent peripheral neuropathy, motor and sensory conduction tests showed minimal recovery 4 and 12 months, respectively, after discontinuation of simvastatin, despite clinical improvement."[561]

Underrecognition of Statin Adverse Effects

As others have observed, "finding potential drug-safety problems requires skillful observation by clinicians who are attuned to the possibility of drug-related adverse events."[890] and (according to FDA officials) "physicians need to think 'adverse drug reactions' when encountering unexpected symptoms in their patients."[891]

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Even for the most commonly reported AEs involving statins, patients state that physicians often dismiss the *possibility* that their AE may be statin related.[432] Failure to recognize drug AEs can prevent needed reassessment of the risk-benefit profile for statin treatment – and where appropriate, modification of the treatment regimen, in the face of possible or probable statin AEs. This may reduce quality of patient care, reduce medication compliance relative to a modified regimen, and place patient safety in peril both for morbidity and mortality from not only the AEs, but also perhaps from the conditions the medication is designed to treat.

The converse is also true: awareness of statin AEs is vitally important as it may improve recognition of these effects when they arise, enable more informed treatment decisions by patient and provider, improve the quality of patient care – and reduce patient suffering and morbidity.

It has been observed that "as more information is learned through the results of clinical trials, LDL-C goals become more stringent and difficult to attain. Large doses of high-potency statins, sometimes given in combination with other lipid-lowering agents, are frequently necessary to achieve these goals. As a result, the frequency of AEs from statin therapy may be expected to increase, and less common AEs may occur more often."[734] This increases the importance of recognition of statin AEs.

As reviewed here, AEs on statins may signal a mitochondrial vulnerability, which may alter or perhaps even reverse an otherwise favorable impact of statins on cell energetics. And AEs may signal occurrence of a net prooxidant rather than antioxidant effect of statins[53] with possible unfavorable implications for a range of statins' proposed pleiotropic effects.[892]

Conclusion

When possible side effects arise in a patient on any drug, the risk-benefit balance of treatment should be reassessed. Statins are a linchpin of current approaches to cardiovascular protection: however, AEs of statins are neither vanishingly rare nor of trivial impact. For statins, as for all medications, vigilance for potential AEs is imperative. Recognition of potential statin AEs is needed and may be fostered by an improved awareness both of relevant literature and of its limitations.

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Table I

Muscle Effects Reported on Statins

Muscle Problem	Description and Citations	Comment
Muscle AEs Generally[a]	– Reported incidence is low in clinical trials but higher in studies of real world use. – In a French longitudinal study, statin users showed a 10.5% incidence of muscle AEs over 6 months, with a median time to onset of 1 month.[34] – In a French study, among 815 adults on lipid therapy in a cardiovascular prevention unit, 165 (23%) reportedly had experienced or currently experienced muscle symptoms they attributed to lipid therapy.[79] AEs commonly appeared soon after drug initiation and/or abated with drug discontinuation. Approximately 40% required pain medications. Cramps, stiffness, and tendinitis were common. Many reported pain during rest. In many, other family members had also experienced muscle AEs on lipid treatment.[79] – A European study prospectively identified patients with muscle complaints limiting daily activity during statin use. Of 18 patients with muscle AEs deemed probably attributable to statins in whom CK was evaluated, 28% showed no CK elevation and 33% showed a minor increase only. Symptoms resolved with statin discontinuation and CK normalized in 11 of 13 showing elevated CK. Authors concluded “Statins may cause clinically important muscle symptoms without inducing a marked creatine kinase elevation.”[80] – A double-blind crossover biopsy study affirmed presence of a partially reversible mitochondrial myopathy in four subjects with non-CK-elevating or minimally CK-elevating statin muscle AEs.[31] – In a patient-targeted adverse event surveillance effort, in patients citing statin muscle AEs who had improved on statin discontinuation, most who were rechallenged with equivalent or higher expected potency agents experienced recurrence; while recurrence occurred significantly less frequently in those rechallenged with lower potency agents.[37]	
Rhabdomyolysis [a]	- Severe muscle breakdown leading to markedly elevated CK is termed rhabdomyolysis; some definitions also require kidney involvement. The kidneys can be overwhelmed, leading to myoglobinuria, with renal failure and death a well recognized, serious complication that can occur with statins alone and in combination with fibrates or other interacting agents.[81-89] - In one (atypical) case, rhabdomyolysis was reported to occur after a single statin dose.[90] In other cases, it has occurred 2-4 days after statin initiation[91, 92] or addition of	Statin rhabdomyolysis reports include a range of instances in which there is multiple organ failure,[96, 97] including renal failure,[96-104] respiratory failure,[98] pancreatitis,[96, 105] hepatitis or hepatotoxicity,[97, 100, 106-108] heart failure or cardiac rhabdomyolysis,[91, 96, 109-111] MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes),[112] and cognitive failure.[96]

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Muscle Problem	Description and Citations	Comment
	other drugs to lipid-lowering treatment.[93] - While muscle pain and weakness may be characteristic, physicians should be aware that rhabdomyolysis may present atypically, as fatigue, low back pain, flu-like illness, or shortness of breath.[94, 95] Symptoms can build over several weeks; the mean time to occurrence after statin initiation in one analysis was a year.[94]	
New Difficulty Walking[a]	Statins were a significant (partially) reversible cause of new difficulty walking in patients presenting to a rehabilitation clinic.[113]	
Exercise Limitations or Exercise-induced Muscle Symptoms[a]	- Statin associated exercise-induced muscle pain.[114] - Professional athletes with familial hyperlipidemia seldom tolerate statins due to muscle adverse effects.[58] - Combined statins and beta blockers adversely affect perceived effort and cardiorespiratory function.[59] - Statin-induced myopathy in a competitive cyclist[115] - Increases in CK after exercise have been reported with statins.[116] - Variations of statin-associated exercise-induced muscle pain without CK elevation have been reported.[114] - See also 'Exercise limitation and fatigue/lack of energy,' Table VIII.	- In animals, exercise exacerbated statin-induced muscle injury.[60] - In humans, statins exacerbated exercise-induced muscle injury.[61] - In a placebo-controlled study, high-dose atorvastatin 80mg had little effect on muscle gene expression at rest in healthy volunteers, but it affected expression of 56 genes when combined with exercise (18% involved in the ubiquitin proteasome pathway and 20% involved in protein folding/catabolism & apoptosis). The authors speculated this mechanism may be involved in exercise-related symptoms arising on statins.[62] - Effect modification: Statins have increased walking distance on average in persons with and without peripheral artery disease.[29] - Mitochondrial pathology can be associated with exercise intolerance, and mitochondrial abnormalities can cause exercise limitation in otherwise normal adults.[117-123]
Inflammatory Myopathies[a]	Dermatomyositis, polymyositis and inflammatory myopathies have been reported in association with statins (see also 'Immune, autoimmune' entry, Table VIII).[63-75]	- Statins' prooxidant effects may predominate in some patients,[51] and may contribute to proinflammatory effects.[76, 77] - Effect modification: Statins have anti-inflammatory effects (in part via antioxidant effects that predominate in many),[51] and in clinical trial samples, have on average reduced markers of inflammation (e.g. C-reactive protein). For this reason, statins have undergone testing for a range of inflammatory conditions. - Statins reduce LDL-C transport and/or production of key anti-inflammatory nutrients or their precursors, including coenzyme Q10, retinol (vitamin A), cholecalciferol (vitamin D). They affect the omega-3 to omega-6 ratio, which may foster inflammation.[17]

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Muscle Problem	Description and Citations	Comment
Myasthenia Gravis (MG)[a]	Occurrence, exacerbation, or mimic of MG have been reported in the literature.[78, 124, 125]	- Muscle weakness from statins may exacerbate existing conditions or mimic other conditions involving muscle weakness. - In the case of MG, drug interactions with dual mitochondrial toxicity may play a role. AChE inhibitors used to treat MG are potent oxidative stressors[126, 127] and patients with this condition have mitochondrial pathology[128] whether by disease or drug treatment.
Rippling Muscle Disease[a]	Rippling muscle disease comprising “stiffness, myalgias, and classic rippling” arose on statins, was relieved with discontinuation, and recurred with rechallenge.[129]	
Guillain Barre (GB) or GB-like Syndrome[a]	GB (or GB-like syndromes, i.e. acute polyradiculo-neuropathy) in apparent association with statins has been reported.[130]	Although GB is by definition a radiculoneuropathy, it is clinically manifested by muscle weakness and for this reason is included in this Table.
Tendinopathy[a]	- Tendinopathy and tendon disorders, often reproducible with rechallenge, have been reported in a case series.[79, 131-134] - A report from New Zealand noted, “A search of the WHO database revealed 205 reports of tendonitis, tendon disorder or tendon rupture associated with statins.”[135] - In a French series where 165 of 815 hypolipidemic patients on lipid-lowering therapy reported muscle symptoms, nearly half included tendonitis-associated pain among their symptoms.[79] - Of 96 patients with tendon complaints in a French pharmacovigilance database, 63 exhibited tendinitis and 33 tendon rupture. Statin reinitiation occurred in 7 cases with recurrence of tendinopathy in all.[136]	- As one instance, in a case of spontaneous biceps tendon rupture in a physician, rechallenge led to tendinopathy in the contralateral biceps tendon that improved with statin discontinuation.[133] - A mitochondrial mechanism may underlie statin-related tendinopathy as reported for other classes of drugs with tendon toxicity (such as fluoroquinolones[137-139]) which have also been linked to myopathy, arthralgia and rhabdomyolysis.[140-142]
Shoulder Stiffness[a]	Citation reported that “nearly one-tenth of women (6/66)” taking statins reported drug-related shoulder stiffness.[143]	
Amyotrophic Lateral Sclerosis (ALS) or ALS-Like Syndromes [a]	Based on pharmacovigilance data, an apparent disproportionate reporting (possible “signal”) of ALS and ALS-like problems on statins has been reported.[144, 145] (Although ALS is a motor neuron condition, it leads clinically to muscle weakness and atrophy, prompting its inclusion in this table.) See Table VIII for further discussion.	- An apparent signal of increased ALS in patients on statins was also reported by one of the authors (Golomb, November 2005 and November 2006 Robert Wood Johnson Generalist Physician Faculty Scholars program). Although association is not causation, it was noted that other factors are present that suggest possible causality. For instance, biological plausibility is present since statins lower concentrations of coenzyme Q10, while supplementation with coenzyme Q10 protects against animal models of neurodegeneration including ALS and Parkinson's disease. - Bidirectional influences by statins on ALS cannot be excluded, since statins have both pro-oxidant and antioxidant effects, and in different

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Muscle Problem	Description and Citations	Comment
		individuals either effect may dominate.[145] (This is analogous to findings we have shown for statin effects on muscle, kidney, etc.)
Other Progressive Wasting Conditions [a]	Citation reported a case of progressive bilateral muscle weakness attributed to statin therapy, with dysphagia, dysarthria, and dyspnea. Progression continued after statin discontinuation, culminating in death.[146] (A low vitamin D level was noted, which can produce a severe myopathy.[147] Of note cholesterol is the biochemical precursor for vitamin D.)	- See discussion for amyotrophic lateral sclerosis – a condition that has been found to involve mitochondrial defects in muscle, not just motor neurons.[148-152]
Compartment Syndrome	Has been reported with statin myositis, and produced myonecrosis.[153, 154]	

AChE = acetylcholinesterase; CK = creatine kinase; LDL-C = low density lipoprotein cholesterol.

[a] Our study group has also received reports of these and a variety of additional conditions from patients and/or physicians.

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Table II

Evidence For, and Suggestive Of, Dose/Potency Dependence of Statin Adverse Effects (AEs)

AE	Comment
All AEs	- OR 1.4; 95% CI 1.09-1.80, p=0.008 statin therapy vs placebo[175] (meta-analysis of placebo-controlled RCTs). - OR 1.44; 95% CI 1.33-1.55, p<0.001 intensive- vs moderate-dose statin therapy[176] (meta-analysis of RCTs).
AEs Leading to Discontinuation of Therapy	- OR 1.28; 95% CI 1.18-1.39, p<0.001 intensive- vs moderate-dose statin therapy[176] (meta-analysis of RCTs). Note: Though intensive-dose statins lead to more discontinuation due to AEs than moderate-dose statins, moderate-dose statins do not necessarily lead to more discontinuation due to AEs than placebo[177] (meta-analysis of RCTs).
CK Elevation	Although some meta-analyses fail to show significant CK elevations with statins (usually moderate dose) vs placebo,[177] meta-analysis of head-to-head RCTs of high- vs low- potency statins showed a significant increase in CK elevation with high-dose statins: • CK elevation OR 6.12 with higher- vs lower- dose statin therapy (95% CI 1.36-27.5).[178] The odds appeared to be greater for lipophilic statins, which can more readily enter muscle tissue. • CK elevation OR 9.97 with intensive vs less intensive statins (95% CI 1.3-77.9, p=0.028).[176]
LFT Elevation	- Meta-analyses of RCTs show significant increases in LFTs with statin vs placebo (risk difference per 1000 patients 4.2, 95% CI 1.5-6.9).[177] - Meta-analysis of head-to-head RCTs of higher- vs lower- potency statins showed significant increase in LFT elevation with higher-dose statins: • LFT (transaminase) elevation OR 2.7 (1.5-5.0) with higher vs lower dose statins.[178] The effect appeared to be greater for hydrophilic statins (pravastatin, the most hydrophilic, is actively taken up into the liver). • LFT elevation (alanine or aspartate aminotransferase ≥3 times the ULN) OR 4.5 (95% CI 3.3-6.2) with intensive- vs nonintensive- statin therapy.[176] - In a different study design, looking not at dose, but LDL-C reduction, the magnitude of LDL-C drop was not related to AE risk. In contrast, the higher the statin dose needed to achieve a given LDL-C reduction, the higher the rates of elevated LFTs.[181] For many reasons, this type of study is less interpretable from a dose-response standpoint.[a]
Rhabdomyolysis	- Excess rhabdomyolysis cases on cerivastatin primarily involved high-potency use and/or combination with gemfibrozil, which increases the effective dose.[170, 171, 179] - Drugs that inhibit the CYP3A4 system and thereby increase statin concentrations (e.g. for atorvastatin, simvastatin, lovastatin, and cerivastatin) increase risk for statin AEs (including rhabdomyolysis) 6-fold,[167] supporting a dose relationship of statins to AEs. - In a VA database, when statins were combined with agents that inhibit their clearance (CYP3A4 inhibitors) the rate of rhabdomyolysis was increased 3- to 5-fold.[185] - US FDA Advisory advised caution with high-dose (40mg) rosuvastatin due to elevated risk of rhabdomyolysis.[180] - In a meta-analysis of RCTs, the percent LDL-C reduction was not associated with rhabdomyolysis risk. (However, LDL-C reduction is a problematic metric – see footnote a; and footnote b in Table IV – and more so across trials since sample differences can swamp dose effects.[181*a*]) - In the SEARCH trial in which 12,064 subjects were randomized to 20 or 80mg simvastatin, there were 49

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AE	Comment
	cases of "definite myopathy" in the simvastatin 80mg group and 2 in the simvastatin 20mg group.[186b] There were 49 of "incipient myopathy" in the simvastatin 80mg group and 6 in the simvastatin 20mg group.[b] - See also Table IV, 'Risk Factors for Statin Adverse Effects (AEs).'
Non-CK Elevating Muscle Symptoms	Recurrence of statin AEs was significantly higher when subjects were rechallenged with an equivalent expected potency statin, relative to a lower potency statin (~95% vs 55%, p<0.01).[37]
Cancer	According to a meta-analysis of statin RCTs, achieved LDL-C levels were significantly inversely related to cancer risk (p=0.009), though LDL-C reduction was not.[181] On average statins do not increase cancer in those under age 70 years in clinical trials (see Table VII). One could postulate a relation to LDL-C transport of antioxidants or cholesterol status as a precursor to vitamin D.
Proteinuria	FDA Advisory: "Mild, transient proteinuria (or protein in the urine, usually from the tubules), with and without microscopic hematuria (minute amounts of blood in the urine), occurred with Crestor [rosuvastatin], as it has with other statins, in Crestor's pre-approval trials. The frequency of occurrence of proteinuria appeared dose-related." [180]
Glycemia	- Atorvastatin 80mg increased glycemia significantly on average in the PROVE-IT –TIMI trial.[184] - Rosuvastatin 20mg vs placebo significantly increased HbA1c (p=0.001), and increased newly diagnosed diabetes mellitus (relative risk 1.25; p=0.01) in the JUPITER trial.[187] - Lower statin potencies have led to reproducible elevations in glucose in individual subjects,[182] but elevations in glucose or HbA1c have usually not been reported on average in RCTs of low- or moderate-dose statins (although in one RCT the statin group exhibited a modest but statistically significant increase in HbA1c[183]).

ALT = alanine aminotransferase; CK = creatine kinase; CYP = cytochrome P450; HbA1c = glycosylated hemoglobin; JUPITER = Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; LDL-C = low-density lipoprotein cholesterol; LFTs = liver function tests; OR = odds ratio; PROVE-IT–TIMI = Pravastatin or Atorvastatin Evaluation and Infection Therapy – Thrombolysis in Myocardial Infarction trial; RCT = randomized controlled trial; SEARCH = Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine; ULN = upper limit of normal; VA = US Department of Veterans Affairs.

[a] Statin use is associated with transcriptional upregulation of HMG-CoA reductase.[188] We suggest that persons on statins with more unfavorable antioxidant/oxidant state may (on average) upregulate HMG-CoA reductase especially strongly in response to statins. Lesser LDL-C reduction for the same dose may signal a less favorable oxidant/antioxidant milieu on average,[189] which in turn may be associated with higher risk of statin AEs.[51-53] Consistent with this, LDL-C tachyphylaxis occurred with high-dose atorvastatin, but not if coenzyme Q10 was concurrently administered (2005 International Coenzyme Q10 Association Meeting presentation[190]). LDL-C reduction for a *given* dose may not be a good way to examine dose effects. For some persons, the same statin dose may confer a *lesser* LDL-C reduction due to factors that promote oxidation and thus may also increase AE risk. In contrast, for some persons, the same statin dose may confer *greater* LDL-C reduction due to factors that increase statin assimilation or reduce clearance, which may also, by causing functionally greater statin 'dose,' increase AE risk. (See also Table IV, footnote b.)

[b] "Definite myopathy" was defined as muscle symptoms with CK elevations exceeding 10× ULN (meeting definitions of rhabdomyolysis that do not require renal involvement); "incipient myopathy" was defined as CK exceeding 3× ULN and more than 5× baseline CK, coupled with an ALT elevation exceeding 1.7× baseline ALT without an isolated ALT elevation at any other visit, irrespective of muscle symptoms.[186] (Note that ALT elevation reflects liver compromise and is not a characteristic of myopathy. However, concurrent muscle and liver dysfunction may signal widespread cellular consequences of statins.)

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Table III

Drug Interactions Reported in Statin Rhabdomyolysis

Drug Class/ Drug	Examples	Comments
Fibric Acid Derivatives (Especially Gemfibrozil)[226]	Gemfibrozil.[105, 196-199, 202, 210, 227, 234] Bezafibrate.[228] Fenofibrate.[229]	- This likely reflects two major factors: **1** Fibrates affect the metabolic pathways of statins, leading to a functionally increased dose. Indeed, a high plurality of excess rhabdomyolysis cases on cerivastatin (now withdrawn) occurred in combination expressly with gemfibrozil.[169] Gemfibrozil significantly inhibits both major metabolic pathways for cerivastatin (oxidation and glucuronidation); it affects metabolic pathways less for other statins.[170, 171, 179] Overall gemfibrozil-statin combinations have been more problematic than fenofibrate-statin combinations.[195] **2** Fibrates are generally used in the setting of high triglycerides, a marker of impaired fatty acid oxidation that may signal mitochondrial vulnerability[155] (see 'High triglycerides' as a risk factor, **Table IV**). - Gemfibrozil inhibits glucuronidation and also CYP2C8 (non-CYP3) oxidation of statin hydroxy acids. The CYP2C8 pathway has specific relevance to cerivastatin. Thus gemfibrozil increases statin concentrations to a greater degree than do other fibrates, an effect that is far stronger for cerivastatin due to the added effect on oxidation. This is likely responsible for the disproportionately higher rates of rhabdomyolysis with gemfibrozil, specifically, with gemfibrozil in combination with cerivastatin.[170, 171, 179]
Other Lipid-lowering Drugs	Cholestyramine.[223] Niacin.[224] Ezetimibe.[225, 230, 231]	Although combinations of statins with all lipid drugs may pose risk, there are comparatively few reports of rhabdomyolysis with statins in combination with niacin.
Macrolide Antibiotics[226, 232, 233, 235]	Erythromycin.[236] Clarithromycin.[237-241] Azithromycin.[237] Roxithromycin.[242]	CYP3A4 inhibitors.
Azole Antifungals[226, 232]	Ketoconazole[106, 243-245] Itraconazole[203, 246-248] Fluconazole[89, 249, 250]	CYP3A4 inhibitors.
Cyclosporin[232]	For reports see.[203, 226, 247, 251-255]	CYP3A4 inhibitors.
Calcium Channel Blockers	Diltiazem.[172, 226, 256] Verapamil.[257] Mibefradil.[226, 258, 259]	CYP3A4 inhibitors. - In subjects assigned to simvastatin 80mg (SEARCH trial), the use of calcium channel blockers at baseline was linked to increased "definite or incipient myopathy" with a relative risk of 1.7 (95% CI 1.2-2.6) overall (n=98); and 2.7 (95% CI 1.6-4.5) in the first year (n=56).[186 *a*] (After the first year, the relative risk was 0.9, 95% CI 0.4 -1.8; n=42; however, subjects on and off calcium channel blocker at baseline may have changed calcium channel blocker status by later years.)
Antipsychotics	Risperidone.[260-262]	- Some antipsychotics have CYP3A4 inhibiting properties (quetiapine,[263,264] risperidone[264]), may have mitochondrial toxicity,[265] and can cause rhabdomyolysis.[260,266]

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Drug Class/ Drug	Examples	Comments
		277 - Antipsychotics are a marker for schizophrenia which has been associated with mitochondrial pathology – either intrinsically or as a result of these drugs.[278]
Amiodarone	For reports see.[107, 279-281]	- This drug has mitochondrial toxicity,[282-288] and is also a weak CYP3A4 inhibitor. - In subjects assigned to simvastatin 80mg (SEARCH trial), the use of amiodarone at baseline was associated with increased "definite or incipient myopathy," with a relative risk in the first year of 8.8 (95% CI 4.2-18.4).[186 *a*] After detection of the association early in the trial, those on amiodarone in the 80mg group were switched to 20mg (it was not specified precisely when). It was observed that this may explain the lesser relative risk after the first year of 3.5 (95% CI 1.1-11.6); with an overall relative risk of 6.4 (95% CI 3.4 -12.1).
Antiretrovirals[214, 281, 289]	Ritonavir.[290] Nelfinavir.[86] Atazanavir.[281]	- These classes of drugs are mitochondrial toxins,[291-299] and have been associated with rhabdomyolysis.[300] - They are also CYP3A4 inhibitors, and can serve as a marker for a condition, AIDS, that has been associated with mitochondrial dysfunction.[301] - According to one report looking at pharmacokinetic interactions between these drugs and statins, in patients receiving ritonavir and saquinavir, the "area under the curve increased about fivefold for atorvastatin and about 32-fold for simvastatin, but decreased 0.5-fold for pravastatin."[302] (This refers to the area under the plasma concentration-time curve.)
Nefazodone	For reports see.[303-306]	
Reports of Other Drug Interactions	Sildenafil.[307] Warfarin.[226, 308] Chlorzoxazone.[108] Digoxin.[226] Amoxicillin.[309] Danazol.[310] Colchicine.[311-313] Thiazolidinediones with atorvastatin.[314] Erlotinib.[315] Multiple interacting medications.[281]	Atorvastatin AE reports were 3.1 times as likely to list thiazolidinediones (pioglitizone, rosiglitizone) as concomitant medication than simvastatin AE reports. Possibly: - Thiazolidinediones are reportedly mild *inducers* (i.e. opposite of inhibitors) of CYP3 and thus slightly *reduce* simvastatin concentrations.[316] Note that thiazolidinediones also induce mitochondrial toxicity.[317] - Patients with diabeties mellitus may be more often placed on the more potent agent, atorvastatin, because they are considered by many to be CAD equivalent in terms of cardiac risk and to require lower LDL-C targets.[314]

AE = adverse effect; ALT = alanine aminotransferase; CAD = coronary artery disease; CK = creatine kinase; CYP = cytochrome P450; LDL-C = low-density lipoprotein cholesterol; SEARCH = Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine; ULN = upper limit of normal.

[a] The SEARCH trial randomly allocated 12,064 subjects with prior myocardial infarction to 20 or 80mg of simvastatin. Relative risks for developing "definite/incipient myopathy" based on baseline characteristics were calculated from the 6031 subjects assigned to 80mg of simvastatin. "Definite myopathy" was defined as muscle symptoms with CK elevations exceeding 10 × ULN (meeting definitions of rhabdomyolysis that do not require renal involvement). "Incipient myopathy" was defined as CK exceeding 3 × ULN and more than 5 × baseline, coupled with an ALT elevation exceeding 1.7 × baseline without an isolated ALT elevation at any other visit, irrespective of muscle symptoms. 50% of cases were 'definite.' (Note that ALT elevation reflects liver function and is not a characteristic of myopathy. However, conjoint muscle and liver dysfunction may signal widespread cellular consequences of statins.)

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Table IV

Risk Factors for Statin Adverse Effects (AEs)

Risk Factor	Considerations
Dose (or Potency; see Table II)[36, 37, 163, 176, 178, 180, 185, 334]	- As discussed in the text (section 'Dose Response'), many statin AEs are dose dependent. - Although some literature advises "the lower the better" with regard to LDL-C and aggressive statin use,[191, 192] the US FDA states "all statins…should be prescribed at the lowest dose that achieves the goals of therapy (e.g., target LDL-C level)."[180]
Other Interacting Drugs (see Table III)[36, 163, 180] and Polypharmacy[341]	- As discussed in the text (section 'Drug Interactions'), many drug interactions functionally increase dose. In some cases, interacting drugs may, in addition, cause/compound mitochondrial toxicity (e.g. amiodarone;[283, 288] HIV protease inhibitors[335, 336]), and may themselves conduce to rhabdomyolysis.[300] - Use of CYP3A4 inhibitors were associated with a 6.0-fold increase in hospitalizations for myopathy including rhabdomyolysis in patients on lipid therapy (95% CI 2.1-17.4), and a 2.3-fold increase in hospitalizations for renal AEs (95% CI 1.6-3.2) based on administrative claims data, matching controls to cases on age, sex, geographic region, length of follow-up, and time of index drug fill.[167]
'Frailty' or Small Body Frame[94, 325, 337]	Small size and frailty may signal higher mg/kg dose (and also lower clinical or cellular reserve).
Surgery[94, 338-340]	- Intraoperative or perioperative rhabdomyolysis. - Surgery may increase energy demands, which may be a problem in settings of marginal supply if mitochondrial effects that are otherwise subclinical are present. Surgery may also be associated with use of interacting drugs. Surgery may worsen oxidative stress, aggravating risk in those subjects for whom statins increase lipid peroxidation markers.[51-53, 342] - Coenzyme Q10 has reportedly improved surgical outcomes and reduced reperfusion injury in some human and animal studies[343-346] (statins reduce coenzyme Q10 concentrations). - However, while animal studies have suggested worsening of myocardial stunning with statin pretreatment,[347] in a range of human studies, statins have apparently improved surgical outcomes for vascular and heart surgery,[348-350] possibly via statin antioxidant effects that predominate in many people.[51]
Infection[351-354]	- One possible mechanism is that infection may increase energy demands, which may be a problem in settings of marginal supply if statin mitochondrial effects occur that might otherwise be subclinical. Infection may also be associated with use of drugs that interact with statins, such as macrolide antibiotics. - Some evidence suggests statin users may have lower incidence of sepsis. However, confounding (by indication [i.e. if high LDL-C rather than statins drives the protection] or by socioeconomic status,[355-357] for instance) cannot be excluded as a basis of such findings.
Exertion[94, 351, 358]	- Exertion may increase energy demands, which may be a problem in settings of marginal supply if mitochondrial effects that are otherwise subclinical are present. - Treadmill exercise increased incidence and severity of statin damage in Type 2 fiber-predominant muscles.[60]

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Risk Factor	Considerations
	- Statins alter gene expression selectively with exercise.[62]
'Elderly' or Older Age: >65, >70, >75, >80 Years in Different Sources[34, 94, 163, 180, 325, 340, 359]	- A nested case control study of a cohort of 252,460 new users of lipid-lowering medications found the odds of rhabdomyolysis for those over age 65 relative to those under were 4.36 (95% CI 1.5-14.1).[360] - In subjects assigned to simvastatin 80mg (SEARCH trial), age ≥65 at baseline was linked to increased "definite or incipient myopathy" with a relative risk of 2.2 (95% CI 1.4 -3.4) overall (n=98); and 2.3 (95% CI 1.3-4.1) in the first year (n=56).[186a] (The relative risk was 2.0 in later years, 95% CI 1.1-3.9, n=42.) - Older age signals both higher effective dose (through impaired clearance, increased polypharmacy with more potential drug interactions,[361] and sometimes smaller body frame), and pre-existing mitochondrial vulnerability (since DNA mutations rise with age[362,363]).
Asian Ethnicity (Japanese or Chinese)[36, 180]	Asian ethnicity has been associated with elevated blood levels (higher functional dose, reduced clearance) for rosuvastatin.[364]
Female Gender[337, 340, 359]	- A nested case control study of a cohort of 252,460 new users of lipid-lowering medication found a trend to increased odds of rhabdomyolysis in females (OR 2.53; 95% CI 0.91-7.3).[360] - The risk-benefit balance of statins, as indexed by the available objective metric (total mortality), appears less favorable in women than in men, for those major clinical trials for which data are available.[8, 9, 365, 366] - In subjects assigned to simvastatin 80mg (SEARCH trial), female gender at baseline was linked to increased "definite or incipient myopathy" with a relative risk of 1.8 (95% CI 1.1-2.8) overall (n=98); and 2.0 (95% CI 1.0-3.9) after the first year (n=42).[186a] (The relative risk was 1.6 in the first year, 95% CI 0.9-3.0, n=56.) Possible considerations include: - Smaller body size for the same dose may imply a higher effective dose for the same milligram dose. Whether for this and/or other reasons, greater statin-induced reductions in lipids have been reported in women.[367] - Women have increased AEs to many medications and vaccinations.[368] - If statins modestly lower estrogens (a product of cholesterol) as they have been found to lower testosterone,[15, 369] they may diminish levels of an essential antioxidant mediator for women that affords key mitochondrial protection.[370]
Renal Insufficiency[36, 94, 180, 340, 359]	- In subjects assigned to simvastatin 80mg (SEARCH trial), low glomerular filtration rate (<60 mL/min/1.73m^2) was linked to increased "definite or incipient myopathy" with a relative risk of 2.5 (95% CI 1.6-3.9) overall (n=98); and 2.6 (95% CI 1.3-5.1) after the first year (n=42).[186a] (The relative risk was 2.4 in the first year, 95% CI 1.3-4.3, n=56.) - In subjects assigned to simvastatin 80mg (SEARCH trial), elevated Creatinine (≥85μmol/L; i.e. 1.0mg/dL) was linked to increased "definite or incipient myopathy" with a relative risk of 2.0 (95% CI 1.3-3.1) overall (n=98); and 2.5 (95% CI 1.4 -4.6) in the first year (n=56).[186a] (The relative risk was 1.5 after the first year, 95% CI 0.8-2.8, n=42.) - A number of case reports describe complications of statins arising with renal insufficiency.[371] - A nested case control study of a cohort of 252,460 new users of lipid-lowering medication found increased odds of rhabdomyolysis, testing the joint effect of high statin dose

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Risk Factor	Considerations
	and renal disease (p=0.022).[360]
Hepatic Dysfunction[94, 163, 340]	- May increase drug levels by impaired hepatic clearance; for instance, fatty liver is reportedly associated with reduced CYP3A activity.[372] - May in some instances signal mitochondrial dysfunction, at least in the liver (e.g. with fatty liver i.e. hepatic steatosis, whether or not of alcohol origin[373-375]).
Alcohol Abuse[36, 94]	Potential mechanisms (same as for drug interactions) include the following factors: - Alcohol may increase drug levels if hepatic function is impaired. - Alcohol is a mitochondrial toxin.[376]
Hypertension[167]	- Hypertension was associated with a 5.1-fold increase in hospitalizations for myopathy including rhabdomyolysis in patients on lipid therapy (95% CI 2.4-10.9), a 7.0-fold increase in hospitalizations for renal AEs (95% CI 3.7-13.4), and a 2.6-fold increase in hospitalizations for hepatic events (95% CI 1.8–3.7) based on administrative claims data, matching controls to cases on age, sex, geographic region, length of follow-up, and time of index drug fill.[167] - Essential hypertension is strongly tied to mitochondrial dysfunction, with an estimated 55% (95% CI 45%-65%) of hypertension cases associated with mitochondrial DNA mutations.[377]
Diabetes Mellitus[167, 340, 341]	- Diabetes mellitus was associated with a 2.8-fold increase in hospitalizations for renal AEs in patients on lipid therapy (95% CI 2.4-3.3), and a 1.8-fold increase in hospitalizations for hepatic events (95% CI 1.5-2.3) based on administrative claims data, matching controls to cases on age, sex, geographic region, length of follow-up, and time of index drug fill.[167] - In subjects assigned to simvastatin 80mg (SEARCH trial), diabetes mellitus at baseline was linked to increased “definite or incipient myopathy” with a relative risk of 1.7 (95% CI 1.0-2.9) overall (n=98); and 2.3 (95% CI 1.1-4.9) after the first year (n=42).[186*a*] (The relative risk was 1.2 in the first year, 95% CI 0.6-2.7; n=56.) - Type 2 diabetes mellitus is strongly linked to impaired mitochondrial function, with an estimated 22% (95% CI 6%-38%) of type 2 diabetes mellitus associated with mitochondrial DNA defects.[377]
Obesity[378]	In a study of statin AEs in the transplant setting, “the incidence of confirmed statin-related complications was higher among patients with BMI>29kg/m^2 than among those with lower BMI (p=0.055).”[378]
High Triglycerides[94, 333]	- Triglyceride concentrations were commonly high in patients with myopathy (n=972) or rhabdomyolysis (n=81), with a mean triglyceride value in the combined sample of 341mg/dL.[94, 333] - High triglycerides arise in settings of impaired fatty acid beta oxidation and may signal existing metabolic/ mitochondrial derangement. - In mice, high triglycerides increased resting respiration and predispose animals to mitochondrial permeability transition.[379]
History of CK Elevation[34]	- OR 2.04; 95% CI 1.55-2.68, p<0.0001 for development of statin muscle AEs in the setting of history of high CK.[34] - Elevated CK may signal existing metabolic derangement.
Thyroid Disorders, Hypothyroidism, Including Unnoticed or Asymptomatic	- Thyroid hormone is critically involved in regulation of oxidative phosphorylation (mitochondrial function), and thyroid pathology, even if treated, may signal

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Risk Factor	Considerations
Hypothyroidism[36, 94, 163, 180, 222, 353, 380-382]	metabolic vulnerability because of the importance of triiodothyronine (thyroid replacement focuses on thyroxine).[383-389] - Thyroid problems alone are a risk factor for rhabdomyolysis.[222] - Statins have rarely aggravated hypothyroidism – produced loss of stable control on thyroid medication, with control restored on statin discontinuation.[390, 391] One case involved amiodarone-induced hypothyroidism.[391] Since both statins and amiodarone produce AEs through mitochondrial toxicity,[282] we suggest thyroid dyscontrol on statins may occur in cases of hypothyroidism linked to mitochondrial or energetic impairment.[392]
Personal History or Family History of Hereditary Muscle Problems[36, 393]	Possible mechanisms include: - May signal pre-existing mitochondrial or metabolic vulnerability. - May provide for a lower threshold at which damage to muscle is clinically evident.
Prior Muscle Problems on Statins or Other Cholesterol Drugs[34, 36, 180]	- OR was reported to be 10.1, 95% CI 8.2-12.5 for statin muscle AEs ($p<0.0001$).[34,35] - Not merely an index of vulnerability, but of expressed problems.
Hyperkalemia[163, 394]	- Risk may arise in part with hyperkalemia serving as a marker of mitochondrial derangements that produce lactic acidosis, which can cause elevated potassium.[395] - Statins might therefore be expected to sometimes cause potassium elevation, and indeed have been reported to do so.[394, 396]
Genetic Mutations Associated with Mitochondrial Dysfunction[155, 397]	- Just as adequate coenzyme Q10 'bypasses' and renders clinically silent a range of respiratory chain defects, so statin-induced reductions in coenzyme Q10 may 'unmask' previously clinically silent mitochondrial pathology, such as that demonstrated in a plurality of cases of statin-induced mitochondrial myopathy.[155] - The term 'unmask' may be misunderstood to imply that a clinical condition was always present. There is no basis to presume clinical expression would necessarily have occurred in the absence of pharmacological reduction of coenzyme Q10: in the pre-drug state, the subjects may have had adequate physiological compensatory mechanisms in place. - Mutations in the *COQ2* gene are associated with primary coenzyme Q10 deficiency and severe inherited myopathy. Mild common variants were associated with vulnerability to myopathy on statin monotherapy (113 myopathy subjects, 158 matched statin tolerators).[397]
Other Genetic Variants	- The C-allele of the rs4149056 single-nucleotide polymorphism (SNP), located within *SLCO1B1* on chromosome 12,[b] was associated with increased risk, with OR 4.5 (95% CI 2.6-7.7) per copy of the C-allele, and 16.9 (95% CI 4.7-61.1) for CC homozygotes relative to TT homozygotes.[a] More than 60% of the 'myopathy' cases in that trial (SEARCH trial) could reportedly be attributed to the C variant.[186] The C-allele has a prevalence of approximately 15% in those of European descent. - Genetic polymorphism of CYP2D6 have been linked to susceptibility to atorvastatin AEs;[398] and to simvastatin AEs in some studies[331,398,399] but not others.[400] - In a case-control discovery study the CYP2D6*4 isoform was linked to atorvastatin muscle AEs (OR 2.5, $p=0.001$, frequency ~50% in cases vs 28% in controls) and simvastatin muscle AEs (OR 1.7, 49% of cases, $p=0.067$).[398] Sources disagree about the role for CYP2D6 in simvastatin metabolism[331,398,399]. The

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Risk Factor	Considerations
	excess in AEs with one genetic group was not accompanied by greater absolute lipid reduction.[399] - CYP2D6 variants are involved in toxin (e.g. pesticide) detoxification and both inactivation and bioactivation[401,402]. We conjecture that some CYP2D6 variants may heighten vulnerability to oxidative stressors. While adequate coenzyme Q10 levels may functionally 'bypass' resulting mitochondrial defects,[23,25,403] dose-dependent reductions in coenzyme Q10 by more potent statins,[20,21] like atorvastatin and simvastatin, may 'unmask' mitochondrial dysfunction and lead to muscle symptoms. - One study reported an association of *ABCB1* gene polymorphisms and AEs on simvastatin.[404] - Genetic variants in serotonin receptor genes have been presumptively linked to statin myalgia, an effect hypothesized to be mediated by influences on pain pathways.[405]

ALT = alanine aminotransferase; BMI = body mass index; CK = creatine kinase; CYP = cytochrome P450; LDL-C = low-density lipoprotein cholesterol; OR = odds ratio; SEARCH = Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine; ULN = upper limit of normal.

[a] The SEARCH trial randomly allocated 12,064 subjects with prior myocardial infarction to 20 or 80mg of simvastatin. Relative risks for developing "definite/incipient myopathy" based on baseline characteristics were calclulated from the 6031 subjects assigned to 80mg of simvastatin. ORs for genetic characteristics in genome-wide association studies were based on 85 cases of "definite or incipient myopathy" that arose on 80mg of simvastatin within that trial, compared to 90 age, sex, glomerular filtration rate, and amiodarone-use 'matched' simvastatin controls who did not develop "definite or incipient myopathy. " "Definitemyopathy" was defined as muscle symptoms with CK elevations exceeding 10 × ULN (meeting definitions of rhabdomyolysis that do not require renal involvement). "Incipient myopathy" was defined as CK exceeding 3 × ULN and more than 5 × baseline, coupled with an ALT elevation exceeding 1.7 × baseline without an isolated ALT elevation at any other visit, irrespective of muscle symptoms. 50% of cases were 'definite.' (Note that ALT elevation reflects liver function and is not a characteristic of myopathy. However, joint muscle and liver dysfunction may signal widespread cellular consequences of statins.)

[b] Comment: SLCO1B1 encodes OATP1B1, an organic anion-transporting polypeptide that regulates hepatic uptake of statins. The C-allele retards hepatic uptake of statins, and in most reports increases statin serum concentrations, while slightly attenuating the LDL-C reduction by simvastatin.[186] Of note, the study found that the G variant of rs 2306283 showed lower risk of myopathy – and was associated with lower statin concentrations.[186]

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Table V

Mitochondrial (mt) Effects Reported in Patients Treated with Statins[a]

Study (year)	Finding	Specifics	Comments
Vladutiu et al.[155] **(2006)**	Mt pathology on biopsy in patients with statin-associated muscle symptoms.	52% of muscle biopsies (among biopsied persons with statin muscle symptoms) showed significant biochemical abnormalities in mt or fatty acid metabolism, with 31% having multiple defects.[155]	Fraction of abnormalities that represent cause of statin vulnerability vs consequence of statin cannot be ascertained from these data (i.e. degree to which the mt pathology preceded and predisposed to symptoms on statins, vs resulted from the statins, remains unclear).
Oh et al.[397] **(2007)**	Genetic impairment in coenzyme Q10 production is linked to risk of statin myopathy.	Mild common mutations in a gene involved in production of coenzyme Q10 were linked to risk of statin myopathy.[397]	Persons with rarer and more severe mutations linked to primary coenzyme Q10 deficiency, a severe condition, can have myopathy without statins.
Gambelli et al.[406] **(2004)**	Mt pathology on biopsy in patients with statin-associated muscle symptoms.	In nine patients with "various myopathic syndromes" taking statins, muscle biopsy showed mt alterations such as COX-negative staining fibers. Findings were felt to "confirm that statins may cause muscle damage and impair oxidative metabolism."[406]	Cause vs consequence ambiguity.
Meyer et al.[407] **(2005)**	Patients on statins showed altered ^{31}P-MRS spectra.	Elevated muscle phosphodiesterase was seen in ^{31}P-MRS spectra of patients on statins relative to controls.[407] (However, still more marked alterations were seen in one control subject – who had recently discontinued statins due to muscle symptoms.)	In the person experiencing muscle AEs, there remains cause vs consequence ambiguity.
Schick et al.[408] **(2007)**	High-dose (lipophilic) statins significantly reduced muscle coenzyme Q10 and muscle mt DNA.	Decreased skeletal muscle mt DNA was seen in muscle biopsies of patients treated with high-dose simvastatin (80mg); this correlated with reductions in muscle ubiquinone (coenzyme Q10).[408]	Study involved high-dose simvastatin (80mg) vs atorvastatin (40mg) vs placebo. Effects appeared to be most marked for coenzyme Q10 reduction and mt DNA/nuclear DNA in the simvastatin group (p=0.002).
Guis et al.[409] **(2006)**	Statin myopathy patients showed abnormal pH recovery on ^{31}P-MRS.	Patients with CK elevation and muscle symptoms on statins did not show altered phosphocreatine recovery of ^{31}P-MRS or mt defects on gross histology, but ^{31}P-MRS did show slowed pH recovery kinetics.[409] (Biopsies were not	

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Study (year)	Finding	Specifics	Comments
		assessed by up-to-date mt testing techniques.)	
Phillips et al.[31] **(2002)**	Statin myopathy was associated with partially reversible mt myopathy in a double-blind, crossover, biopsy study.	In four patients with non-CK -elevating or minimally-CK -elevating muscle symptoms on statins who underwent double-blind, crossover, biopsy study, muscle biopsies showed evidence of mt dysfunction that included "abnormally increased lipid stores, fibers that did not stain for cytochrome oxidase activity, and ragged red fibers. These findings reversed in the three patients who had repeated biopsy while off statins."[31]	
Phillips et al.[158] **(2004)**	Statin use increased RER consistent with reduced lipid oxidation. Statin myopathy patients had high RER even off statins.	- Statin myotoxicity is associated with abnormal lipid oxidation.[158] - Statins significantly increased fasting RER in 16 normal controls (with decreased lipid oxidation) (p=0.00001).[158] - Persons who had had statin myopathy (and were off statins) had abnormally high fasting RER relative to controls (n=11, p=0.00001). - Post-myositis patients had a depressed anaerobic threshold (p=0.009). Patients included those with rhabdomyolysis (defined here as muscle symptoms with CK ≥ 10 × ULN) or myositis (defined here as muscle symptoms with any CK elevation).	In the post-myositis group, it is again unclear the degree to which the high RER preexisted and predisposed to statin myopathy, vs was caused by statins in the setting of statin myopathy.
Paiva et al.[410] **(2005)**	Patients on high potency simvastatin showed reduced muscle coenzyme Q10, reduced respiratory enzyme and citrate synthase activity on biopsy, and reduced mt volume.	- 48 patients (33 men, 15 women) with hyperlipidemia were randomly assigned, 16 per group, to simvastatin 80mg, atorvastatin 40mg, or placebo for 8 weeks with muscle biopsy at baseline and end.[410] - The ratio of plasma lathosterol: cholesterol decreased 66% in both statin groups. Muscle campesterol increased similarly in the two statin groups (simvastatin 21 ± 7 to 41 ± 27nmol/g; atorvastatin 23 ± 9 to 40 ± 19nmol/g, p=0.005). Muscle coenzyme Q10 dropped significantly in the simvastatin group only (40 ± 14 to 26 ±	Larger sample may clarify if qualitatively similar effects occur in a subset of patients on atorvastatin as well.

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Study (year)	Finding	Specifics	Comments
		8nmol/g, p=0.03). - Respiratory chain enzyme and citrate synthase activities dropped significantly in those with marked reductions in muscle coenzyme Q10 on simvastatin 80mg, compared with 'matched' patients on atorvastatin 40mg or placebo (n=6 in each group).	
De Pinieux et al.[22] **(1996)**	Statins (but not fibrates) significantly lowered coenzyme Q10 and increased the lactate : pyruvate ratio, used as a marker of mt function.	80 hyperlipidemic persons on statins (n=40), on fibrates (n=20), or untreated (n=20), and 20 healthy controls were compared.[22] Statin use was linked to significantly higher lactate: pyruvate ratios than in untreated subjects ($p<0.05$) or healthy controls ($p<0.001$). Coenzyme Q10 was lower in statin-treated than in untreated patients (0.75 ± 0.04mg/L vs 0.95 ± 0.09mg/L, $p<0.05$).	

AE = adverse effect; CK = creatine kinase; COX = cytochrome C oxidase; MRS = magnetic resonance spectroscopy; RER = respiratory exchange ratio; ULN = upper limit of normal.

[a] Either in settings of statin use or of statin AEs.

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Table VI

Mitochondrial Adverse Effects (AEs) with Statins in Individuals and Families: Evidence from Case Reports[a]

Study (year)	Statin mitochondrial AE	Description
Chariot et al.[112] (1993)	MELAS.	MELAS followed a case of simvastatin-induced rhabdomyolysis.[112]
Thomas et al.[411] (2007)	MELAS.	Statin associated with MELAS syndrome (case report).[411]
Neale et al.[412] (2004)	Lactic acidosis.	Statin induced lactic acidosis: An 82-year-old woman presented with lactic acidosis that resolved with discontinuation of atorvastatin.[412]
Goli et al.[413] (2002)	Lactic acidosis.	Lactic acidosis accompanied rhabdomyolysis and hepatitis as a statin AE.[413]
England et al.[413] (1995)	Mitochondrial myopathy.	Mitochondrial myopathy developed on treatment with statins: simvastatin and pravastatin.[162]
Diaczok et al.[414] (2003)	Mitochondrial myopathy.	Statins ‘unmasked’ a mitochondrial myopathy.[414]
Troseid et al.[32] (2005)	Mitochondrial myopathy.	Statin-associated myopathy with normal CK levels occurred in four members of one Norwegian family with evidence of mitochondrial myopathy on biopsy in some but not all.[32]

CK = creatine kinase; MELAS = Mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes.

[a]As this Table indicates, mitochondrial encephalomyopathy, not just myopathy, has been reported in association with statins. Low coenzyme Q10 is classically associated with brain as well as muscle symptoms.[429]

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Table VII

Statin Adverse Effects (AEs) Supported by Evidence from Randomized Controlled Trials (RCTs)[a]

Domain	Evidence	Comment
Muscle	- A meta-analysis of randomized, double-blind, head-to-head, statin comparisons showed more CK elevation with higher dose statins.[178] - A meta-analysis of RCTs showed an increase in myositis on statins (with myositis defined here as CK ≥ 10 × ULN).[28] - Placebo-controlled, double-blind, crossover, biopsy study showed partially reversible mitochondrial myopathy on statins in persons reporting non-CK-elevating or minimally-CK-elevating muscle symptoms on statins.[31] This study has the validity attached to randomization and blinding that support a true causal occurrence of muscle AEs on statins; but does not have implications for the likelihood of occurrence in the average statin vs placebo user.	
Cognition	- Two RCTs of statins vs placebo in relatively younger healthier samples (lovastatin in one, simvastatin in the other) showed significant worsening of cognitive indices relative to placebo.[458, 459] - Effect modification by age and CVD risk: ○ Two trials in older, high-CVD-risk sample showed an average neutral effect on cognition.[460, 461] (One trial, the Heart Protection Study, employed limited cognitive assessment and more troublingly employed an active drug compliance run-in:[461] This may bias outcomes because people who experience memory problems from statins may forget to take their pills reliably and thus be excluded from randomization.[483] Additionally, noncompliance on statins has been linked to statin AEs.[484]) ○ One trial with subjects of younger and older age showed intermediate findings and preliminary evidence for mitochondrially based effect modification.[462] Note: Two trials in Alzheimer samples suggest possible trends to cognitive benefit, although these appeared to dissipate at 1 year.[463, 464] - Case reports and case series complement RCT data citing instances of cognitive loss on statins that resolve with discontinuation and recurred with rechallenge.[465-471]	- Muscle and brain are classically affected in coenzyme-Q10-deficiency mitochondrial syndromes. The same predominant pattern is seen in patient-targeted statin AE surveillance. - In one study, postoperative statins significantly reduced cognitive recovery following bypass (*post hoc* analysis, p=0.011), although preoperative statins did not affect it.[472] - Potential mechanisms include low central serotonin[485-487] (conceivably including vitamin D influences[488] because cholesterol is the precursor to vitamin D; however, little information is available on the impact of statins on vitamin D), and altered omega-3 to omega-6 ratios.[17, 489] We here add the suggestion of impaired cell energetics and oxidation. This offers the possibility that benefits may predominate in some persons through endothelial function/flow as well as anti-inflammatory benefits.
Cancer	- The sole randomized trial in the elderly (age >70) showed significant increase in incident cancer with statin use relative to placebo (HR 1.25, 95% CI 1.04-1.51, p=0.02).[460] - Effect modification: meta-analyses of randomized trials in samples of generally middle age persons clearly and reproducibly show average neutrality of statins on cancer, with risk ratios squarely centered at 1.0.[490, 491] One study affirmed an (age × pravastatin) interaction on cancer risk.[473] - A meta-analysis found that statin effects on cancer were significant	- It may merit note that elderly have greater pre-existing mitochondrial vulnerability. - Lower LDL-C signals lower coenzyme Q10 and antioxidant carrying capacity. - There is a case, from triangulating animal and human literature, that statins could reduce risk of melanoma.

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Domain	Evidence	Comment
	and determined by achieved LDL-C.[181]	
Liver	A meta-analysis of randomized, double-blind, head-to-head, statin comparisons showed more LFT elevations with higher dose statins.[178]	RCT data of LFT elevations are buttressed by many cases of statin hepatopathy arising alone or in concert with statin rhabdomyolysis.[96, 107, 108, 172, 375, 474-481, 492-513]
Hemorrhagic Stroke	- The RCT arguably best powered to look at effects on stroke (in a sample with prior TIA or stroke given high-dose statin vs placebo) showed a significant increase in hemorrhagic stroke (adjusted HR 1.66, 95% CI 1.08-2.55).[514] - Statins lead to average significant reductions in stroke in meta-analyses of RCTs of subjects primarily in middle age.[515-517] They do not in elderly (at high cardiovascular risk): no trend to stroke reduction was seen in the sole clinical trial targeted to that group.[460] - Note that in samples where ischemic stroke benefit is seen, including the study with elevated hemorrhagic stroke, ischemic stroke is more prevalent than hemorrhagic stroke, and the ischemic stroke benefits of statins dominate the impact of statins on stroke overall. However, results might differ in individuals with history of or risk factors for hemorrhagic stroke.	- This extends evidence from observational data showing higher hemorrhagic stroke risk with low cholesterol,[518-521] and prestatin randomized trials supporting an association of lipid therapy to increased hemorrhagic stroke.[522] - Statins have reported antithrombotic and antiplatelet effects.[523-526]
Blood Glucose	- High-dose statins led to statistically significant increase in glycemia in the PROVE-IT–TIMI trial.[184] - In the JUPITER trial, those randomized to rosuvastatin 20mg vs placebo showed a significant increase in HbA1c (p=0.001) and in newly diagnosed diabetes mellitus (relative risk 1.25; p=0.01).[187] - These supplement data from another RCT, showing a significant but modest average increase in HbA1c with (non-high-dose) statins.[183]	- Lower dose statins have not led to average increases in glycemia in most trials, but case reports clarify that large increases can arise in selected individuals reproducibly with statins.[182, 527] - One observational study reports that patients on statins may be less likely to develop diabetes mellitus after renal transplant;[528] however (particularly in light of PROVE-IT–TIMI and JUPITER results), this could reflect indication bias.
Sleep	Significant reductions in average sleep quality were seen with simvastatin but not pravastatin relative to placebo.[447] Significant increases in self-rated ‘sleep problems’ occurred on simvastatin relative to placebo; results for pravastatin were intermediate between those of simvastatin and placebo (as were LDL-C reductions).[447]	- Also, there are case reports and case series of sleep problems[444, 529, 530] and nightmares;[531, 532] and reports of sleep AEs in clinical trials of statins.[196, 533-535] - A small study reported development of objective sleep problems on lovastatin but not pravastatin[536] (although other small studies reported no objective findings). - In one statin AE evaluation study in Spain, 26 patients were referred for oral evaluation; however, it was noted that 17% of these subjects cited insomnia, with 16/17 improving with

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Domain	Evidence	Comment
		interruption of statin treatment.[537]

CK = creatine kinase; CVD = cardiovascular disease; HbA1c = glycosylated hemoglobin; HR = hazard ratio; JUPITER = Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; LDL-C = low-density lipoprotein cholesterol; LFTs = liver function tests; PROVE-IT-TIMI = Pravastatin or Atorvastatin Evaluation and Infection Therapy – Thrombolysis in Myocardial Infarction trial; TIA = transient ischemic attack; ULN = upper limit of normal.

[a]For the sample employed in that RCT. Effect modification can lead to effects that differ in different samples.

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Table VIII

Statin Adverse Effects (AEs) Supported or Suggested by Case Series, Case Studies and Observational Designs[a,b]

Statin AE	Relevant reports	Triangulating evidence and effect modification
Peripheral Neuropathy (PN)[c]	- High-quality case control study using Danish databases.[442] - Also, many case reports/case series.[561-575] - Includes reports of multiple mononeuropathy.[538, 576] - Reversibility is not complete in all cases, inferable from some case reports; from rate in former relative to current statin users[442] and shown in Australian Adverse Drug Reaction Advisory Committee report.[561]	- Hypo–lipoproteinemia is linked to PN.[577-581] - Cholesterol transports antioxidants essential to protection against PN.[539-542] - We also observe that statins impair mitochondrial function, and impaired mitochondrial function has been linked to PN.[543, 544]
Sexual Dysfunction[c]	Numerous case reports, case series, including several from European and Australian AE databases.[444, 545-555, 582, 583]	- Cholesterol is the biochemical precursor to testosterone. - Experimental and RCT evidence shows that statins reduce testosterone in men, though the average effect is modest.[15, 369, 558] (Studies in small samples and /or with lower statin doses do not show a significant change in testosterone on average.) Clinical data showing testosterone reductions complement *in vitro* studies demonstrating statin effects on human testicular testosterone synthesis;[584] and animal studies demonstrating statin effects on morphology and function of Leydig cells.[559] - Mitochondrial dysfunction associated with gonadal dysfunction[560] – of potential relevance given statin effects on mitochondrial function. - Oxidative stress associated with gonadal dysfunction[585] – of potential relevance given adverse statin effects on oxidation in some.[51, 52] - Testicular morphologic changes occurred in an animal study of high-dose statins, in which it was stated that testicular tissue (in dogs) was “the only organ for which a comparably low margin of safety was observed.”[586] - Note that statins have also been reported to improve erectile function[587] and the sexual benefits of sildenafil (Viagra™) in some subjects through endothelial function benefits,[588-590] which may rely on the antioxidant effects of statins[591-593] that predominate over pro-oxidant effects in many.[51]
Male Endocrine, Other[c]	- Gynecomastia: several reports of gynecomastia associated with statins.[594-596] Statin use in organ transplant recipients was associated with increased risk of gynecomastia (statin use in 83.3% of those with gynecomastia, 39.6% of those without, p=0.041).[597]	See above, “Sexual dysfunction.”

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Statin AE	Relevant reports	Triangulating evidence and effect modification
	- Oligospermia.[556] - Questions have been raised about male infertility with statins.[557] - Testicular pain: Case report.[598]	
Thyroid Dysfunction	See discussion in Table IV under 'Thyroid disorders.'	
Renal[c]	- Renal tubule toxicity.[599] - Proteinuria: statins, particularly, high-dose statins, have led to proteinuria and hematuria.[180, 600] - Statins have led to renal failure and death from renal failure in the context of rhabdomyolysis.[82, 98-100, 102-104, 110, 202, 219, 247, 308, 419, 431, 601-605]	- Statins have been reported, in an observational study, to be associated with less contrast nephropathy.[606] This could reflect that statins signal higher lipids (and fat-soluble antioxidant transport) – i.e. indication bias, or could result from antioxidant effects of statins (antioxidants have been reported to reduce contrast nephropathy). - Statins have reduced proteinuria in some groups on average but may not do so in other groups (meta-analysis of RCTs – proteinuria was not reduced, e.g. in diabetes mellitus or hypertension).[607, 608] Moreover, statins have been reported to increase proteinuria in some.[180] In one study, statin use (compared with placebo) was associated with lower creatinine,[609] which was presumed to reflect better kidney function.[609] However, because muscle mass correlates with creatinine, and statins can reduce muscle mass, it is unclear the extent to which the creatinine reduction was driven by benefit to the kidney versus harm to the muscle (subclinical muscle wasting).[60]
Irritability/Aggression / Behavior Change[c]	- Case series of severe irritability and/or aggression reproducibly arising on statins,[443] also in pharmacovigilance database.[467] - Observational study showing women on statins are more aggressive.[610]	- Low cholesterol linked to conduct disorder, violent antisocial personality disorder, and violent crime prospectively; to violent death in numerous observational studies; and in animal studies to aggression.[611-623] - Several meta-analyses of prestatin cholesterol-lowering RCTs (including those with the most appropriate inclusion/exclusion criteria[624, 625]) showed significant increases in violent death.[611] Statin meta-analysis has not.[626] - Elucidated potential mechanisms include low central serotonin[486, 611] and altered omega-3 to omega-6 ratios.[17] Here, we add the suggestion of impaired cell energetics and oxidative stress, which are associated with a number of other aggression- and irritability related exposures.[127, 627-641] This offers the possibility that benefits may predominate in some persons through benefits to endothelial function/ flow and/or anti-inflammation, consistent with bidirectional effects suggested in an RCT.[642]
Pulmonary, Respiratory, Shortness of Breath (see also 'Cardiac	- Shortness of breath as a symptom in statin AEs (including reports of dyspnea as the presenting symptom of otherwise asymptomatic rhabdomyolysis,[95] associated with lactic	- Cardiopulmonary function and respiratory exchange ratio are affected by statins.[156, 157] - Mitochondrial (cellular) respiration is affected by statins (see section 5).

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Statin AE	Relevant reports	Triangulating evidence and effect modification
Function and Heart Failure')[C]	acidosis[412]). - Respiratory failure has accompanied statin rhabdomyolysis.[98] The following have also been reported in association with statins: - Chylothorax.[643] - Dermatomyositis with lung involvement/pulmonary fibrosis.[65, 74] - Eosinophilic pneumonia.[644] - Interstitial lung disease.[282, 645-647] - Pulmonary fibrosis.[74, 648] - Pleural effusion (see also 'Cardiac function and heart failure').[645, 649, 650] - Hypersensitivity pneumonitis.[651, 652] - Autoimmune conditions affecting pulmonary function (see 'Immune, autoimmune'). - Cough (see 'Oral cavity').	- Statins accelerate aging effect on (rat) diaphragm mitochondrial cellular respiration[426] – affecting the major muscle of breathing. - Myopathy arises with statins (see section 1): effective respiration relies on skeletal muscles such as the diaphragm. -Statin pulmonary restrictive disease occurs, and resembles amiodarone pulmonary disease[647] compatible with common mitochondrial origin.[282] - Statins lower cholesterol, which is the precursor to vitamin D, which is associated with protection against autoimmune diseases, including lupus. - See also 'Cardiac function and heart failure.'
Cardiac Function and Heart Failure[C]	- Heart failure, pulmonary edema, and cardiac muscle rhabdomyolysis have been reported in cases of statin rhabdomyolysis.[91, 109, 111] - In an observational study, statins adversely affected cardiac diastolic function in a fashion that was partially reversed by coenzyme Q10.[653]	- The heart muscle, like other muscles, may be affected in myopathy. - Statins lower coenzyme Q10, while addition of coenzyme Q10 in RCTs has reduced hospitalizations for heart failure and pulmonary edema.[654] - Statins reduce coenzyme Q10, and coenzyme Q10 reportedly improves diastolic function,[655] which is strongly ATP dependent. Diastolic function has reportedly been reduced with statins, an effect reversed by coenzyme Q10[653] (study prospective but not placebo-controlled). - Statins lead to average improvement in heart failure or left ventricular systolic function in some studies, including randomized trials.[656, 657]
Heart Rhythm Disturbance:[C] Heart Block, Atrial Fibrillation	- Atrioventricular block with rhabdomyolysis reported.[239] - Bradycardia including heart block in a range of US FDA reports (secured under the Freedom of Information Act dated 8-1-06). - Atrial fibrillation with statin use reported.[658]	- Statins lower coenzyme Q10, and coenzyme Q10 has reportedly reduced arrhythmia in a range of settings.[659, 660] - Patients with atrial fibrillation show greater oxidative damage to atrial mitochondrial DNA than those without,[661] consistent with a role for statin oxidative/antioxidant effects. - Statins have reportedly produced heart block.[239] They have also produced lactic acidosis[22, 411, 413] and hyperkalemia,[209, 396] each of which have been linked to heart block.[662, 663]

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Statin AE	Relevant reports	Triangulating evidence and effect modification
		- Heart block may arise because of the energy dependence of cell signaling (with mitochondrial impairments impeding these) or due to alterations in tissue excitability (due to change in pH etc.). Heart block has been induced in other settings in which mitochondrial dysfunction induced high lactate.[395] - Low cholesterol, associated with lower transport of fat-soluble antioxidants, has been linked observationally to higher atrial fibrillation rates.[664] - Statins have pro-oxidant and antioxidant, proinflammatory and anti-inflammatory effects, with each dominating in different persons (more commonly, antioxidant and anti-inflammatory at modest doses in clinical-trial-equivalent middle-aged men). Atrial fibrillation has been linked to oxidant and inflammatory mechanisms, and its protection to the reverse.[665-669] - Statins have reduced arrhythmia/atrial fibrillation in a clinical trial setting;[670] individual effects may depart from average effects.
Hyperkalemia	See discussion under 'Heart rhythm disturbance' (immediately above).	
Weight Gain[C]	Observational study with high rate of weight gain in high-dose statin group.[27]	- Statins lead to dose-dependent reductions in coenzyme Q10.[20, 21] - Coenzyme Q10 supplementation has reduced appetite in patients with hyperphagia,[671] and also improved insulin sensitivity.[672]
Neurodegenerative Disease: Parkinson Disease, also ALS or ALS-like Syndrome[C]	Case reports[673] and case series.[144, 145]	- Statins reduce coenzyme Q10.[20, 21] - Coenzyme Q10 protects against neurodegeneration in animal models; and retards progression of early Parkinson disease in humans.[674-677] - Low LDL-C has been linked to increased risk of Parkinson disease.[678] - Higher cholesterol has been linked to increased survival with ALS.[679] - LDL-C transports (and statins reduce) key fat-soluble antioxidants;[680] reduced antioxidant transport unfavorably affects redox state (and mitochondrial function), which has a role in neurodegeneration protection.[681-684] - Statins may be selectively toxic to muscle satellite cells, the stem cells for muscle that have (finite) regenerative potential.[685] This may impair recovery of muscle in some statin users who experience normal or increased muscle injury on statins. (However, this is based on *in vitro* study.) - Observational studies link lower but not higher potency statins with dramatically lower rates of neurodegeneration[686-688] and have implied there is causality, although this is incompatible with findings from RCTs, and is more consistent with confounding, e.g. by education and

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Statin AE	Relevant reports	Triangulating evidence and effect modification
		indication. Confounding by education was a likely factor in the similar apparent association of HRT to lower Alzheimer disease rates, which similarly suggested vastly lower rates of dementia in users;[689] however, in fact, significantly increased rates of dementia arose with HRT when compared to placebo in RCTs, i.e. when treatment and placebo groups were chosen to be otherwise similar.[690, 691] Confounding by indication[356] is also a significant possibility given the protective association of higher LDL-C to lower Parkinson disease rates,[678] and the use of LDL-C as a criterion for statin use.[692] (That is, statin use is a proxy for higher LDL-C prior to and often despite statin treatment – except with the most potent statins.) - Authors of recent studies continued not to control for lipids,[688, 693] despite prior criticisms[355, 356] noting potential for indication bias in similar studies.[687] A later study attributed the lesser benefit of the more potent atorvastatin to selective benefits by simvastatin – the less potent statin in that study (vs alternative explanations such as atorvastatin more effectively overcoming benefit of high LDL-C). However, in the same authors' prior study, simvastatin was the more potent statin, and the one with which statin "benefit" was lost.[687] The author holds a patent on simvastatin for Alzheimer disease. - Findings are potentially consistent with confounding by indication for Parkinson disease (given the association of higher LDL-C with Parkinson disease protection, and the association of statins as a proxy for higher prior, perhaps lifelong, and often current LDL-C); and confounding by education (higher education is linked to lower rates of incident dementia, and also higher use of preventive healthcare).[355, 356] - It merits additional note that pro-oxidant conditions may spawn physiologic adaptations that ramp up antioxidant access, which may include elevation of lipid levels to boost antioxidant delivery. Association of higher lipid levels to conditions[679] may reflect protective adaptations rather than causal predisposition. See in-depth discussion of proposed mechanism for statin-associated neurodegeneration.[145]
Immune, Autoimmune[C]	- Case series and reports of lupus-like syndrome, autoimmune hepatitis, dermatomyositis and other.[67, 71, 72, 74, 475, 498, 502, 503, 506, 694-710] - See above (Table I) for case reports of Guillain Barre-like syndrome and myasthenia gravis on statins.	- Cholesterol is the precursor to vitamin D. High levels of vitamin D are associated with lower autoimmune disease risk, which we propose as a possible mechanism.[711-723] - Enthusiasm for trials of statins has been expressed in autoimmune diseases, particularly those with inflammatory components.[724]
Pancreatitis[C]	Case reports of statin-induced pancreatitis alone or associated with statin rhabdomyolysis or	See also discussion in this table, in rows entitled 'Gastrointestinal' and 'Immune, autoimmune.'

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Statin AE	Relevant reports	Triangulating evidence and effect modification
	muscle pain;[105, 725-739] including recurrent cases.[726, 737, 740, 741]	- A population-based case-control study using Danish databases reported the adjusted OR for acute pancreatitis "among ever, current, new and former users of statins" (respectively) were: 1.44 (95% CI 1.12-1.80), 1.26 (95% CI 0.96-1.64), 1.01 (95% CI 0.43-2.37), and 2.02 (95% CI 1.37-2.97).[742] The authors suggest this may imply protection by statins. However, this conclusion does not follow from this study design. Former users may disproportionately include those who experienced statin AEs (statin 'noncompliance' is linked to statin AEs[484]) and attendant mitochondrial injury (arising with and contributing to statin use). Occurrence of pancreatitis accompanying statin rhabdomyolysis suggest causal mediation by shared mitochondrial effects of statins, which may persist after treatment is discontinued; and mitochondrial pathology has repeatedly been linked to acute, chronic, and recurrent pancreatitits.[743-750] However, it is also possible that statins may, analogously to the case for muscle and kidney function, both protect from pancreatitis and conduce to it in different subjects (based on predominance, e.g. of statin antioxidant vs pro-oxidant effects).
Liver Pathology[C]	Case reports of statin hepatitis or hepatic dysfunction alone or associated with rhabdomyolysis: autoimmune hepatitis, cholestasis, cholestatic hepatitis, steatosis, viral-like hepatitis, microvesicular hepatitis, hepatic fibrosis, progression to cirrhosis.[96, 107, 108, 172, 474, 475, 477-479, 481, 492-504, 506, 508, 512, 513, 751, 752]	Includes documentation of hepatic failure necessitating liver transplant.[753]
MELAS, Lactic Acidosis, other Mitochondrial Syndromes[C]	- Statin induced lactic acidosis as an AE.[413] - 'Unmasking' of mitochondrial myopathy as an AE, reduced fatty oxidation. - Statin induced MELAS alone or associated with rhabdomyolysis.[112, 411]	See section 5 for discussion of mitochondrial effects of statins.
Dermatologic[C]	- See also "Immune, autoimmune" (dermatomyositis, lupus and lupus-like reactions). - Actinic dermatitis (chronic).[754,755] - Acute generalized exanthematous pustulosis.[756] - Alopecia.[757-759] - Angioneurotic edema.[760] - IgA bullous dermatosis.[702] - Cheilitis.[761] - Contact dermatitis.[762,763] - Dermatographism.[764] - Drug eruption.[765] - Eczema.[766,767]	- Range of potential mechanisms: hypersensitivity, autoimmune, nutritional. - Cholesterol is important in skin barrier function.[782-785] - Icthyosis and disorders of cornification have been reported with several lipid-lowering agents.[769] - Statins were reported to possibly improve skin response to sodium lauryl sulfate in one experiment.[786] - Statins have been theorized as potential treatments for a range of skin disorders.[787] - Regression of vitiligo with high-dose simvastatin was reported in one case.[788]

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Statin AE	Relevant reports	Triangulating evidence and effect modification
	- Eosinophilic fasciitis.[768] - Ichthyosis.[769,770] - Lichen planus pemphagoides.[771] - Lichenoid drug eruption.[772-775] - Photosensitivity/ Phototoxicity.[776,777] - Radiation recall.[778] - Skin lesions.[779] - Toxic epidermal necrolysis.[780] - Urticaria (chronic).[781]	
Oral Cavity	- Dry mouth.[537] - Bitterness.[537] - Oral paresthesias or itching.[537] - Cough.[537]	Oral symptoms were appraised in a study in which 26 patients (50-70 years of age) with hyperlipidemia on statins in a general practice were referred over a month for oral evaluation.[537] Of these, 23 reported dry mouth, 15 oral itch or paresthesia, 14 bitterness, and 12 cough. A trial of 2 weeks off statins led to marked abatement or resolution in each of these symptoms in 74%, 87%, 93%, and 92%, respectively.[537]
Vision[c]	- Cataracts.[789-791] - External ophthalmoplegia.[792] - A case series of 256 pharmacovigilance reports of ptosis, diplopia, and ophthalmoplegia on statins included 62 positive dechallenge and 14 positive rechallenge reports.[793] Reports include 23 instances of total ophthalmoplegia; 8 of ptosis alone and 18 of ptosis in concert with diplopia.	- Lens opacity seen in animal studies (high-dose).[586] These led to concerns about cataracts with statins, but cataracts have not been increased *on average* in small studies of humans.[794-796] Cataracts are thought to be induced by oxidative stress;[794,797,798] so statins' bi-directional effects on oxidation with effect modification may be operative. Cataracts have been described in mitochondrial cytopathy.[797] - In a British study, the unadjusted OR linking any recorded statin exposure to cataract was 1.41 (95% CI 1.21-1.65). It was 1.04 (95% CI 0.89-1.23, p=0.6) after "adjustment for consultation rate."[795] This is difficult to interpret: those seen more due to lipid therapy could have better access to cataract diagnosis leading to incorrect inferences in absence of adjustment; however, such adjustment could also extinguish a true association, through collinearity. - In a US study, incidence of nuclear cataract was lower in statin users relative to nonusers controlling for age (OR 0.55; 95% CI 0.36-0.84).[799] Five-year incidence of cortical cataract showed the opposite trend (OR 1.28; 95% CI 0.79-2.08) but was not significant.[799] Confounding is a major concern in such correlational studies, and associations observed may be different in magnitude and direction from true relationships. - Statins lower coenzymye Q10 and alter omega-3 to omega-6 balance;[17] combination of coenzyme Q10 with omega-3 (and one other substance) reportedly reversed early age-related macular degeneration in an RCT.[800] - External ophthalmoplegia has been widely described in

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Statin AE	Relevant reports	Triangulating evidence and effect modification
		mitochondrial disease,[801-806] and has been linked to deficiencies of fat-soluble vitamins transported by cholesterol.[807]
Olfaction	Hyposmia.[808]	Lipids transport carotenoids,[809] the precursor to retinol (vitamin A), which is important in smell and has been used in treatment of anosmia.[810-812]
Hematologic and Bone Marrow, Including Hemorrhagic[C]	- See 'Hemorrhagic Stroke' Table VII. - Ocular hemorrhage reported as a statin AE.[813] - Hematuria (microscopic).[110, 180] - Bone marrow toxicity among multiple-organ toxicity arising on statins.[96, 173] - Thrombocytopenia.[814] - Petechia, and thrombotic thrombocytopenic purpura.[815-822] - Hemolytic anemia.[823] - Nonhemolytic anemia.[96]	- Statin use has been observationally linked to lower bleeding, possibly as a proxy for higher cholesterol (and vitamin K?) in studies not adjusted for lipids.[824, 825] (In one, only long-term [not current] statin use was linked to this, and those patients started on statins in an earlier era had higher average lipids.[825]) - After percutaneous coronary intervention, acquired thrombocytopenia developed more frequently, assessed by multivariate analysis, in patients who had previous statin administration (OR 3.28; p=0.0002).[814] - Statins reportedly have antithrombotic effects, inhibit platelet aggregation, decrease platelet activity, have anticoagulant activity, affect blood viscosity, RBC deformability, and 'improve' von Willebrand factor activity.[826-829] - Erosions and hemorrhage in the gastrointestinal tract and the brain in animal studies (high-dose).[586] - Hemorrhage in gall bladder and brain, erosions in large intestines in animal study.[830] - Mitochondrial mechanisms have been linked to ineffective erythropoiesis.[831] - Statins inhibit bone-marrow-derived dendritic cell maturation – *in vitro*.[174]
Hypotension[C]	Hypotension and angioedema have been described in a case of an atorvastatin hypersensitivity reaction entailing shock and collapse – with recurrence of angioedema on rechallenge.[760]	Statins (simvastatin and pravastatin), compared to placebo, led on average to modest but significant reductions in systolic and diastolic blood pressure in an RCT. The effect extended to persons with blood pressure below the sample median.[832]
Gastrointestinal [C]	- Ulcerative colitis.[833, 834] - Severe gastric ulceration (with abdominal pain).[835] - Ileus in association with statin rhabdomyolysis.[431] - Protein-losing enteropathy.[836] - Gastrointestinal AEs were the most common AE class in an analysis of AEs from clinical trials;[837] and were the second most common in a small study.[26]	- Statins affect omega-3 to omega-6 ratio;[17] omega-3s provisionally associated with reduced gastrointestinal inflammation.[838] - Additionally, cholesterol is the precursor to vitamin D, which has been linked to protection against inflammatory bowel disease.[712, 839, 840] - Mitochondrial dysfunction can produce gastrointestinal symptomatology.[448, 841-844]

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Statin AE	Relevant reports	Triangulating evidence and effect modification
	- Patients who are noncompliant on statins are more likely to have AEs – e.g. gastrointestinal and neurologic.[484]	
Exercise Limitation[c] and Fatigue/Lack of Energy	- See 'Exercise limitations or exercise-induced muscle symptoms,' Table I. - Fatigue without muscle pain on statins was reported and evaluated in three patients.[845] All were found to have low serum coenzyme Q10. Coenzyme Q10 supplements conferred subjective benefit to energy and reduced fatigue with exertion.[845]	Combined statins and beta blockers affect perceived effort and cardiorespiratory function.[59]
Psychiatric[c]	- See also 'Irritability/aggression/behavior change' in this table and 'Sleep' in Table VII. - Reports of psychosis, depression, paranoia, anxiety, and personality change, to surveillance databases (including Scandinavian and New Zealand pharmacoviligance databases as well as our UCSD Statin Effects Study patient targeted statin AE surveillance database).[444, 445, 467, 846] - One report described four cases of depression arising with initiation of pravastatin and reversing on discontinuation, including one case with "the likelihood of suicide."[446]	Mitochondrial dysfunction can produce psychiatric symptoms.[455, 456, 847-857]
Headache[c]	- Headache.[858, 859] - Migraine (altitude associated).[860] - A case of yawning headache was described in a patient with statin-induced myopathy and neuropathy, but was not ascribed to statins.[861]	- Mitochondrial dysfunction is linked to migraines.[862-867] - Migraine occurrence in migraineurs has been shown to be reduced with coenzyme Q10 in an RCT.[868]
Other	- Acid maltase deficiency.[161] - Vasospasm after subarachnoid hemorrhage reported to be greater in statin users[869] (possibly from statin withdrawal or indication bias, however). - Nasal obstruction and nasal polyps resolving with statin discontinuation; three cases reported.[870] - Temperature dysregulation[c], including hyperthermia.[871-873]	

ALS = amyotrophic lateral sclerosis; CI = confidence interval; HRT = hormone-replacement therapy; LDL-C = low-density lipoprotein cholesterol; MELAS = Mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes; OR = odds ratio; RBC = red blood cells; RCT = randomized controlled trial; UCSD = University of California, San Diego.

[a] List is not complete.

[b] Comment: statins are contraindicated during pregnancy due to concerns about teratogenicity.[874-880]

[c] Also reported to our UCSD Statin Effects Study group.