REVIEW

# CLINICAL COMMENTARY STATINS AS A CAUSE OF MYOPATHY: KEY CONSIDERATIONS FOR THE CLINICIAN

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## ABSTRACT

**The current gold standard of managing the patient at high risk for cardiovascular (CV) disease risk is reduction of low density lipoprotein (LDL) to <70 mg/dl. Statin therapy is currently the treatment of choice to achieve and maintain this level. There is, however, some evidence that statins may be associated with myopathy. The incidence of statin-related myopathy has been difficult to determine due to varying clinical definitions, but up to 10.5% appears to be an appropriate estimate. What we do know is that short-term randomized controlled clinical trials generally report a lower incidence of myopathy than long-term trials. Also, the incidence of myopathy tends to be less with lower statin dosages. This is important since the LDL goal can be achieved in many cases with statins at safer, lower doses. For example, ezetimibe can contribute significantly to LDL reduction in the average at-risk patient. Note, however, that there is one clinical situation, acute coronary syndrome, in which initial use of a high statin dose is backed by clinical evidence (e.g., controlled clinical trials with atorvastatin). Genetics may play a role in the risk of myopathy, as studies have shown that certain patients are more genetically predisposed to developing myopathy. This may assume importance in future management of patients as the realm of genetics advances. While a myopathy may occur with one statin, it may not occur with other statins. When myopathy has been a problem, a useful approach is to administer rosuvastatin in a low dose twice a week or every three days, as supported by clinical evidence. Statins have been shown to interfere with the cellular functional role of coenzyme Q10 and also to contribute to its depletion. Coenzyme Q10 may decrease or prevent statin myopathy, and may even provide some benefit, although this has not been clearly established by controlled trials. The occurrence of the most serious complication of myopathy—rhabdomyolysis—is rare. When it does occur, awareness of the problem, its risks, and careful preventive follow-up of the patient are indicated.**


**Abbreviations**

| | |
|---|---|
| **ACS:** | **Acute coronary syndrome** |
| **CHD:** | **Coronary heart disease** |
| **CPK:** | **Creatine phosphokinase** |
| **CV:** | **Cardiovascular** |
| **HMG-CoA:** | **3-hydroxy-3-methylglutaryl-coenzyme A** |
| **LDL:** | **Low density lipoprotein** |
| **PVD:** | **Peripheral vascular disease** |
| **RCCTs:** | **Randomized Controlled Clinical Trials** |
| **SREBPs:** | **Sterol regulatory element binding proteins** |

## INTRODUCTION

The association of myopathy with statin use has been minimized in the literature, especially in randomized controlled clinical trials (RCCTs) performed over a finite time period. While the incidence of significant rhabdomyolysis is fortunately very low, the number of patients who do not tolerate statins due to myopathy-like symptoms is significant. In many cases there may be another etiology of the symptoms (such as fibromyalgia); however, if a patient believes his or her symptoms are due to a statin medication,

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there is usually little choice but to stop the medication. In the interest of providing appropriate patient care, it is important for the physician to understand the definition of myopathy, the true incidence of muscle symptoms attributable to a statin, and the various clinical approaches that may make it possible to help the high-risk CV patient maintain essential statin therapy since this represents optimal management in most cases.

## Definition of myopathy

The symptoms of myopathy involve aches and weakness of large muscles in general, are somewhat imprecise and the association of statins is not well understood. Two serious events involving myopathy include "significant myopathy" and rhabdomyolysis. Fortunately, such events are infrequent and the number needed to harm has been reported as 3,400 for both of them combined.[1] Significant myopathy is defined as creatine phosphokinase (CPK) >10 times the upper limit of normal. Despite this definition, some patients with statin-related symptoms of myopathy, including demonstrable muscle weakness as well as histopathologic findings of myopathy, have normal serum CPK levels.[2] Therefore, it is always essential for the physician to pay attention to the patient. If he or she is convinced that a prescribed statin is causing muscle aches representative of myopathy, the prescribing clinician must, in most cases, stop the particular statin, even in the presence of a normal CPK or one less than 10 times the upper limit of normal. This is appropriate even when it seems that the muscle aches represent fibromyalgia.

## True incidence of myopathy and relationship to statin dose

Myopathy has been measured in various ways, both subjectively by considering symptomatic complaints, and objectively by measuring clinical outcomes (i.e., adverse events) or CPK levels. These varied methods confound assessment of the true incidence of statin-related myopathy as well as evaluation of the risk of myopathy associated with intensive statin therapy.[3]

Subjective measures from prospective observational data yield estimates of "myopathic-like" complaints in >10% of patients taking high-dose statins. One large observational study with 32,225 patients reported that 5.8% of diabetic patients and 6.7% of non-diabetic patients developed myalgias related to statins.[4] Another large observational study, PRIMO (Prediction of Muscular Risk in Observational Conditions), was comprised of 7,924 patients in France taking high-dose statins. In this study, 10.5% of patients developed muscle-related symptoms with a median onset time of 1 month following initiation of statin therapy.[5] As is evident from this trial, current data suggest that statin-drug pharmacokinetics and statin-drug interactions play a causative role in myopathy and that myopathy is more related to statin dose than to LDL reduction.[6]

On the other hand, objective measures from fairly long-term prospective clinical outcomes studies have reported zero to very few adverse events attributable to statins.[7-10] Likewise, various short-term RCCTs have reported a zero incidence of myopathy.[11-13] One meta-analysis of 4 RCCTs comparing intensive versus low/moderate-dose statin therapy showed that patients in the intensive therapy group had CPK levels >10 times the upper limit of normal (e.g., significant myopathy) even when myalgia symptoms were absent (odds ratio 9.97; P = 0.028).[14] Contrarily, yet consistent with some short-term limited RCCTs[11-13] which have not shown any increase in myopathy in the treatment group and no relationship of increased myopathy to intensive dosing, a recent meta-analysis of 7 RCCTs (29,395 patients) failed to show any statistically increased myopathy risk with intensive therapy although events consistent with myopathy were reported in some of the component trials, and overall there was a 0.5% higher incidence of myopathy with more intensive therapy.[15]

The inconsistency in occurrence of myopathy and its reporting is symptomatic of searching the literature to try to determine the true incidence and problem of statin myopathy.[15] However, despite the possible value of CPK levels, their value is problematic as already noted because it is possible to have a clinically significant pathologically demonstrable myopathy with altered mitochondria in the presence of normal CPK levels.[2]

In addition to the failure of some long-term prospective clinical outcomes studies and some short-term statin clinical trials to show any significant

myopathy, at least one pharmaceutical company has claimed that their statin has no more complications at its highest dose than at its lowest dose.[16] The reality, however, appears to be contradictory. In fact, data submitted for United States Food and Drug Administration (FDA) approval of any statin and data obtained in most clinical studies with more than short-term follow-up have shown more myopathy with higher doses of any statin.[17] Also, the greatest risk for developing a statin-related myopathy is associated with exposure to the medication either via a higher dose or in association with another medication that interferes with statin metabolism, rendering the statin dose more toxic. Such medications include fibrates (especially gemfibrozil), cyclosporine, macrolide antibiotics, azole antifungal agents, antiretroviral agents, and drinking more than a quart (roughly 1 liter) of grapefruit juice per day.[18]

The bottom line for the practicing clinician is that statin-related myopathy symptoms occur in up to 10.5% of patients taking statins (Table-1). For patients at high risk for coronary heart disease (CHD) and peripheral vascular disease (PVD) this creates a significant problem in terms of adherence to these essential medications. Note that the estimate of 10.5% is consistent with the percent which appears to be observed in a clinical practice, separate from controlled clinical trials. The risk for myopathy appears to be greater when patients are associated with older age, frailty, multisystem diseases, and multiple medications,[5,18] some of which have specific associations as noted above.

The Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) found that at least one common genotypic variant of the SLC01B1 gene significantly alters the risk of occurrence of a simvastatin-induced myopathy. In SEARCH, a genome wide association study was carried out using approximately 300,000 markers in 85 subjects with definite or incipient myopathy and in 90 controls. All of the subjects and controls were taking simvastatin 80 mg daily in a trial involving 12,000 participants. Repeatability was evaluated in a study of simvastatin 40 mg daily involving 20,000 participants. The single-nucleotide polymorphism (SNP), rs4149056, located within gene SLC01B1 on chromosome 12 has been linked to statin metabolism. The SLC01B1 rs4149056 CC genotype has a 1-year 15.25% association with myopathy when taking simvastatin 80 mg daily whereas the association with the CT genotype is 1.38% and with the TT genotype is 0.34%. Therefore, the C allele of the rs4149056 polymorphism appears to have a particularly high risk of myopathy, also demonstrated in a trial of simvastatin 40 mg daily, and general evidence indicates that this C allele is associated with higher statin blood concentrations. Hence, medications that interfere with statin metabolism may be especially likely to contribute to myopathy in patients taking statins, especially in high doses and even more so in those who have the C allele of the rs4149056 polymorphism.

SLC01B1 encodes the organic anion-transporting polypeptide OATP1B1, known to mediate the hepatic uptake of various drugs including most statins. The findings in SEARCH are likely to apply to other statins because myopathy is a class effect and SLC01B1 polymorphisms affect the blood levels of several statins.[19] Therefore, when clinical practicality

***Table-1 : Objective versus Subjective Measures of Myopathy and Outcomes***

| Trials | Patients with Symptoms | Clinical Evidence |
|---|---|---|
| Observational study with 32,225 patients[4] | 5.8% diabetics<br>6.7% non-diabetics | no |
| PRIMO with 7,924 patients[5] | 10.5% after 1 mo | no |
| Long-term prospective trials[7-10] | 0-very few | no |
| Short-term RCCTs[11-13] | 0 | no |
| Meta-analysis of 4 RCCTs with intensive vs low-moderate dose[14] | 0 | CPK levels >10 times the upper limit with intensive treatment |
| Meta-analysis of 7 RCCTs with 29,395 patients[15] | 0.5% higher risk with intensive therapy | no |

## Relationship of genetics to statin myopathy

The suggestion has been presented that a specific genome may be associated with statin myopathy.[19]

can be achieved in the future, genotyping of SLC01B1 polymorphisms may be useful in planning statin dose and monitoring safety, especially when statins are used in combination with other drugs with known interactions and especially during the first year of statin treatment when the absolute risk of myopathy is greatest.

## The occurrence of rhabdomyolysis

The most serious risk of statins is myopathy/myositis with associated rhabdomyolysis. Fortunately, this risk is rare. It was emphasized by the withdrawal of cerivastatin in August 2001 after the drug was linked with approximately 100 rhabdomyolysis-related deaths.[17] Rhabdomyolysis can be defined literally as the dissolution of skeletal muscle.[20] It is characterized by the leakage of muscle-cell contents including electrolytes, myoglobin and CPK into the circulation. Massive necrosis is manifested as limb weakness, myalgia, swelling and frequently gross myoglobinuria with pigment and yet without hematuria and these occur in nontraumatic (e.g. statin-related) as well as traumatic rhabdomyolysis. The myoglobinuria can cause acute kidney injury and the prognosis is significantly worse if acute renal failure occurs. The administration of fluids intravenously is essential. There is no specific proven fluid replacement regimen but administration of both normal saline and sodium bicarbonate appear to be reasonable. If kidney injury is severe enough, intermittent hemodialysis may be necessary. Outcome is usually good if significant renal failure does not develop. Mortality among patients with rhabdomyolysis from illicit drugs and alcohol has been reported to be 3.4%[21] among patients with acute kidney injury, whereas rhabdomyolysis from limb ischemia has been reported at 32%.[22]

In a study looking at statins and fatal rhabdomyolysis per million prescriptions, cerivastatin had 3.16 deaths per million prescriptions, leading to withdrawal of the statin from the market. For comparison, the rates for other statins were: lovastatin 0.19, simvastatin 0.12, atorvastatin 0.04, pravastatin 0.045 and fluvastatin 0.00.[23] Rosuvastatin was not available when that data was collected but the safety profile of rosuvastatin has been reviewed in 12,569 patients.[24] Rosuvastatin 10 to 40 mg demonstrated a similar adverse event profile to those for atorvastatin 10 to 80 mg, simvastatin 10 to 80 mg, and pravastatin 10 to 40 mg. Myopathy attributable to rosuvastatin was defined as muscle symptoms plus serum CPK 10 times the upper limit of normal and occurred in 0.03% of patients receiving rosuvastatin 10 to 40 mg. In this review, no cases of rhabdomyolysis occurred in patients receiving rosuvastatin 10 to 40 mg. Therefore, safety with rosuvastatin appears at least comparable to the other available statins.

## Low density lipoprotein (LDL) and cardiovascular (CV) risk

One of the established standards for CV risk management, either CHD or PVD, is the LDL level reduction. When either CHD or PVD is present, there is a very high probability that the other is present as well,[25] and therefore the goal when either of these two forms of CV disease exists or in any patient with elevated CV risk is to attain an LDL level <70 mg/dl. A high-risk patient can be defined as anyone with a markedly increased CV risk factor, anyone who has sustained a previous CV event, any patient with multiple CV risk factors and any patient with diabetes mellitus.[26] There is currently much interest in inflammatory risk factors, such as high-sensitivity C-reactive protein, but only LDL has well-established, widely-accepted medical evidence to support that its treatment can decrease the incidence of acute and chronic CV events, including both CHD and PVD.

## Indications for high statin dose

Cost savings is one issue used to support the use of a high statin dose since it may help avoid the addition of a second medication to lower the LDL. Many medications such as statins have close to flat pricing in various programs such that higher doses may cost essentially the same as the lowest dose.[27] Also, clinical evidence for the early management of acute coronary syndrome (ACS) supports the occurrence of fewer adverse events in association with a high statin dose. In the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study of ACS, atorvastatin 80 mg/d reduced recurrent ischemic events, which were mostly recurrent symptomatic ischemia requiring rehospitalization in the first 16 weeks.[28] A comparable observation was made with atorvastatin 80 mg/d in the Pravastatin or

Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE-IT) study in which patients with recent ACS were shown to have greater protection against death or major CV events from the maximum high atorvastatin dose.[12] Therefore, in the acute inflammatory state immediately following ACS, there is evidence-based medicine to support the use of a high statin dose, especially atorvastatin, but this clinical evidence is not available for the quiescent period extending indefinitely from a few weeks following the acute event.

## Approach to keeping statin dose low

With statin monotherapy, the majority of LDL reduction is seen with the initial dose; thereafter, on average, each doubling of the statin dose reduces LDL only another 6%.[29] In addition, higher statin doses definitely cause more problems, especially myopathy, as documented in the data initially submitted to the U.S. FDA for each statin. Despite some statements from short-term studies that there is no increase in myopathy with a high-dose statin,[12, 30] the apparent incidence of statin-related myopathy is up to 10.5%.[5] Therefore, since LDL lowering is the gold standard of CV risk reduction, the use of a medication such as ezetimibe that can lower LDL another 25% while keeping the statin at a safer, lower, long-term dose appears advantageous.[31] This occurs while at the same time preserving the great majority of statin benefit and pleiotropic effects and therefore warrants serious consideration unless there is specific clinical evidence to use a high-dose statin as in the early period after ACS as described above.

## Use of different statins

All statins have a similar mechanism of action in lowering total cholesterol and LDL cholesterol, starting with their inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This is the enzyme that converts HMG-CoA into mevalonic acid, a cholesterol precursor. This active site is the key control point in cholesterol biosynthesis. With intracellular cholesterol thereby reduced, the activation of a protease, which slices the sterol regulatory element binding proteins (SREBPs) from the endoplasmic reticulum, is induced. These SREBPs are translocated at the level of the nucleus where they augment the gene expression for the LDL receptor. This thereby, especially in hepatocytes, leads to an increase in cell surface LDL receptors, which determine the reduction of circulating LDL and its precursors (intermediate density and very low density lipoproteins).[32] However, despite this common mechanism for total cholesterol and LDL reduction, all of the statins have different organic chemical structures. Because of this, patient problems with one statin may not occur with another statin or be markedly different or of lesser severity.

## Lower statin dose using biweekly dosing

In 2008, Gadarla et al. studied 40 patients intolerant of a daily statin dose and evaluated the efficacy of rosuvastatin twice a week in these patients. Doses of rosuvastatin use included 5 mg and 10 mg, each twice a week.[33] Compared to statins with a short half-life (all others except for atorvastatin), rosuvastatin is a long-acting statin with a mean plasma elimination half-life of 19 hours. The half-life for atorvastatin is similarly long at around 14 hours. Of the patients, 30 received rosuvastatin 5 mg twice weekly and 10 patients received rosuvastatin 10 mg twice weekly. After taking rosuvastatin for ≤3 weeks, total cholesterol was decreased 19%, LDL was decreased 26% and triglycerides were decreased 14% ($P<0.05$ for all observations). Of the 40 patients, 8 stopped the twice-weekly rosuvastatin after the 3-week lipid measurements due to myalgias but were included in the lipid analysis. The remaining 32 patients continued rosuvastatin twice weekly for a mean of 3 months (range 2 to 12 months). The authors demonstrated that rosuvastatin given twice weekly in a markedly lower total weekly dose resulted in significant reductions in total cholesterol, LDL and triglycerides. Atorvastatin, which also has a long half-life, could probably be used in a similar way.

## Coenzyme Q10

Coenzyme Q10 is considered to have an uncertain benefit to risk ratio but there is suggestive information that its use can decrease the myositis-causing toxicity of statins. This possible benefit seems reasonable because coenzyme Q10 plays a role in mitochondrial energy transduction, is a functional

element in all cell membranes, plays an apparent role in regeneration of redox capacity and has antioxidant function.[34] There is also a control function for membrane channels and their biosynthesis and this control function has been shown to be inhibited by statins. Statins also inhibit the functional role of coenzyme Q10 in mitochondria and the endoplasmic reticulum. Also, coenzyme Q10 depletion by statins (decreased biosynthesis) has been described with conjecture about this depletion as a cause of statin-associated adverse effects such as myopathy and thereby the suggestion of coenzyme Q10 supplementation as a possible treatment.[35] In Parkinson's Disease, use of coenzyme Q10 in a dose up to 3,000 mg/d has been reported. A suggested dose for initial coenzyme Q10 supplementation when using a statin is 200 mg/d. This appears appropriate when there is increased risk of myopathy in patients on a high dose of a statin, who have had a problem with a previous different statin or who are on another medication that increases the risk of statin myopathy such as fenofibrate (gemfibrozil should never be used with a statin due to an unacceptable risk of toxicity).

## CONCLUSIONS

Statin myopathy is a significant problem in up to 10.5% of patients taking a statin. Fortunately, there is rarely a problem with rhabdomyolysis but symptoms of myopathy lead a significant number of patients at high CV risk to stop this critical class of medications. Therefore, awareness of the problem and paying attention to a patient's symptoms of myalgias are essential. Confusion regarding the actual status of the problem has been created because reported symptoms appear to be less in short-term RCCTs and some pharmaceutical company literature implies a less than actual incidence. Statins are essential medications in the management of the majority of patients with increased CV risk and some measures discussed such as changing statin, the possible but still unproven benefit of coenzyme Q10 and decreased frequency of statin dosing may improve medication tolerance and adherence.

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