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# A review of muscle-related adverse effects of statins

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**Abstract**
3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors or statins are lipid lowering agents and effective for reducing low density lipoprotein cholesterol (LDL-C) and thereby reducing cardiovascular events. Statin intolerance is associated with various side effects including statin-associated muscle symptoms (SAMS), diabetes mellitus (DM), hepatotoxicity, renal toxicity, neurological and neurocognitive effect. Statins can cause very serious muscle condition called rhabdomyolysis but this is rare. SAMS are most common adverse effects of statins and also the major reason for discontinuation of statin therapy. Pain and weakness in SAMS are generally affected on large muscle groups including thighs, buttocks, calves and back muscles. The diagnosis of SAMS is difficult because there are no validated clinical tests and diagnostic criteria. Management of SAMS requires possible diagnosis, discontinuation of statins or rechallenge, alternative lipid lowering therapy and alternative dosing strategies.

**Keywords:** 3-hydroxy-3-methylglutaryl coenzyme A, Statin-associated muscle symptoms, rhabdomyolysis, rechallenge

## Introduction

The 3-hydroxy-3-methylglutaryl coenzyme-A reductase inhibitors (statins) are a widely prescribed drug class and include the best-selling prescription drug in the world.[4].statins are the most effective medications for reducing elevated concentrations of low-density lipoprotein cholesterol (LDL-C) and produce remarkable reductions in cardiovascular events [3]. The most commonly reported adverse effects are muscle-related problems (i.e., muscle pain, weakness, and/or fatigue), which can occur in the absence of creatine kinase (CK) level elevation. Blinded N-of-1 crossover biopsy data indicate that muscle-related problems with normal or minimally elevated CK levels reflect a (partially) reversible mitochondrial myopathy [4].

Generally, statins are well indulged with few serious side effects. However, adherence can be limited by patients' concern about serious muscle toxicity and by more frequent but less severe side effects of muscle aches, pain, weakness, and cramps. Because statins must be taken long-term and are potentially life-saving, their tolerability and adherence are a major concern. Overall, muscle side effects (including symptoms or creatine kinase elevations or both) are recognized as the most common adverse effect associated with statin use, but their extent is not well-defined [2]. Statins are widely and safely used as a cholesterol-lowering medication and have been shown to significantly reduce cardiovascular mortality and morbidity in patients with a high risk of cardiovascular disease (CVD) and cause serious ADRs only in a very small minority of patient [5].

Although their overall safety profile is excellent, myalgia without functional muscle impairment commonly affects patients taking statins. The clinical manifestations of statin-associated myopathy include pain and muscle weakness [1]. The widespread use of statins to lower cholesterol and reduce cardiovascular morbidity and mortality, discontinuation, and nonadherence to statin therapy remains an ongoing problem. The major reason for the discontinuation of statin therapy is statin-associated muscle symptoms (SAMSs), which are the most-well-documented side effect of statins [10]. Statins can produce life-threatening rhabdomyolysis, but this is rare. Statins are more frequently associated with mild muscle complaints including myalgia, cramps, and weakness which may compromise medication compliance and quality of life [3]. Advancing age has been associated with an increased risk of statin-induced muscle disorders. Also, the medical effects of statin-associated muscle effects (e.g. functional impairment, risk of falls, and/or disability) are likely to be greatest in older persons [6]. In addition, other more serious adverse effects of statins may also occur, with the next most established being new-onset type 2 diabetes mellitus for which the mechanisms are far less clear. Other side effects include neurological and neurocognitive effects, hepatotoxicity, renal toxicity, and others (gastrointestinal, urogenital, reproductive), which currently have no established validity [10].

## Statin Associated Muscle Symptoms (SAMS)

SAMSs is by far the most prevalent and important adverse event, with up to 72% of all statin adverse events being muscle-related. These can present as myalgia, myopathy, myositis with elevated CK (creatinine kinase), or at its most severe, rhabdomyolysis, with some people reporting additional joint and abdominal pain [10]. SAMS can occur without creatine kinase (CK) elevations, and that this is the most frequent SAMS presentation [7]. Other skeletal-related side effects include tendinopathies and tendon disorders, as well as arthralgias, although these are rarely evaluated in large randomized controlled trials [10].

## Assessment and diagnosis of SAMS

The diagnosis of SAMS, such as myalgia and cramps, is subjective for both patient and physician because there are no

validated clinical tests or diagnostic criteria. CK levels are repeatedly normal in patients with possible SAMS, whereas many asymptomatic patients on statin therapy have increased CK levels. The NLA has proposed a point/scoring system based on observational studies, such as the PRIMO (Prediction of Muscular Risk in Observational Conditions) study and our STOMP (Effect of Statins On Skeletal Muscle Performance) study [7].

The Effect of Statins on Skeletal Muscle Function and Performance (STOMP) study assessed symptoms and measured creatine kinase (CK), exercise capacity, and muscle strength before and after atorvastatin 80 mg or placebo were administered for 6 months to 420 healthy, statin-native subjects. STOMP predefined myalgia, requiring subjects to report unexplained new or increased myalgia, cramps, or muscle aching that lasted at least 2 weeks, resolved within 2 weeks of treatment cessation, and returned within 4 weeks of drug re-initiation. Subjects were called every 2 weeks and queried about muscle symptoms. No individual CK value surpassed 10 times normal, but average CK increased with atorvastatin. Twenty-three atorvastatin and 14 placebo subjects disclosed new, unexplained muscle pain. Of these, 19 atorvastatin and 10 placebo subjects met the study myalgia definition. There were no significant changes in several measures of muscle strength or exercise capacity with atorvastatin, but more atorvastatin than placebo subjects developed myalgia (19 vs 10) [3].

From the study "Statin-Associated Muscle-Related Adverse Effects" by Cham *et al*, Patients with perceived statin-associated MAEs completed a survey assessing statin drugs and dosages; characteristics of the MAEs; time course of onset, resolution, or reappearance; and impact on quality of life (QOL). Cases were assessed for putative drug adverse-effect causality by using the Naranjo adverse drug reaction probability scale criteria and were evaluated for inclusion in groups for which mortality benefit with statins has been shown. Patients reported muscle pain (93%), muscle fatigue (88%), and muscle weakness (85%) associated with statin use. Ninety-four percent of atorvastatin usages (240/255) generated MAEs versus 61% of lovastatin usages (38/62, $p<0.0001$). Time course of onset after statin initiation varied (median 14 wks); some MAEs occurred after long-term symptom-free use. Two hundred thirty-two patients (66%) reported cessation of statin therapy after experiencing muscle-related symptoms; of these, 174 patients (75%) cited some recovery on discontinuation of the statin, with 66 patients (28%) citing complete recovery of their muscle-related symptoms with discontinuation [4].

From the study "Association between statin-associated myopathy and skeletal muscle damage" by Mohaupt *et al*; they obtained biopsy samples from the vastus lateralis muscle of 83 patients. Of the 44 patients with clinically identified statin-associated myopathy, 29 were presently taking a statin, and 15 had ceased statin therapy before the biopsy (minimal duration of discontinuation 3 weeks). They also included 19 patients who were taking statins and had no myopathy and 20 patients who had never taken statins and had no myopathy. They classified the muscles as injured if 2% or more of the muscle fibers in a biopsy sample showed damage. Using reverse transcriptase-polymerase chain reaction, they evaluated the expression levels of candidate genes potentially related to myocyte injury.

Patients with myopathy reported generally slight weakness. They communicated having trouble in rising from a chair without arm support. Muscle pain was reported predominately in the trunk and proximal muscle groups and was exacerbated by exercise. Patients reported that their symptoms were severe enough to interfere with the activities of daily living and that they had decreased exercise capacity. The symptoms had lasted for several weeks. Normally, the symptoms departed within days after cessation of statin therapy. In 3 cases, the symptoms persisted after statin therapy had been discontinued for more than 1 month. One patient, who presented with overt rhabdomyolysis (creatine phosphokinase 57657U/L), required admission to hospital for the management of muscle pain.Compared to control patients, those who currently ($p < 0.001$) or previously ($p < 0.001$) used statins had significantly more muscle damage.Muscle injury was observed in 25 (of 44) patients with myopathy and 1 patient without myopathy. Only 1 patient with structural injury had a circulating level of creatine phosphokinase that was elevated more than 1950 U/L (10× the upper limit of normal). appearance of ryanodine receptor 3 was significantly up synchronized in patients with biopsy evidence of structural damage (1.7, standard error of the mean 0.3) [1].

From the study "Prevalence of Musculoskeletal Pain and Statin Use" by Buettner *et al*; Cross-sectional analysis using data from the National Health and Nutrition Examination Survey (NHANES) 1999–2002. Members were 3,580 adults ≥40 years devoid of arthritis who were interviewed at home and examined in a mobile assessment center. Participants were asked about sociodemographic characteristics, health conditions, medication use, and musculoskeletal pain. Height, weight, blood pressure, ankle-brachial index, and cholesterol were measured. Popularity and adjusted odds ratios (OR) of any musculoskeletal pain and musculoskeletal pain in 4 different anatomical regions (neck/upper back, upper extremities, lower back, and lower extremities) by statin use during the last 30 days. Among statin users (n=402), 22.0% reported musculoskeletal pain in at least 1 anatomical region during the last 30 days, compared with 16.7% of those who did not use a statin. The dominance of lower extremity pain was particularly high among statin users collated with statin nonusers. Compared to persons who did not use statins, those who used statins had multivariable-adjusted odds ratios (95%CI; p-value) of 1.50 (1.07–2.11; p=.01) for any musculoskeletal pain, 1.59(1.04–2.44,p=.03) for lower back pain,and1.50(1.02–2.22,p=.03)for lower extremity pain [2].

A definitive diagnosis of SAMS is difficult because symptoms are subjective and there is no 'gold standard' diagnostic test. Importantly, there is also no validated muscle symptom questionnaire, although the National Lipid Association (NLA) has proposed a symptom scoring system based on the STOMP trial and the PRIMO. Evaluation of the possibility of SAMS being due to a statin take account of the nature of the muscle features, the elevation in CK levels, and their temporal involvement with statin initiation, discontinuation, and re-challenge. Note that this is a clinical definition, which may not be appropriate for regulatory purposes [8].

In the absence of a standardized classification of SAMS, propose to integrate all muscle-related complaints (e.g. pain, weakness, or cramps) as 'muscle symptoms', subdivided by the existence or absence of CK elevation. Pain and weakness in typical SAMS are usually symmetrical and proximal, and generally influence large

muscle groups including the thighs, buttocks, calves, and back muscles. Discomfort and weakness typically occur early (within 4–6 weeks after starting statin therapy), but may still occur after many years of management. The onset of novel symptoms may occur with an increase in statin dose or the commencement of an interacting drug. The symptoms emerge to be more normal in physically active persons [7].

Statin-associated muscle symptoms are more possible to be caused by statins when elevated CK levels decrease after end of either the statin or the interacting drug, or when symptoms revert markedly within a few weeks of cessation of the statin and/or reappear within a month of drug re-challenge. Time to the reappearance of symptoms is also influenced by the dose of statin and the duration of the re-challenge. Individual patient drug–placebo clinical trials have been suggested as an approach to confirming diagnosis of SAMS, but are not feasible in the routine outpatient setting [8].

**Rhabdomyolysis**

Rhabdomyolysis, a CK >10× ULN, occurred in 10% of statin-treated and 0.04% of placebo-treated patients in randomized controlled clinical trials. Subjects were remarked from 0.5 to 6.1 years, giving an enormously low yearly occurrence of rhabdomyolysis. The incidence of rhabdomyolysis in clinical practice has been examined using national health records and health insurance databases. An examination of health claims from 473,343 patients treated with lipid-lowering agents, of whom 86% received statin monotherapy, found 144 claims coded for rhabdomyolysis, of which 44 were confirmed by physician review. The incidence of statin-coupled rhabdomyolysis was 2.0 cases/10,000 person-years of management and ranged from 0.3 cases for lovastatin to 8.4 cases for cerivastatin. The rates were 0.6 for atorvastatin and 1.2 for rosuvastatin/10,000 person-years. Cerivastatin has been removed from the market because of its rhabdomyolysis risk, so the current incidence of rhabdomyolysis is approximately 1 case/10,000 person-years [7].

**Possible Mechanisms for the Development of SAMS**

Mechanistically, statin toxicity is thought to arise because of HMG-CoA reductase inhibition effects, direct cellular and subcellular effects, or a combination of both. Other possible causes include genetic factors, drug-drug interactions, vitamin D status, and other metabolic or immune effects [10].

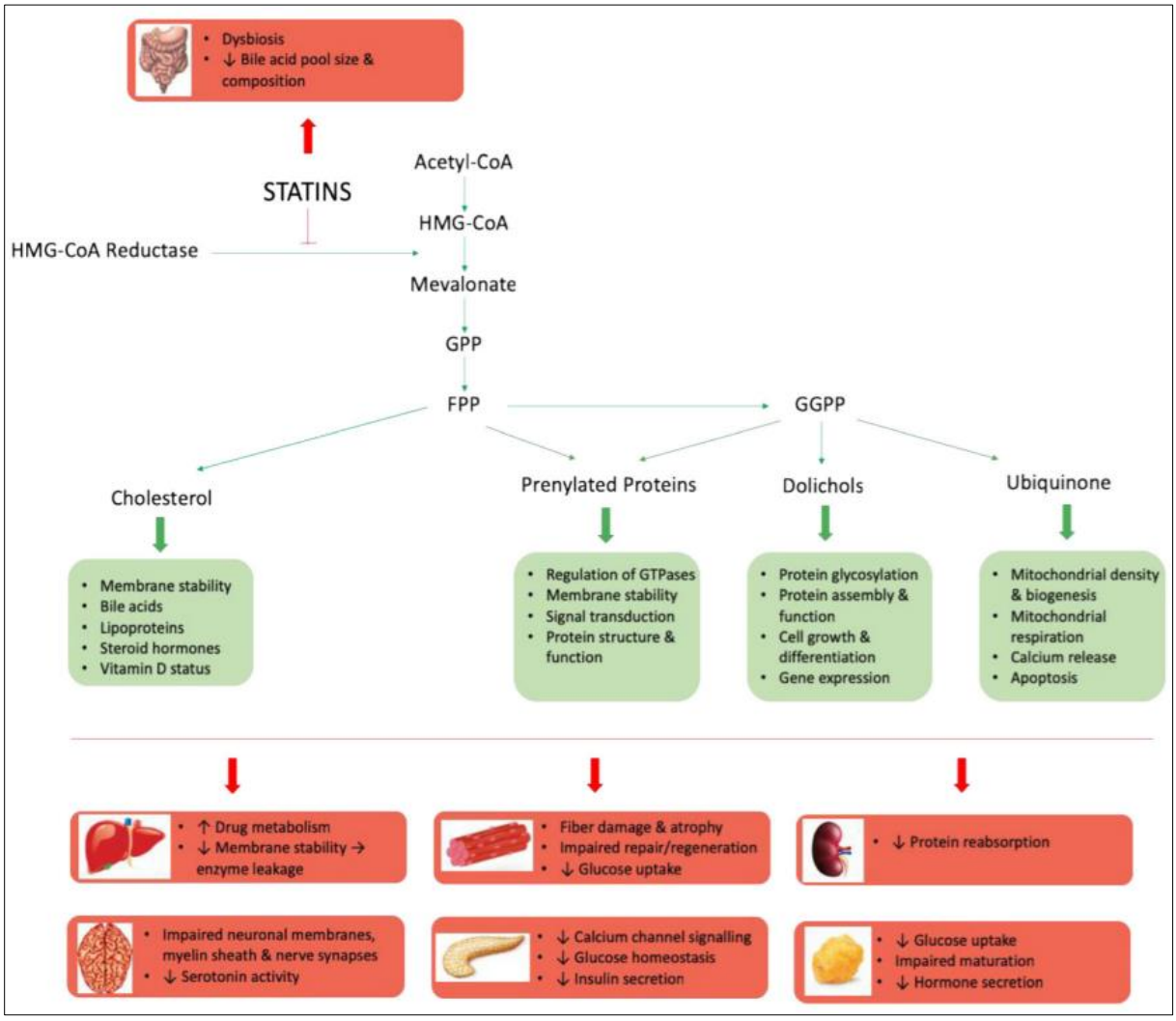


**Fig 1:** Potential mechanisms for the development of statin toxicity. FPP indicates farnesyl pyrophosphate; GGPP geranylgeranyl pyrophosphate; GPP, geranyl pyrophosphate; and HMG-CoA reductase, hydroxymethylglutaryl-coenzyme A reductase.

Mechanisms for SAMS include HMG-CoA reductase pathway-mediated effects, cellular and subcellular effects, genetic factors, and effects on skeletal muscle. These can modify muscle cell membrane stability, fluidity, as well as protein signaling and action; impact mitochondrial function, and reduce membrane cholesterol substance. Alterations to statin uptake or metabolism can also result in increased exposure of skeletal muscle to statins, which can lead to altered mitochondrial function, calcium signaling, and cell cycle pathways [10].

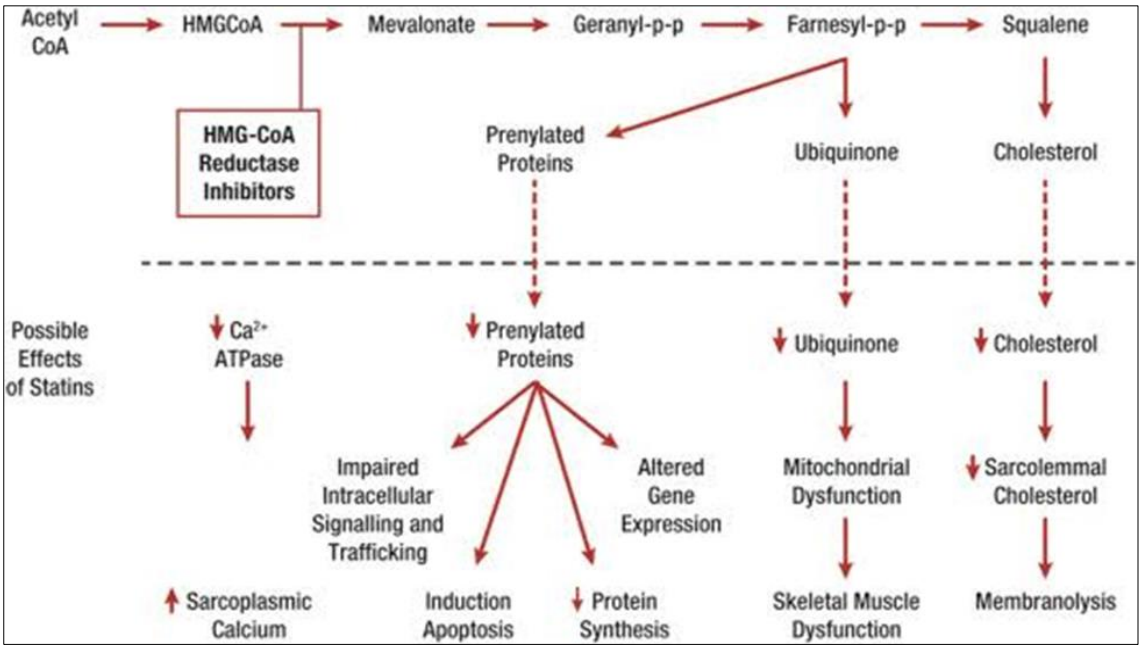


**Fig 2:** Potential mechanisms for the development of statin-associated muscle symptoms.

The highly conserved mevalonate pathway is an important metabolic pathway, which plays a key role in many cellular processes via the synthesis of sterol and nonsterol isoprenoids.[10] Statins inhibit HMG-CoA reductase, the rate-limiting enzyme in the mevalonate pathway that produces cholesterol, farnesyl pyrophosphate (FPP), and geranylgeranyl pyrophosphate (GGPP). FPP and GGPP activate a variety of small guanosine triphosphate (GTP)-binding regulatory proteins by prenylation or the addition of specific carbon atoms to the protein.[7] Reticence of HMG-CoA reductase can guide to alterations to muscle protein signaling and action can occur. These include impaired skeletal PI3k (phosphatidylinositol 3-kinase)/ Akt (protein kinase B), resulting in inductions in ubiquitin and lysosomal proteolysis through upregulation of the FOXO (Forkhead box protein O) downstream target genes of muscle atrophy [10].

The preeminent proof suggests that statins affect muscle by activating the phosphoinositide 3-kinase (PI3K)/Akt pathway. This trail can lead to either muscle hypertrophy via activation of the mechanistic target of rapamycin (mTOR) or muscle atrophy via activation of the forkhead box class O protein group (FOXO). FOXO activates muscle-specific ubiquitin ligases, including atrogin-1 and muscle-specific ring finger (MuRF)-1. Atrogin-1 and MuRF-1 cause protein degradation and muscle atrophy. Akt phosphorylation leads to FOXO phosphorylation, which prevents FOXO from entering the nucleus. It is proposed that decreased FFP from statin therapy reduces the production of the small prenylated proteins that phosphorylate Akt. This allows unphosphorylated FOXO to enter the nucleus and increase the expression of iatrogenic proteins. Interestingly, FOXO also activates the transcription of pyruvate dehydrogenase kinase (PDK). Up-regulation of PDK inactivates the muscle pyruvate dehydrogenase complex, limiting carbohydrate oxidation. Consequently, the same mechanisms that increase SAMS may also produce glucose intolerance with statin therapy.[7]

The straight effects on cellular and subcellular structures are predominately liable for statin-related mitochondrial toxicity and calcium overload. These can result in increased oxidative phosphorylation, which can lead to a decrease in ATP levels, loss of mitochondrial membrane potential, activation of mitochondria permeability transition, decreased mitochondrial density and biogenesis, apoptosis, and calpain-mediated cell death. In addition, these effects can trigger massive calcium release either via the RYR (ryanodine receptor) in the sarcoplasmic reticulum or the permeability, changeover pore and sodium-calcium exchanger in the mitochondria. Impaired calcium signaling can then result in mitochondrial depolarization and calcium release, resulting in cytoplasmic calcium waves and subsequent caspase activation and apoptosis. Increased cytosolic calcium can also increase calcium and phospholipid-dependent PKC (protein kinase C) activity, which promotes the closing of the chloride-1 channel, resulting in membrane hyperexcitability.[10]

Mitochondrial effects can also outcome from a decline in the formation of coenzyme Q10, an end product of the mevalonate pathway. Coenzyme Q10 is an important component of the electron transport chain of the inner mitochondrial membrane where it facilitates electron transport between complexes I and II during oxidative phosphorylation. Inhibition of this pathway results in anomalous mitochondrial respiratory function and subsequent mitochondrial dysfunction. Mitochondrial dysfunction, typically at complex I in the respiratory chain, increases mitochondrial NADH and the intracellular redox potential (NADH/NAD+ ratio), activates PDK (pyruvate

dehydrogenase kinase), and inhibits flux via the PDC (pyruvate dehydrogenase complex). Interestingly, although most studies demonstrate a reduction in serum coenzyme Q10 levels with statin treatment, this is thought to be predominant because of a reduction in LDL-c, the main carrier of coenzyme Q10, with tissue levels largely unaffected. Moreover, studies that have examined the effect of coenzyme Q10 supplementation in patients with statin-induced muscle effects found no difference in muscle pain or plasma CK between the placebo or coenzyme Q10-treated groups [10].

**Management of SAMS**

The majority (~60%) of adults who discontinue statins report SAMS as the primary reason for statin non-adherence and discontinuation. The adverse impact of SAMS on optimal statin dosing and adherence has substantial health impacts.[8] For example, from the study " Statin-Associated Muscle-Related Adverse Effects " by Cham *et al*; of 354 patients,232 patients (66%) reported cessation of statin therapy after experiencing muscle-related symptoms; of these, 174 patients (75%) cited some recovery on discontinuation of the statin, with 66 patients (28%) citing complete recovery of their muscle-related symptoms with discontinuation [4].

Patients who discontinued their treatment exhibited the peak LDL-C increases and were smallest amount to achieve an LDL-C <100 mg/dL and <70 mg/dL. Moreover, statin intolerance is associated with a 36% higher rate of recurrent MI, a 43% higher rate of CHD events, and a 15% higher rate of all-cause mortality. Therefore, clinicians must use a variety of strategies to manage and treat SAMS [8].

If a patient complains of muscle symptoms, the clinician needs to evaluate risk factors that can predispose to statin-associated myopathy, exclude secondary causes(especially hypothyroidism and other common myopathies such as polymyalgia rheumatica, or increased physical activity), and review the indication for statin use. The clinician should bear in mind that other commonly prescribed drugs such as anti-inflammatory (glucocorticoids), antipsychotic(risperidone, haloperidol), immunosuppressant or antiviral agents (human immunodeficiency virus protease inhibitors), lipid-modifying drugs (gemfibrozil), as well as substances of abuse (alcohol, opioids, and cocaine) may also cause muscle-related side effects. Several factors including female sex, ethnicity, multisystem disease, and small body frame predispose to SAMS, with the presence of an increasing number of factors associated with greater risk (box 1) [9].

| Risk factor | Description |
|---|---|
| Anthropometric | • Age >80 years (general caution advised for age >75)<br>• Female<br>• Low body mass index<br>• Asian descent |
| Concurrent conditions | • Acute infection<br>• Hypothyroidism (untreated or undertreated)<br>• Impaired renal (chronic kidney disease classification 3, 4, and 5) or liver function<br>• Obstruction in biliary tree<br>• Organ transplant recipients<br>• Severe trauma<br>• Human immunodeficiency virus<br>• Diabetes mellitus<br>• Vitamin D deficiency |
| Surgery | Surgery with high metabolic demands. The American Heart Association recommends temporary cessation of statins prior to major surgery. |
| Related history | • History of creatine kinase elevation, especially >10× the upper limit of the normal range<br>• History of pre-existing/unexplained muscle/joint/tendon pain<br>• Inflammatory or inherited metabolic, neuromuscular/muscle defects (e.g. McArdle disease, carnitine palmitoyl transferase II deficiency, myoadenylate deaminase deficiency, and malignant hyperthermia)<br>• Previous statin-induced myotoxicity<br>• History of myopathy while receiving another lipid-lowering therapy |
| Genetics | Genetic factors such as polymorphisms in genes encoding cytochrome P450 isoenzymes or drug transporters |
| Other risk factors | • High level of physical activity<br>• Dietary effects (excessive grapefruit or cranberry juice)<br>• Excess alcohol<br>• Drug abuse (cocaine, amphetamines, heroin) |

**Fig 3:** Risk factors for statin-associated muscle symptoms.

Additionally, pharmacokinetic drug-drug interactions (DDIs) that increase statin exposure increase the risk of statin-associated myopathy (Box2) [9].

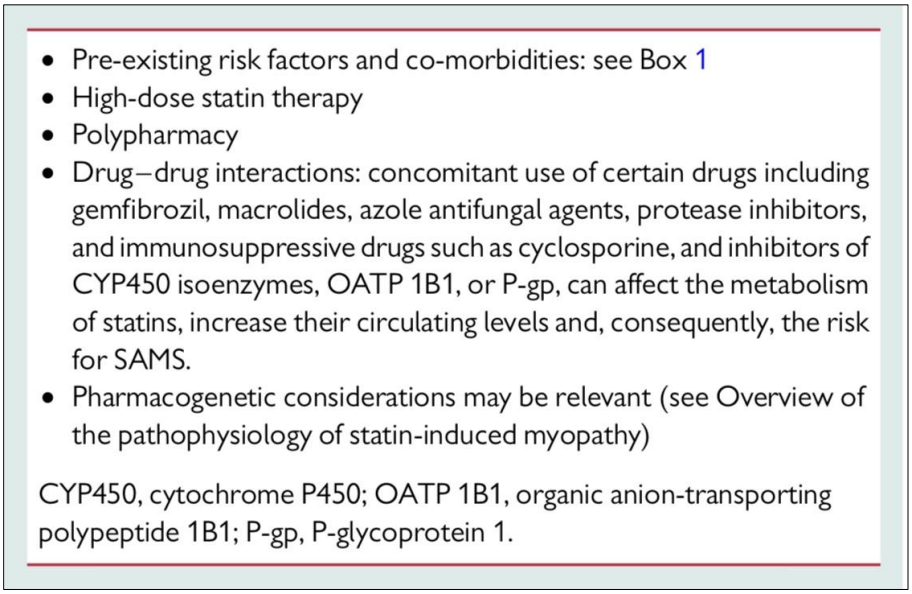


**Fig 4:** Factors that influence the pharmacokinetics of statins and risk for statin-associated muscle symptoms (SAMS)

Managing the patient with possible SAMS requires a sequence of steps, which may vary by clinician and patient. Treatment requires reassessing the benefit of statin therapy, making the tentative diagnosis, eliminating contributing factors, reassuring the patient that SAMS is not permanent, trying alternative statins and doses, and prescribing alternative treatment strategies (Fig.5) [8].

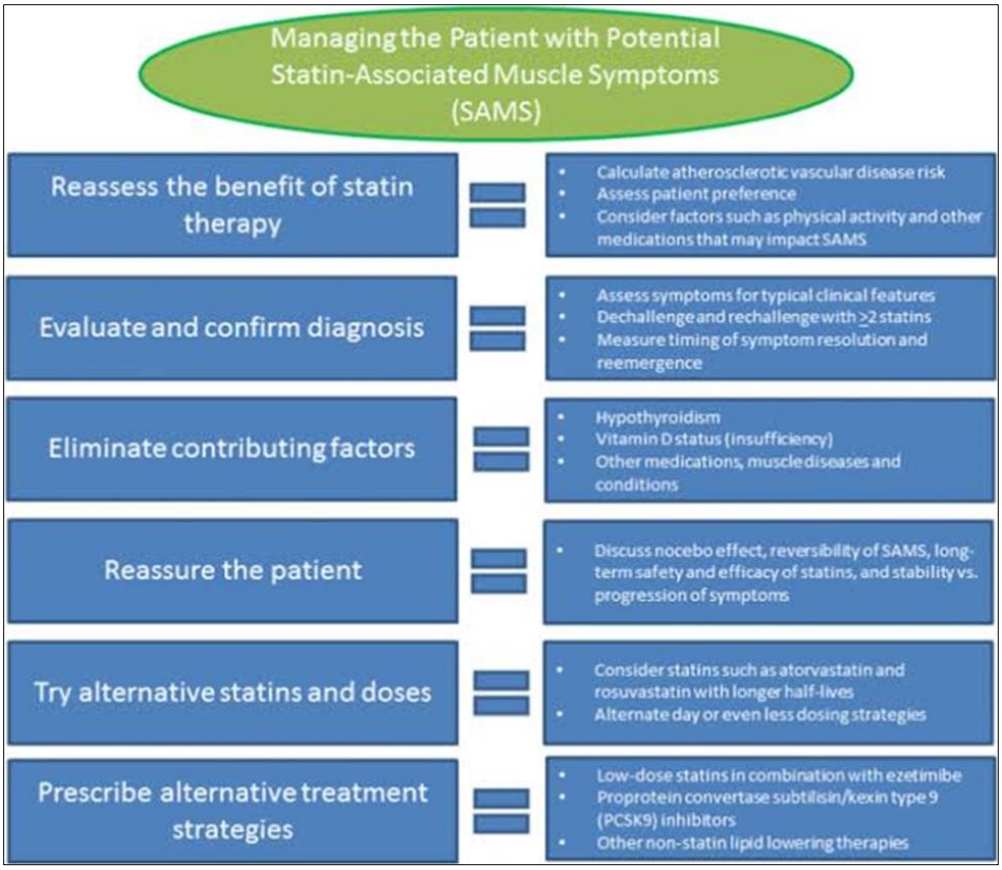


**Fig 5:** A schematic of the diagnosis, treatment, and management strategies for SAMS

Repetitive CK measurements can be beneficial to exclude clinically intimidating muscle injury and to assist with the judgment because small increases in CK levels from baseline (~20 U/L) may help identify individuals who are truly

experiencing SAMS, although again the large intra-individual variability in the measurement must be taken into consideration when interpreting changes with statin therapy. It is equally important to exclude potentially contributing factors such as hypothyroidism and other medications and to evaluate the patient for other muscle diseases and conditions.

The critical step in the initial diagnosis and treatment of SAMS involves reassuring patients that statins are extremely safe and effective and that SAMS is reversible with drug cessation. Many patients are disturbed about statin side effects, and negative media reports about statins are coupled with their early discontinuation.

After thorough diagnostic steps, 2 pharmaceutical strategies can be used to treat blood lipids to goal in the patient truly experiencing SAMS: alternate-day dosing and use of other, non-statin medications alone or in combination with low dose statin therapy. Statins with longer half-lives such as rosuvastatin, atorvastatin, and pitavastatin can be given every other day or even less frequently [8].

**Patients with muscle symptoms with serum creatine kinase (<4 x upper limit of normal)**

The majority of patients who complain of muscle symptoms have normal or mild/moderately elevated CK levels (<4×ULN). For patients at low CVD risk, their need for a statin should be reassessed and the benefits of therapeutic lifestyle changes, such as cessation of cigarette smoking, blood pressure control, and adoption of a Mediterranean style diet, should be balanced against the risk of continuing statin therapy. Conversely, for those patients at high CVD risk including those with CVD or diabetes mellitus, the benefits of ongoing statin therapy need to be weighed against the burden of muscle symptoms. Withdrawal of statin therapy followed by one or more re-challenges (after a washout) can often help in determining causality; additional approaches include the use of an alternative statin, a statin at the lowest dose, intermittent (i.e. non-daily) dosing of a highly efficacious statin, or the use of other lipid-lowering medications [9].

**Patients with muscle symptoms and elevated serum creatine kinase levels (>4 x upper limit of normal)**

For patients at low CVD risk who have symptoms with CK >4× ULN, the statin should be stopped and the need for statin reassessed. If considered important, a lesser dose of an alternative statin should be tried and CK monitored. For patients at high CVD risk with muscle symptoms and a CK of >4×ULN(but,10<ULN), statin therapy can be continued with concomitant monitoring of CK, but stopped (at least temporarily) if the levels exceed 10× ULN. In this case, that particular statin regimen should not be restarted. If CK levels decrease after stopping the statin, restarting at a lower statin dose with CK monitoring should be tried. If however, CK elevation persists, there may be an underlying myopathy (e.g. hypothyroidism or a metabolic muscle disorder), and referral to a neuromuscular specialist should be considered.

In patients with a CK >10× ULN for which no secondary cause (e.g. exercise) can be found, statin therapy should be stopped because of the potential risk of rhabdomyolysis. If the CK level subsequently returns to normal, re-challenge with a lower dose of an alternative statin and careful monitoring of symptoms and CK may be considered. If rhabdomyolysis is suspected, the statin should not be reintroduced. Rhabdomyolysis should be considered if there is severe muscular pain, general weakness, and signs of myoglobinaemia or myoglobinuria. These patients, and those with very high CK levels (e.g.>40×ULN), should be referred for evaluation of renal damage (urinalysis, serum creatinine levels). Intravenous hydration and urine alkalinization are recommended for the treatment of rhabdomyolysis depending on the severity and the presence of kidney injury. If indicated, non-statin LDL-C lowering agents should be used [9].

**Non-statin based lipid-lowering therapy**

If LDL-C remains above target despite maximally tolerated statin dosage, the addition of an alternative LDL-C lowering agent should be considered in patients at high CVD risk to improve LDL-C reduction. The most commonly used non-statin medications are ezetimibe and monoclonal antibody proprotein convertase subtilisin/Kexin type 9 (PCSK9) inhibitors [8]. Ezetimibe reduces LDL-C by 15–20%, is easy to take with few side effects, and has been shown to reduce CVD events. In patients with SAMS, the combination of ezetimibe plus fluvastatin XL reduced LDL-C by 46% and was as well tolerated as ezetimibe alone. Bile acid sequestrants can reduce LDL-C levels by 15–25% depending on the type and dose used, and may also improve glycemia in patients with diabetes. The combination of a bile acid sequestrant and ezetimibe can reduce LDL-C by ~30–35%.[9] The 2 accepted PCSK9 inhibitors (alirocumab and evolocumab) are used for lowering LDL-C in patients who are unable to reach desired LDL-C levels with diet and maximally tolerated lipid-lowering treatment alone. These PCSK9 inhibitors reduce LDL-C by an additional 50 to 70% in patients on statin (and other lipid-lowering) therapy [8].

Fenofibrate can lower LDL-C by 15–20% in patients with high baseline levels who do not have concomitant hypertriglyceridemia. This fibrate is easy to take and has shown an excellent safety record in the Action to Control Cardiovascular Risk in Diabetes and Fenofibrate Intervention and Event Lowering in Diabetes trials, although additional CVD benefit has not been demonstrated, and serum creatinine was reversibly increased during treatment. Physicians and health care professionals should therefore consider the use of ezetimibe as firstchoice, potentially followed by bile acid sequestrants or fibrates in combination with ezetimibe, as needed to achieve LDL-C lowering consistently with guidelines [9].

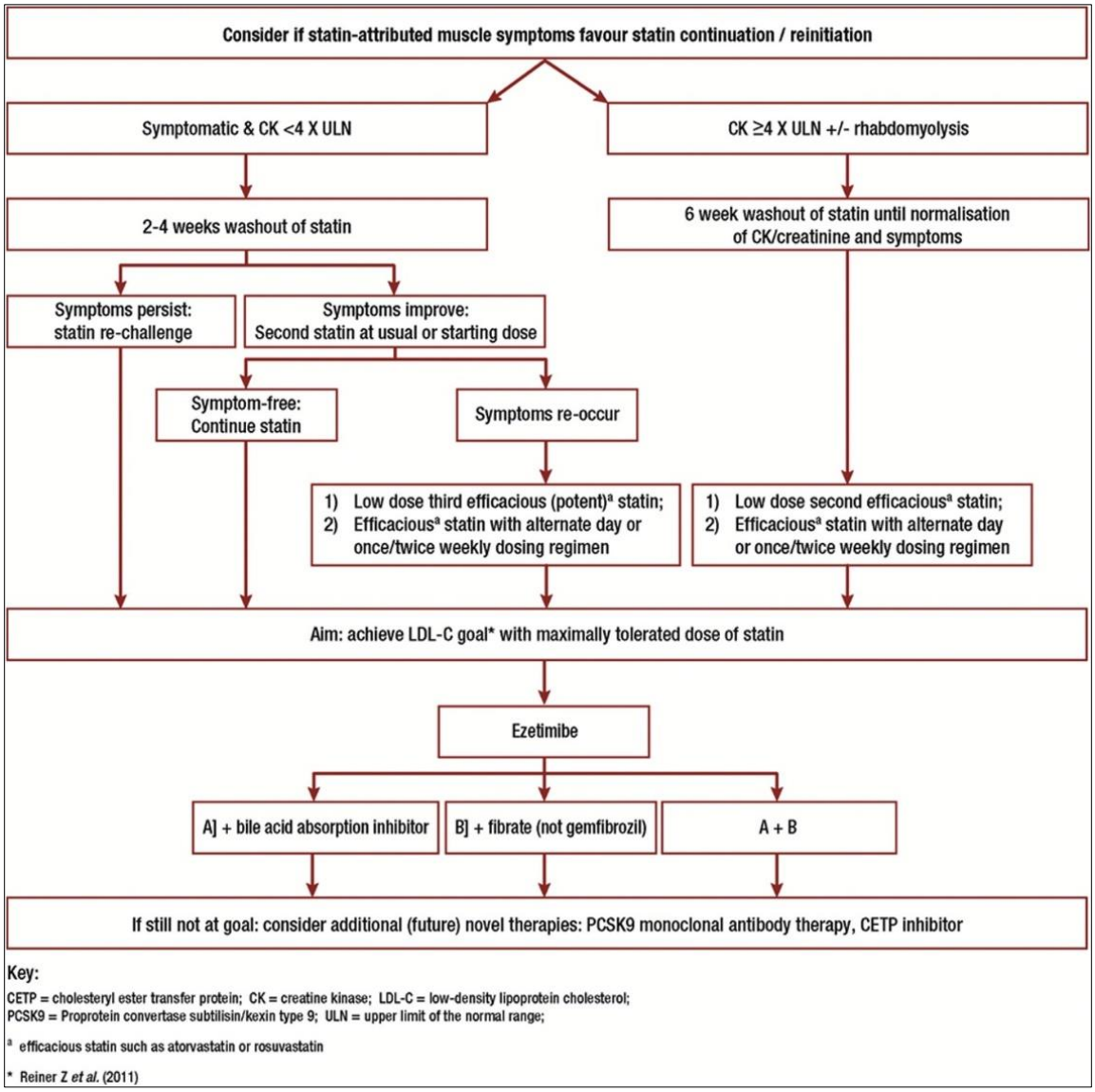


**Fig 6:** Therapeutic flow-chart for management of patients with statin-associated muscle symptoms.

## Conclusion

Muscle complaints are common in adults over 40 years without arthritis. In many studies, statin users were significantly more likely to report muscle complaints.

Research studies confirm that statins increase muscle complaints and also statins produce mild muscle injury. Statin use also causes myopathy, myalgia muscle weakness, and fatigue. some muscle-related ADR occurs after a long time of statin use.

Statin-associated symptoms, and especially SAMS, the predominant statin-associated symptom, appear to be frequent in clinical practice.. The diagnosis of SAMS is intricate because there are no validated tests or clinical criteria, but for increases in CK, but CK increases are absent in most myalgic patients. Patient management requires patient reassurance, diagnosis by clinical criteria and statin discontinuation or rechallenge, and treatment using different statins or alternative dosing strategies, often in combination with other lipid-lowering agents such as ezetimibe, bile sequestrants, fenofibrate, and PCSK9 inhibitors.

However, statins are widely and effectively used drugs to reduce cholesterol levels and also shown to reduce cardiovascular events.

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## Conflict of Interest

The authors declare that no conflict of interest

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