

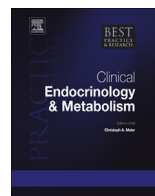


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11

Overcoming toxicity and side-effects of lipid-lowering therapies



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Lowering serum lipid levels is part of the foundation of treating and preventing clinically significant cardiovascular disease. Recently, the American Heart Association/American College of Cardiology released cholesterol guidelines which advocate for high efficacy statins rather than LDL-c goals for five patient subgroups at high risk for cardiovascular disease. Therefore, it is critical that clinicians have an approach for managing side-effects of statin therapy. Statins are associated with myopathy, transaminase elevations, and an increased risk of incident diabetes mellitus among some patients; connections between statins and other processes, such as renal and neurologic function, have also been studied with mixed results. Statin-related adverse effects might be minimized by careful assessment of patient risk factors. Strategies to continue statin therapy despite adverse effects include switching to another statin at a lower dose and titrating up, giving intermittent doses of statins, and adding non-statin agents. Non-statin lipid-lowering drugs have their own unique limitations. Management strategies and algorithms for statin-associated toxicities are available to help guide clinicians. Clinical practice should emphasize tailoring therapy to address each individual's cholesterol goals and risk of developing adverse effects on lipid-lowering drugs.

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Introduction

Lipid altering drugs, especially statins, are among the most widely prescribed drugs in the world. Clinical trials over the past 25 years demonstrate that statins are well tolerated and prevent cardiovascular (CV) deaths, major CV events (stroke, myocardial infarction), and total mortality in high risk patients [1]. Although a significant decline in cardiovascular mortality began prior to the regulatory approval of statins in 1987, cholesterol lowering to prevent coronary heart disease (CHD) has been credited with much of the marked reduction of CHD incidence worldwide [2]. Little controversy remains regarding the clinical benefits of statins in high risk patients, and increasingly data and guidelines support more widespread statin use and more intensive statin therapy [1]. However, a significant number of patients (perhaps 10% or more) [3] develop intolerant symptoms to statins, and another 1–2% develop serious side-effects such as myositis or liver enzyme elevations [4]. The growing number of patients receiving these drugs, and the recent recommendations for higher intensity therapy [1], creates a significant absolute number of people intolerant of statin therapy or who suffer side-effects. Many primary care physicians face the challenge of identifying a therapeutic regimen that achieves desired lipid goals, but also is well tolerated by the patient. Consequently, a leading reason for a referral to a lipid clinic is statin intolerance. The purpose of this review is to identify risk factors for statin-induced side-effects, strategies to overcome true or perceived intolerance, and alternative approaches to treat elevated low-density lipoprotein cholesterol (LDL-c) and non-high-density lipoprotein cholesterol (non-HDL-c) if statins cannot be utilized. In addition, safety issues related to non-statin lipid altering therapy will also be addressed. An enhanced understanding regarding the risk factors for statin-induced toxicity and deploying successful approaches to overcome statin intolerance will hopefully avoid unnecessary ancillary tests or referrals which ultimately could reduce health costs with improved patient outcomes.

Adverse effects of statins

Myopathy

Among the symptoms associated with statins, muscle-related complaints are common and frequently limit the use of statins [5,6]. The term myopathy has been used to describe muscle-related symptoms that occur with evidence of muscle injury (serum creatine kinase (CK) >10 times the upper limit of normal (ULN)) [5]. This definition of myopathy is used by the National Lipid Association. However, the term myopathy may also be used more broadly; for example, the American College of Cardiology (ACC)/American Heart Association (AHA)/National Heart, Lung, and Blood Institute (NHLBI) defines myopathy as any disease of muscles. In the latter case, myalgia, myositis, and rhabdomyolysis may be thought of as representing a spectrum of myopathy, or muscle-related side-effects, ranging from symptoms without CK elevation (myalgia), to myositis (CK elevated above the ULN, but ≤ 10 times the ULN), to rhabdomyolysis. The definition of rhabdomyolysis, typically includes CK elevation >10 times ULN and an elevation in serum creatinine [6].

Symptoms of statin myopathy include muscle cramps, stiffness, and weakness. Statin-associated myalgia typically affects the proximal muscles and tends to occur within the first 6 months of starting a statin. However, the onset of symptoms may occur later. Myalgia tends to resolve within 2 months of discontinuing a statin [6].

The incidence of statin-associated myopathy varies depending on the source of the estimate, specifically whether data are derived from randomized clinical trials, cohort studies, or reported adverse events (such as through the Food and Drug Administration (FDA)). However, in the United States the proportion of patients (including those on combined therapy) affected by significant statin-associated myopathy (CK >10 times ULN), is likely between 0.2 and 0.5% [6].

Another estimate of the incidence of statin-associated myopathy (derived from 21 clinical trials with 180,000 person-years of follow-up data), found that myopathy (defined as muscle symptoms with CK >10 times ULN) occurred in 5 patients per 100,000 person-years. Rhabdomyolysis, as may be expected, was even rarer, occurring in only 1.6 patients per 100,000 person-years [5]. Authors from the FDA performed a review of reports of fatal rhabdomyolysis by accessing the Adverse Event Reporting

System of the FDA. The review found that fatal rhabdomyolysis was extremely rare in patients using statins available on today's market, resulting in much less than 1 death per million statin prescriptions. For example, the reporting rate for atorvastatin was 0.04 per 1 million prescriptions [7].

While the rates of significant myopathy and rhabdomyolysis may be low, the overall incidence of muscle complaints in clinical practice that are associated with statins can be high and varies widely, from 0.3% to 33% [5]. Therefore, primary care physicians, cardiologists, and lipidologists are often faced with managing muscle-related complaints in patients on statins, and determining whether these symptoms are in fact related to statin therapy. An observational study of patients on high dose statins, assessing for mild to moderate muscle-related symptoms found that predictors of muscle symptoms were prior history of muscle pain with lipid-lowering drugs (OR 10.12), unexplained muscle cramps (OR 4.14) and history of elevated CK (OR 2.04). Muscle symptoms were reported commonly with 10.5% of patients complaining of symptoms overall. The median time to onset of symptoms was 1 month after starting statin therapy. Thirty-eight percent of patients experienced muscle pain that prevented moderate exertion, and 4% of patients were unable to work or confined to bed due to these symptoms. Of the statins studied, fluvastatin XL was associated with the lowest rate of muscle-related symptoms at only 5.1% of patients receiving the medication experiencing muscle-related symptoms. The other statins studied (high dose pravastatin, atorvastatin, and simvastatin) were associated with 10.9%, 14.9%, and 18.2% of patients experiencing muscle-related symptoms, respectively [8].

Hepatotoxicity

Hepatotoxicity from statins is rare and most commonly presents as a transaminitis without histopathologic changes. Transaminitis may be secondary to lower lipid levels, as opposed to a specific effect of statin therapy, as it can be seen with other lipid-lowering therapies, including those that are not absorbed into the systemic circulation (namely, bile acid sequestrants). For patients on statins, the incidence of elevated aminotransferase levels above 3 times the ULN is typically no greater than 3%. Transaminitis is asymptomatic and typically resolves (in 70% of cases) with continuation of statin therapy without a change in the specific statin used or the dose of statin. Other types of hepatic injury are very rarely seen in association with statin use, and it is not clear that statins cause any kind of significant liver injury or liver failure [5,6]. As a reflection of this evidence, in 2012 the FDA removed recommendations for routine periodic liver function test (LFT) monitoring from the safety label for statins. Instead, the FDA recommends checking LFTs at baseline and later as clinically warranted [9].

Diabetes mellitus

There has also been research into whether statin use may be related to an increased incidence of diabetes mellitus (DM). A recent meta-analysis found a statistically significant increase in the odds of developing diabetes among patients on statins (9% increase (OR 1.09, 95% CI 1.02–1.17)) [10]. Another recent study, using data from the Women's Health Initiative, found a significantly elevated risk of developing diabetes associated with statin use in this population (HR 1.48), after adjusting for confounders in a multivariate model (95% CI 1.38–1.59). The effect was observed across different statins, and the authors conclude that their findings might be related to a class effect [11]. A recent meta-analysis also found a statistically significant increase in the risk of developing diabetes related to statin therapy (RR 1.13 (95% CI 1.03–1.23)). However, when including the West of Scotland Coronary Prevention Study (WOSCOPS) among the studies analyzed, the risk was no longer significant [12]. The WOSCOPS trial, published in 2001, reported that pravastatin therapy was in fact associated with a 30% reduction ($P = 0.042$) in the hazard of developing diabetes [13]. Based on these findings, other recent studies have sought to determine whether there is a heightened risk of developing diabetes associated with particular statins, as opposed to there being a more homogenous class effect. A very recent retrospective cohort study examined the risk of incident diabetes specific to individual types of statin. Compared to pravastatin, the risk of incident DM was found to be higher with atorvastatin, simvastatin, and rosuvastatin, but not with fluvastatin and lovastatin [14]. Another retrospective cohort study that examined the relationship between statin use and the onset of treated diabetes mellitus found that overall, statin use was associated with a higher risk of treated diabetes. However, when examining

individual statins, only atorvastatin, rosuvastatin, and simvastatin were significantly associated with this effect. The relationship between the incidence of treated diabetes with pravastatin and fluvastatin was not significant [15]. Therefore, there is evidence to support an association between statin use and an increased incidence of diabetes mellitus. Interestingly, there could be varying levels of risk depending on the statin used. Recent guidelines from the ACC/AHA conclude that an increased risk for type-2 diabetes occurs with statin use in patients who already have risk factors for diabetes. The authors also conclude that the benefits of statin therapy outweigh the risk of new onset diabetes in most patients. Statins should not be withheld when patients on statins are diagnosed with diabetes. Instead, statin use should continue in order to reduce the risk of atherosclerotic cardiovascular disease related events, and patient efforts to maintain a healthy lifestyle and body weight should be reinforced [1].

Renal effects

There is not compelling evidence that statins cause kidney injury. The FDA performed a review of reports of kidney injury in patients receiving rosuvastatin, and concluded that there was insufficient evidence to suggest that there was a causal relationship between rosuvastatin and other statins and the occurrence of kidney injury. In fact, there is some evidence of a potential benefit of statin therapy with regard to renal function [5].

Neurologic effects

Concerns for neurologic effects of statins can be broadly divided into those pertaining to the central nervous system (CNS) and those pertaining to the peripheral nervous system. With regard to the CNS, it is not clear whether there is a relationship between statins and dementia or cognitive dysfunction. Although, there is some evidence that if statins have any effect on cognition, they could potentially contribute to improved cognitive function [5]. A recent meta-analysis involving three randomized control trials (RCTs) in patients with dementia who were treated with statins found that there is insufficient evidence to recommend using statins to treat dementia. Importantly, there was no evidence that use of statins worsened cognition [16]. Based on some data, there is a potential relationship between statins and peripheral neuropathy, however this remains unclear. Conclusions by an expert panel suggest that when peripheral neuropathy occurs in patients on statins, alternative explanations should be investigated first. If another cause cannot be identified, it is appropriate to discontinue the statin and monitor for resolution of symptoms. If symptoms resolve, resumption of therapy with another statin should be considered [5].

Risk factors associated with adverse effects from statins

Recent guidelines from the ACC/AHA suggest that patients who would otherwise begin treatment with high dose statin therapy, but who have risk factors for statin intolerance, should be started on moderate doses of statins to avoid side-effects. These risk factors include significant comorbidities (including renal and hepatic dysfunction), history of prior statin intolerance or muscle disorder, unexplained alanine aminotransferase (ALT) elevation >3 times the ULN, presence of factors which might affect statin metabolism (both patient characteristics and use of drugs that might interact with statins), and age >75 years. Other characteristics that should be considered prior to starting higher intensity statins are history of hemorrhagic stroke and Asian ancestry [1].

Specifically with regard to muscle-related symptoms, non-genetic risk factors associated with myopathy and statin use include muscle pain with previous lipid-lowering therapy, unexplained muscle cramps, prior CK elevation, family history of muscle symptoms, family history of muscle symptoms while on lipid-lowering therapy, and hypothyroidism [6,8] (Table 1). Treatment with high doses of particular statins, namely atorvastatin and simvastatin, has also been associated with a higher risk of developing muscle pain [8]. A common trigger of muscle symptoms is heavy physical exertion [6].

Drug interactions are a very important contributor to the risk of statin-associated adverse effects. Not all statins are created equal with respect to risk profile. Lovastatin, simvastatin, and atorvastatin are

Table 1

Risk factors for muscle-related side-effects with statin use.

Intrinsic	Extrinsic
Age >80 (general caution advised for age >75)	High dose statin
Female sex	Type of statin used (high dose simvastatin and high dose atorvastatin may be higher risk)
Asian race	Alcohol abuse
Low BMI, small frame, frailty	Cocaine, amphetamine use
History of pre-existing or unexplained muscle-related pain	Fibrates
History of muscle disease	Nicotinic acid
History of elevated CK	Amiodarone
History of statin intolerance	Verapamil
Family history of myopathy	Warfarin
Family history of myopathy with statin	Cyclosporine
Metabolic muscle disease	Antipsychotics
Severe renal disease	Macrolide antibiotics
Acute or decompensated liver disease	Azole antifungals
Vitamin D deficiency	Protease inhibitors
Hypothyroidism (untreated or undertreated)	Nefazodone
Diabetes mellitus	Significant intake of grapefruit juice (>1 quart daily)
Genetic polymorphisms in CYP isozymes	Surgery with significant metabolic demand
	Heavy or unaccustomed level of exercise

Key: CYP = cytochrome, CK = creatine kinase, BMI = body mass index. Adapted from Mancini et al., 2011, Stone et al., 2013, and Bruckert et al., 2005.

catabolized primarily by the hepatic enzyme cytochrome P (CYP) 3A4 [3]. Drugs known to increase statin concentrations due to CYP3A4 inhibition include macrolide antibiotics, certain antifungal agents, non-dihydropyridine calcium channel blockers, and certain antidepressants and retroviral agents. Fluvastatin, and to a lesser extent, rosuvastatin, are metabolized by CYP2C9. Pravastatin is the only statin not metabolized by the cytochrome P-450 system [17]. Combining statins with other lipid-lowering drugs also poses significant risk for toxicity. As discussed later in this review, extended-release niacin and gemfibrozil have been shown to increase significant myotoxicity when taken concurrently with statins. Careful consideration of drug interactions is critical to reduce the risk of statin-associated myopathy. Consumption of large quantities of grapefruit (such as >1 quart/day) has also been described as a risk factor for statin-associated myopathy [6].

Ongoing research is exploring genetic predisposition to statin intolerance that may be due to rare mutations in intrinsic muscle diseases, or predispositions imparted by common genetic polymorphisms affecting statin drug metabolism [18]. Statins may also unmask or worsen muscular symptoms in patients with pre-existing metabolic myopathies such as McArdle disease or carnitine palmitoyltransferase II (CPT II) deficiency, whether dormant or active [6].

Increasingly, a pharmacogenomic approach to statin therapy and myopathy is being explored. To date, polymorphisms in the *SLCO1B1* gene, which encodes the protein responsible for hepatic uptake of statins, and the *COQ2* gene, important in the synthesis of coenzyme Q10, have been validated as being strongly associated with statin-induced myopathy. The majority of genetic predisposition to myopathy studies have used a candidate gene approach, leading to investigation of genes encoding proteins involved in statin transport and metabolism, as well as those hypothesized to be important in the pathogenesis of statin-induced myopathy [19]. The Study of the Effectiveness of Additional Reduction of Cholesterol and Homocysteine (SEARCH) trial [20] identified common variants in *SLCO1B1* that are strongly associated with an increased risk of statin-induced myopathy. A subsequent randomized control trial demonstrated an increase in mild adverse events in those statin-treated patients with a specific variant of *SLCO1B1* [18]. However, now that the 80 mg dose of simvastatin is generally no longer prescribed, the risk associated with the *SLCO1B1* mutation and statin-induced rhabdomyolysis has decreased significantly because risk was most associated with only this high dose of simvastatin therapy. At the present time, pharmacogenetic testing for potential polymorphisms associated with statin myopathy does not appear to be cost effective, but may provide valuable information regarding the pathogenesis of statin intolerance and therefore is a subject of intense interest.

Diagnosing statin intolerance

Statin intolerance generally involves: development of symptoms while on a statin, resolution of symptoms when the statin is discontinued, and recurrence of symptoms when the same or a different statin is restarted. When symptoms such as myopathy occur, risk factors should be re-evaluated; for example, patients should be asked about changes in physical activity and thyroid function should be re-assessed. Further testing, such as with electromyography and muscle biopsy, may be warranted in cases of severe or poorly explained myopathy [6].

Strategies to reduce statin toxicity

Prior to starting statin therapy, the risk of adverse effects can be minimized by assessing pre-existing risk factors for toxicity. Baseline values of CK, liver enzymes, creatinine, and thyroid-stimulating hormone should be obtained. Some groups suggest that additional CK and liver enzyme levels do not need to be checked in asymptomatic patients on statins. However, others feel it is reasonable to check these lab values 6–12 weeks after initiation of therapy to establish a new baseline for the patient on treatment in the event that symptoms develop in the future. So long as patients remain asymptomatic it may not be necessary to check these labs routinely. If statin intolerance occurs, there are several approaches to management available: 1) Switch to a different statin, or use a lower dose of statin. One may also consider intermittent dosing of a statin. 2) Add, or switch to, other lipid-lowering therapies. 3) Continue statin therapy while attempting to address symptoms [6].

Intermittent statin dosing

Intermittent dosing of statins to address adverse effects has been studied extensively. Specifically, rosuvastatin has been a focus of studies looking at intermittent statin regimens due to its potent cholesterol lowering effects and long half-life (~ 19 h) [21]. A retrospective analysis examined patients who were intolerant to daily statin therapy (76.5% due to myalgia, and 19.5% due to elevated transaminases) and were switched to every other day rosuvastatin. The majority of patients tolerated the every other day rosuvastatin therapy (72.5%); those intolerant to the regimen experienced the same statin-associated symptoms that prompted initial cessation of daily statin therapy. The average LDL-c decreased 34.5% ($p < 0.001$) on the rosuvastatin regimen and about 50% of patients in this group met their LDL-c target. The average dose of rosuvastatin was 5.6 ± 2.9 mg (range 2.5–10 mg). Patients on other lipid altering drugs were included in the study [22].

Additional support for intermittent dosing of rosuvastatin comes from a chart review evaluating twice weekly rosuvastatin in 40 patients intolerant to daily statins. The dose of rosuvastatin used was either 5 mg ($n = 30$) or 10 mg ($n = 10$). When used alone or with other lipid-lowering drugs, twice weekly rosuvastatin reduced LDL-c by 26% ($p < 0.05$). Eight patients stopped twice weekly rosuvastatin due to muscle-aches. Fifty-four percent of patients on twice weekly rosuvastatin met their National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III LDL-c target [23].

Finally, a chart review of 50 patients intolerant to statins, treated with rosuvastatin once a week found that 74% of patients were able to tolerate once a week rosuvastatin, with a dose range of 2.5–20 mg (mean 10 ± 4 mg). Over an average of 4 months ± 2 , LDL-c was lowered by 23%. There were also statistically significant reductions in total cholesterol and triglycerides, and an increase in high-density lipoprotein cholesterol (HDL-c). Twenty-seven percent of participants met their NCEP ATP III LDL-c target. Of note, 92% of patients in the study were taking other lipid-lowering agents in addition to rosuvastatin [21].

Therefore, current evidence supports the use of intermittent dosing with rosuvastatin in patients who cannot tolerate daily statin therapy. Atorvastatin has also been studied in intermittent dosing regimens. The mean half-life of atorvastatin is 11–35.7 h, and its activity is further extended by active metabolites with long half-lives [24]. In one study examining use of ezetimibe and intermittent atorvastatin, patients were treated with ezetimibe monotherapy (10 mg/day) for three months, resulting in LDL-c reduction by 20% ($p < 0.05$), however only 9% had met their LDL-c target. Adding

atorvastatin 10 mg twice a week for an additional three months was well tolerated and resulted in a reduction of LDL-c by 37% ($p < 0.001$) and 84% of patients were able to reach their LDL-c goal [24].

Switching to other statins

Switching to fluvastatin XL from other statins has also been studied as a way of improving tolerability. A recent study included 199 patients, classified as moderate to high risk, with a history of muscle-related side-effects on statins, who were randomized to fluvastatin XL 80 mg daily, ezetimibe 10 mg daily, or fluvastatin plus ezetimibe for 12 weeks. The best outcomes, with regard to LDL-c lowering and ability to meet NCEP ATP III LDL-c goals, were with fluvastatin XL monotherapy and combination therapy. With fluvastatin XL monotherapy, LDL-c was lowered by 32.8%, and 59% of patients in this group met their NCEP ATP III LDL-c goal. With combination therapy, LDL-c was lowered 46.1% and 84% of patients met their NCEP ATP III LDL-c goal. Note that the LDL-c goal for high risk patients used in this study was <100 mg/dl. The regimens were generally well tolerated with regard to muscle-related side-effects, with an incidence of 14% in the combination therapy group versus 17% with fluvastatin XL monotherapy and 24% with ezetimibe [25]. Pitavastatin which has a unique pharmacokinetic profile (efficacy at a 2 mg dose) compared to other statins may also be an option to consider for patients who are intolerant to other statins but as of yet there is no clinical trial evidence that patients who are intolerant to statins can tolerate pitavastatin [26]. Pitavastatin also has been demonstrated to have a favorable pharmacokinetic profile in combination with protease inhibitors [27].

Other lipid-lowering therapies

For patients who are intolerant of statins, even after alternative statin selection and dosing are attempted, other lipid-lowering therapies exist and demonstrate beneficial effects. Of note, minimal randomized control trials of alternative lipid-lowering therapies have been performed in statin-intolerant patients [1].

Fibrates

The most well-studied of alternative therapies are fibrates. Commonly used fibrates worldwide include gemfibrozil, fenofibrate, bezafibrate and ciprofibrate. They appear to have beneficial effects on lipid profiles and their mechanism of action involves the activation of peroxisome proliferator activated receptors [28]. Larger randomized control trials demonstrating efficacy of fibrates include the use of gemfibrozil for secondary prevention [29] and the use of fenofibrate in diabetics [30]. A recent meta-analysis reaffirms previous work that the greatest benefit for patients, with respect to cardiovascular risk reduction, is found in those patients with low HDL-c and elevated triglycerides [31]. Yet, clinical cardiovascular outcomes are less favorable than statins.

A key factor which should be considered both when initiating and continuing fibrate therapy is renal function. Fenofibrate should not be prescribed if estimated glomerular filtration rate (eGFR) is <30 and should be dose reduced if $\text{eGFR} <60$. A population based cohort study demonstrated increases in serum creatinine in fibrate users 90 days after initiation [32] although the mechanism is unclear and longer term analysis has actually demonstrated reduced albuminuria and slowed eGFR decline [33]. The most recent ACC/AHA Blood Cholesterol Guidelines [1] suggest renal function measurement at 3 months and 6 months after initiation, and every 6 months thereafter when initiating fenofibrate.

Fibrates have also been associated with significant muscle toxicity and more pronounced effects on those already taking statins. Gemfibrozil should not be started on patients already on a statin given the risk of rhabdomyolysis [34]. This is likely due to competitive inhibition of CYP3A4. Fenofibrate appears to have much less potential for myopathy [30]. Given the competitive inhibition of CYP3A4 by all fibrates, interaction with concurrent medications must be closely monitored, most notably warfarin and oral hypoglycemics.

Bile acid sequestrants

Mechanistically, bile acid sequestrants (BAS) interrupt reabsorption of bile acids in the gut, thus lowering intrahepatic cholesterol and causing an up-regulation of LDL receptors and reduction of blood

cholesterol. The most commonly used BAS include cholestyramine, colestipol, and colesevelam. Trials of cholestyramine were among the earliest to demonstrate a strong relationship between LDL-c reduction and CHD primary prevention [35]. Yet, the major limitation to their use is gastrointestinal side-effects, including nausea, abdominal cramping, transaminase elevation, and impaired absorption of other medications. Colesevelam demonstrates the best side-effect profile which may ultimately aid in patient compliance [36] as does slow titration of the medication [37].

Niacin

Nicotinic acid (niacin) has complex effects on lipoprotein metabolism including decreasing LDL-c, increasing HDL-c, and the suggestion of anti-atherogenic effects independent of its effect on lipids [38]. Classical studies before the statin era demonstrate dose dependent changes in lipid concentrations and more recent studies have tested niacin in combination with statins [39]. The most recent randomized control trial of extended-release niacin and laropiprant (added to simvastatin treatment) was stopped early due to lack of efficacy and increased non-fatal side-effects, myopathy in particular [40]. These results highlight the potential poor tolerability of niacin, limiting widespread use. Flushing is the most common side-effect. Different preparations have been studied, and niacin has been combined with laropiprant (a highly selective prostaglandin receptor antagonist) to reduce the side effect profile, although currently the best way to minimize prostaglandin mediated side-effects is pretreatment with aspirin or ibuprofen. Another detrimental side effect is an increase in fasting plasma glucose [41], limiting its use in a population with a high-coincidence of diabetes.

Ezetimibe

Newer agents such as ezetimibe are also an option in the statin-intolerant patient. Ezetimibe is a cholesterol absorption inhibitor that targets uptake at the jejunal enterocyte brush border and exerts its main effect on the cholesterol transport protein, Niemann-Pick C1 like 1 protein. A recent meta-analysis [42] looked at eight RCTs of ezetimibe monotherapy in the treatment of primary hypercholesterolemia. Although the meta-analysis was restricted to short term trials (12 weeks) a 19% decrease in LDL-c with ezetimibe, compared to placebo, was seen and was equally well tolerated. A combination of simvastatin and ezetimibe reduced major atherosclerotic events in patients with impaired renal function [43]. However, controversy regarding ezetimibe for improving outcomes remains and is being examined in the IMPROVED Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) which involves approximately 18,000 acute coronary syndrome patients and compares simvastatin 40 mg (with potential to increase to 80 mg during the study, depending on degree of LDL-c reduction) versus a combination of simvastatin plus ezetimibe on major adverse cardiovascular events [44].

Red yeast rice

Chinese red yeast rice extracts (RYR) are popular lipid-lowering dietary supplements containing monacolins that have hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor activity. A meta-analysis published in 2004 [45] examined the effectiveness of several different RYR formulations on lipid levels in patients with primary hyperlipidemia and found favorable results. Two recent randomized control trials examined RYR in populations with statin-associated myalgias. The earlier trial of 62 patients showed a significant LDL-c lowering effect of RYR compared to placebo [46] and a more recent trial of 43 patients demonstrated equal efficacy of LDL-c lowering when comparing RYR to 20 mg of pravastatin daily [47]. The most promising role for red yeast rice is as an alternative lipid-lowering therapy for patients who refuse to take statins because of philosophical reasons or patients who are unable to tolerate statin therapy due to statin-associated myalgias [48]. However, standards and oversight for RYR formulations are lacking and many of these products may contain significant amounts of monacolin K and toxins such as citrinin, which has known renal toxicity. Until standardization of red yeast rice is implemented, providers and patients should remain cautious when using these products [48].

Strategies to address statin-related symptoms

Alternative lipid-lowering therapies are not as efficacious as statin therapy [49]. Given this difference, treating symptoms of statin intolerance, rather than statin discontinuation, is increasingly being

examined. Research suggests deficiency and depletion of coenzyme Q10 (CoQ10) and vitamin D, in the setting of statin use, causes myopathy [50,51]. Thus, repletion and/or supplementation of each may play a role in mitigating symptoms.

Coenzyme Q10

CoQ10, also known as ubiquinone, is a lipid-soluble antioxidant that can be synthesized *de novo* by animal cells. Found in cell membranes, it is particularly well known for its role as a cofactor in the electron transport chain, playing a key role in mitochondrial energy production. Statins block the production of an intermediary needed to produce CoQ10. CoQ10 depletion results in mitochondrial dysfunction and theoretically results in myopathy [50].

Strong evidence exists demonstrating that statin therapy lowers serum CoQ10 levels [52]. Smaller randomized control trials of between 28 and 76 patients [53–58] have yielded conflicting results regarding CoQ10 supplementation and its clinical value in decreasing statin intolerance. These trials used a variety of visual analog scales to quantify changes in myalgia, each studied different CoQ10 preparations, and examined distinct patient populations. As such, inadequate evidence exists to definitively recommend CoQ10 supplementation.

A highly anticipated, more definitive trial is ongoing [59]. It will address the lack of conclusive scientific evidence for the utility of CoQ10 supplementation by examining its effects on the severity of muscle pain during statin treatment in patients with confirmed statin myalgia. This trial is the first to confirm the presence of statin-related myalgia via a crossover run-in trial, during which the presence and absence of symptoms will be documented when treating with a statin or placebo. Dosing of CoQ10 supplementation is also an issue. Supplements may be poorly absorbed and it is unclear how much dietary CoQ10 intake is necessary to offset statin-associated reductions in muscle tissue levels of ubiquinone. However, the safety profile of CoQ10 [60] makes it an attractive medication at higher doses.

Vitamin D

A complex, and not fully understood, relationship exists between vitamin D and statins. Both affect skeletal muscle metabolism and function. Vitamin D deficiency alone has been linked to myalgia [61]. Serum levels of vitamin D may affect statin effectiveness and metabolism [62]. Certain trials demonstrate that statins increase serum vitamin D levels, while others show no significant change [63].

There is a suggestion that vitamin D deficiency is associated with increased statin intolerance due to myopathy [51]. Data are observational and no randomized control trials exist addressing this issue. The most recent data include 150 hypercholesterolemic patients, unable to tolerate ≥ 1 statin because of myalgia, selected by low serum vitamin D. These patients were placed on vitamin D supplementation and restarted on a statin for a median time of 8 months. Eighty-seven percent were free of myalgia and appeared to tolerate statin re-initiation [64].

Ultimately, myalgia in patients taking statins, with underlying vitamin D deficiency, may reflect a reversible interaction between vitamin D deficiency and statins on skeletal muscle. Vitamin D deficiency may potentiate statin myopathy or lead to drug-unrelated myalgias in a subset of statin-treated patients. Insufficient evidence supports testing for vitamin D deficiency in patients with statin-induced myalgia. However, in the patient known to be vitamin D deficient with a history of statin intolerance, re-challenging with a statin once vitamin D levels are replete is a reasonable strategy.

Management strategies for clinical practice

Cholesterol management in clinical practice requires integration of many strategies to help patients both meet their cholesterol goals and avoid side-effects. Certain groups have published guidelines and algorithms to help clinicians manage the possible adverse effects related to statins. We describe aspects of recently published algorithms from two groups intended to help guide management of statin-related myopathy and hepatotoxicity. We conclude this section with an algorithm for statin-associated myopathy which incorporates current guidelines with other pertinent data (Fig. 1).

A Canadian working group recently published a clinical approach to patients on statins presenting with myopathy symptoms and/or CK elevations. Importantly, these guidelines define the degree of CK

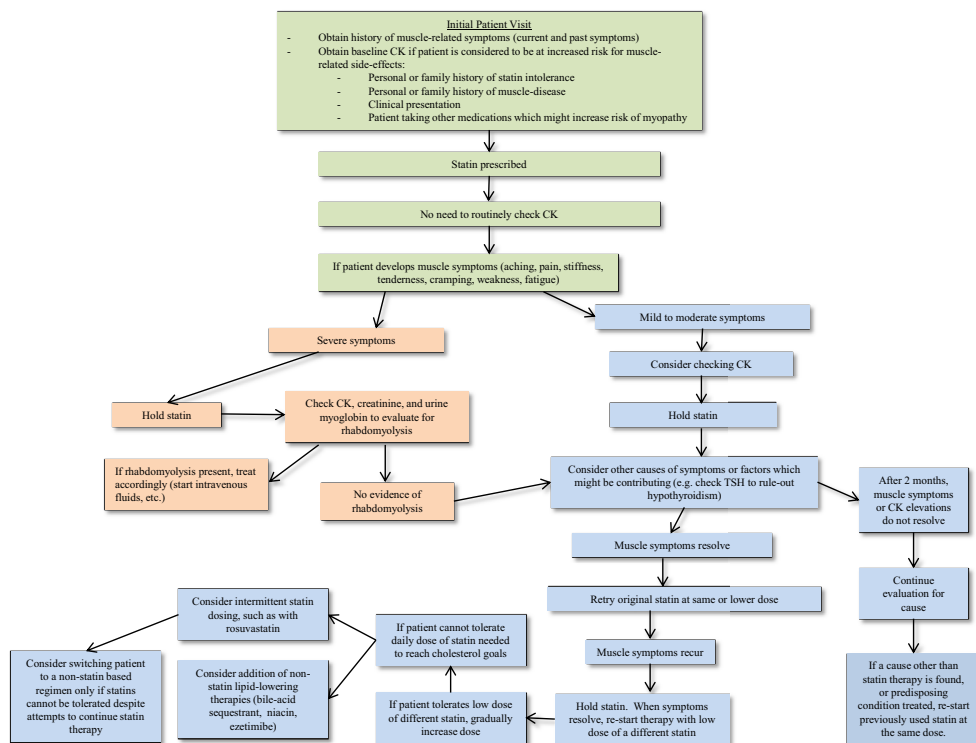


Fig. 1. Approach to patients on statins who present with muscle-related symptoms. Adapted from Stone et al., 2013. CK = creatine kinase, TSH = thyroid-stimulating hormone.

elevation, termed hyperCKemia, as a factor in management decisions. Overall, indications for stopping a statin are based on the degree of CK elevation, and the presence or absence of symptoms. Depending on the scenario, resumption of statins may be appropriate, with or without a dose adjustment or switch to another statin. Importantly, in cases considered moderate or severe, a referral to a specialist is felt to be appropriate to assess the risks and benefits of resuming a statin. The authors suggest use of other lipid-lowering agents as needed (either as adjunct or replacement therapy), and continual effort on the part of the clinician to encourage diet and lifestyle changes which may reduce the intensity of pharmacologic therapy needed to reach lipid goals [6].

More recently, the ACC/AHA published a management strategy for muscle symptoms from statin therapy. Prior to starting statin therapy, a history should be obtained to determine whether the patient has experienced muscle-related symptoms in the past, or currently has muscle symptoms. This will provide a baseline for comparison should symptoms occur while on statins. If the patient develops unexplained severe symptoms or fatigue, stop statin therapy and check CK, creatinine, and urine myoglobin to assess for rhabdomyolysis. If the patient develops mild to moderate muscle related symptoms, stop statin therapy and assess the patient. Evaluate for, and correct if possible, factors which might contribute to increased risk of muscle-related symptoms, such as hypothyroidism and vitamin D deficiency. If the symptoms abate, then resume the same statin at the same dose, or a lower dose. If the symptoms recur (and therefore a causal relationship is established between the particular statin and the muscle-related symptoms), then stop the statin and when symptoms resolve, start a low dose of a different statin. Increase the dose of this other statin as the patient tolerates. If muscle-related symptoms persist for 2 months off of statin therapy, re-consider causes of muscle symptoms other than statins. If muscle symptoms are found to be unrelated to statins, or if the cause of the symptoms is

corrected, then one can resume statin therapy at the original dose [1]. If patients are still unable to tolerate daily doses of a statin, we recommend using intermittent dosing of rosuvastatin [21–23], or intermittent atorvastatin with ezetimibe [24]. Consideration can also be given to using non-statin lipid-lowering agents as adjuncts to statins to help patients reach lipid goals. The goal should be to include a statin in the patient's regimen, however if the patient cannot tolerate any regimen which includes a statin, then consideration should be given to using a regimen that uses only non-statin lipid-lowering therapies (Fig. 1).

The Canadian working group mentioned above also describes a management approach to patients on statins presenting with elevated transaminases. Transaminases should be normal or ≤ 3 times the ULN before starting a statin; if they are elevated above this level, the cause should be explored prior to starting a statin. Of note, patients with cirrhosis and chronic hepatitis B and C can often be safely treated with statins. However, patients with decompensated liver disease may not be good candidates for statin therapy. For patients starting a statin, if after 6–12 weeks transaminases are normal or elevated but the elevation is ≤ 3 times the ULN, no change in therapy is needed and no re-assessment of transaminase levels is needed unless the patient develops symptoms, the dose of statin is increased, or the patient is switched to a different statin. If during this initial assessment transaminases are >3 times the ULN, further management depends on the presence or absence of symptoms. In symptomatic patients, the statin should be stopped. In asymptomatic patients, the authors note that these transaminase elevations will typically resolve with continuation of statin therapy, but that stopping statin therapy for 6–12 weeks is a reasonable approach. Resuming statin therapy can be considered if transaminase levels decrease to ≤ 3 times the ULN after 6–12 weeks off statins. If after this trial off of statins the transaminase levels remain >3 times the ULN (and in the case of an initial presentation with symptoms and transaminase levels > 3 times the ULN), the patient should be evaluated for intrinsic liver disease [6]. We feel that this is a useful strategy for considering how to respond when transaminase levels become elevated on statin therapy, when the decision must be made of whether to continue treatment versus hold statins and pursue further work-up. However, it is important to note that this strategy includes a routine assessment of transaminase levels 6–12 weeks after initiating statins. A recommendation to check baseline transaminase levels (specifically, ALT) is included in recent ACC/AHA guidelines. However, a recommendation for routine transaminase testing after starting a statin is not included in these guidelines. Instead, the ACC/AHA recommends reassessing hepatic function if symptoms arise which are suggestive of hepatotoxicity (namely, loss of appetite, unusual fatigue or weakness, abdominal pain, yellowing of the skin or sclera or dark-colored urine) [1]. Therefore, we feel that the decision of whether to routinely assess transaminases after starting statin therapy, and thereby follow a strategy more similar to that proposed by the Canadian working group, is up to the discretion of the individual clinician.

Summary

Lipid-lowering therapy is proven to reduce the risk of cardiovascular disease and associated events. Statins represent the back-bone of lipid-lowering therapy for patients who have, or are at risk for, clinically significant cardiovascular disease. In patients for whom statin therapy is indicated, the benefits of statins almost always outweigh the risk of adverse effects. Muscle-related side-effects from statins may be reported commonly in clinical practice [5]. However, the incidence of significant muscle-related adverse events, such as severe myopathy and rhabdomyolysis, is very low [5–7], and fear of these conditions should not prevent the use of statins in patients who stand to benefit from taking them. Adverse effects associated with statin use, including myopathy, can be minimized by a careful evaluation of the patient prior to starting therapy. A baseline assessment of prior statin intolerance and risk factors for adverse effects is a key step to preventing side-effects. This includes a careful evaluation of the patient's other medical conditions and need for medications which might increase the risk of side-effects from statins [16]. Efforts should be made to keep patients on statins when there is a high likelihood of benefit with regard to lowering their risk of cardiovascular disease and associated events. Many strategies exist to help keep such patients on statins, such as the use of intermittent doses of statins [21–24] or use of other lipid-lowering agents as adjuncts. Other lipid-lowering agents have their own possible adverse effects which are important for clinicians to be

familiar with. An understanding of the nature of side-effects associated with lipid-lowering therapy (especially those related to statins), and a clinical approach to addressing them, will be very important in the coming era of high-intensity lipid-lowering therapy for high risk groups, as proposed in recent ACC/AHA guidelines [1].

Practice points:

- Statins should be prescribed to patients whenever indicated due to the proven cardiovascular benefits of this drug class.
- Muscle-related side-effects associated with statins can often be avoided by a careful review of patient risk factors.
- Severe muscle-related adverse events are rare with statins and fear of such events should not prevent statins from being prescribed to patients who would otherwise benefit from their use.
- If statin intolerance occurs, strategies such as switching to another statin or using intermittent dosing of rosuvastatin should be used in order to help keep high risk patients on statins.
- To help statin-intolerant patients meet their lipid goals, non-statin lipid-lowering drugs may be added to the maximally tolerated dose, frequency, and potency of statin.
- Non-statin lipid-lowering drugs each have their own adverse effect profile which must be considered prior to their use.

Research agenda:

- Ongoing development of new lipid-lowering therapies (especially, microsomal triglyceride transfer protein (MTP) inhibitors, apolipoprotein B synthesis inhibitors, cholesterol ester transfer protein (CETP) inhibitors, and pro-protein convertase subtilisin/kexin 9 (PCSK9) inhibitors) will provide additional treatment options for patients with statin intolerance.
- Further research is required to determine whether CoQ10 supplementation can help to reduce muscle-related side-effects from statins.
- Further research is required to determine the relationship between statin intolerance and vitamin D, and whether testing for and treating vitamin D deficiency can help to reduce statin intolerance.
- Additional research should help to further define the relationship between statin intolerance and hypothyroidism.
- Further research should be directed at identifying genetic risk factors for statin intolerance. Such research may ultimately lead to the development of clinically relevant screening tests for genetic polymorphisms related to statin intolerance.

Conflict of interest

None declared.

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