

The Challenge: Finding the Most Appropriate Statin and Dose for Each Patient

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KEY TAKEAWAYS

- Discontinuing statin therapy results in increased cardiovascular risk.
- The placebo effect is a common reason for perceived statin intolerance.
- Statin intolerance is much less commonly reported in clinical trials than in clinical practice, suggesting that patient education and other safeguards employed in clinical trials are important to include in clinical practice.
- Several strategies are available that can

enable continuation of statin therapy in patients who are truly statin-intolerant.

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CASE SCENARIO

A 68-year-old male with coronary stents, diabetes mellitus, hypertension, and statin intolerance presents to clinic. He has taken lisinopril, verapamil, metformin, and gemfibrozil for the past few years. However, he has discontinued atorvastatin and the combination of simvastatin/ezetimibe during the past several months “because it was too hard to go up steps.” Symptoms appeared shortly after he started the statin and resolved within a week after discontinuation. Due to his statin intolerance, PCSK9 inhibitor therapy is being considered.

- Cardiac:
 - Systolic blood pressure 125 mm Hg
- Laboratory:
 - Cholesterol: total cholesterol 181 mg/dL, low-density lipoprotein cholesterol (LDL-C) 110 mg/dL, high-density lipoprotein cholesterol (HDL-C) 39 mg/dL, triglycerides 160 mg/dL, non-HDL-C 142 mg/dL
 - A1c 6.5%
- Thyroid and vitamin D normal

INTRODUCTION

Clinicians may believe that statin intolerance is “anything that the patient perceives it to be” because of the frequency

and variety of patient-reported adverse events (AEs). The use of statin therapy is supported by decades of data demonstrating a reduction in morbidity and mortality with a safety profile similar to placebo.^{1,2} Yet unlike study subjects, clinic patients struggle with adhering to statins primarily due to muscle complaints or are skeptical to initiate statin therapy because of misconceptions, which may result in the placebo effect (inverse of the placebo effect).^{3,4}

Major societies provide formalized definitions of statin intolerance. The National Lipid Association (NLA) reports, “Statin intolerance is a clinical syndrome characterized by the inability to tolerate at least two statins: one at the lowest starting daily dose AND another at any daily dose, due to objectionable symptoms (real or perceived) or abnormal lab determinations, which are temporally related to statin treatment, and reversible upon statin discontinuation, but reproducible by rechallenge with other known determinants being excluded.”⁵ Other cardiovascular (CV) societies specifically highlight the importance of drug-drug interactions (DDIs), conditions known to increase statin intolerance (eg, hypothyroidism, underlying muscle disease), and that symptoms must appear within the first 12 weeks of initiation or dose increase, with symptom improvement or disappearance within 4 weeks of discontinuing statin therapy.^{6,7} Even

with guidance by major societies, identifying and managing statin intolerance, whether real or perceived, while finding the maximally tolerated statin and dose to maintain therapy continues to be a challenge for clinicians.

DISCONTINUING OR NOT OPTIMIZING STATIN THERAPY

LDL-C is considered the root cause of atherosclerosis.⁸ This relationship is supported by CV outcomes trials (CVOTs) dating back to 1984 with the Lipid Research Clinics Coronary Primary Prevention Trial, which utilized cholestyramine.⁹ A host of other CVOTs have demonstrated that a reduction in LDL-C, whether using ileal bypass surgery, statins, ezetimibe, or proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors,¹⁰⁻¹³ results in fewer CV events. Finally, CVOTs, such as the Cholesterol Treatment Trialists (CTT) study in patients at low risk of a CV event, conclude that lowering LDL-C by 1 mmol/L (39 mg/dL) lowers CV risk by 23%.² Lipidologists may argue that ignoring LDL-C is comparable to not acknowledging elevated blood pressure given the vast evidence from CVOTs,¹⁴ which is further supported by accumulating data indicating that nonadherence to statin therapy is strongly associated with higher rates of CV morbidity and mortality.^{15,16} Consequently, long-term use of statin therapy at the maximally tolerated dose in eligible patients is a key approach for reducing CV risk.

Because the pharmacology of statins varies within the class, it is critical to properly select the most appropriate statin and dose based on individual patient characteristics. Such guidance is provided by the American College of Cardiology/American Heart Association 2019 Guidelines (<https://www.ahajournals.org/doi/epub/10.1161/CIR.0000000000000678>).¹⁷ These guidelines provide an in-depth discussion of risk stratification and appropriate therapeutic interventions. The guidelines also updated the utility of coronary artery calcium scoring to assist in shared decision-making about initiating statin therapy.

Long-term use of statin therapy can be a challenge often as a result of patient and clinician misperceptions. Once the seed of concern about a statin is planted, it can quickly become the clinical syndrome of statin intolerance as described by the NLA.¹⁸ Further, having to initiate non-statin therapies for LDL-C reduction is associated with prescribing complexities and additional time-consuming hurdles, limited efficacy, and often higher treatment costs.¹⁹ For example, ezetimibe is a safe and effective LDL-C-lowering agent that is generically available but has a relatively limited LDL-C reduction of ~20%. Bile acid resins have a similar limited effect on LDL-C, must be administered 1 hour before or 4 hours after other medications to prevent binding of concomitant agents,

and are further limited by poor palatability and gastrointestinal (GI) AEs.¹⁴ Bempedoic acid is a new statin alternative that lowers LDL-C by ~20%, but often requires prior approval by many third-party payers. Moreover, its impact on CV events has yet to be determined.²⁰ Finally, PCSK9 inhibitors are highly effective, possess a good safety profile, and have demonstrated CV event reduction in CVOTs, but prescribing barriers due to cost and the need for subcutaneous injection can be problematic.¹⁹

CLINICAL ASSESSMENT—WHAT WE HAVE LEARNED

Identifying patients with true statin intolerance and differentiating true intolerance from the placebo effect are critical for managing and maintaining therapy. To help evaluate statin-associated muscle symptoms (SAMS), a clinical index score has been developed to capture objective information given that the frequently used biomarker to assess myotoxicity, creatine kinase (CK), is nonspecific and not always associated with symptoms (**TABLE 1**).^{18,21} The myalgia index closely follows the NLA's definition of statin intolerance and indicates whether the patient's symptoms are probable, possible, or unlikely to be statin-related.²² Assessing and acknowledging underlying muscle, arthralgia, and pain disorders present at baseline is also important to discuss with the patient. Otherwise, such complaints may be attributed to the newly prescribed statin. Further, ruling out common conditions that may mimic SAMS (eg, physical exertion, low serum vitamin D) is imperative.²¹

Other patient-reported AEs and alterations in laboratory values, although less common, are also clinically observed with statins.²³ These include headache, GI disturbances, and elevations in hepatic transaminases, CK, or glycemic markers. Guidance is limited for less common statin-related AEs, but switching statins or reducing the dosage is clinically prudent. For concerns related to laboratory elevations, obtaining baseline values among patients at higher risk for such abnormalities (eg, people with prediabetes or nonalcoholic fatty liver disease) may be considered; otherwise the correlation to statin therapy will be unclear and may cause apprehension for both the patient and clinician. Marked elevations in hepatic transaminases are uncommon and dose-dependent, so if causation is linked to statin therapy, dosage reduction may be considered. A dose-dependent relationship also exists for statins and incident diabetes. Evidence suggests that atorvastatin, rosuvastatin, and simvastatin are more likely to worsen glycemic indices, while fluvastatin, lovastatin, pitavastatin, and pravastatin appear to have little or no effect.²⁴⁻²⁶ Preexisting risk factors for diabetes mellitus appear to play a role.^{27,28}

Much has been learned regarding the risk factors for statin-related myotoxicity since the first case reports of rhabdomyolysis involving lovastatin were published over 30 years ago.²⁹

TABLE 1. Proposed statin myalgia clinical index score¹⁸

Clinical symptoms (new or increased unexplained muscle symptoms)	
Regional distribution/pattern	
Symmetric hip flexors/thigh aches	3
Symmetric calf aches	2
Symmetric upper proximal aches	2
Nonspecific asymmetric, intermittent	1
Temporal pattern	
Symptoms onset <4 weeks	3
Symptoms onset 4-12 weeks	2
Symptoms onset >12 weeks	1
Dechallenge	
Improves upon withdrawal (<2 weeks)	2
Improves upon withdrawal (2-4 weeks)	1
Does not improve upon withdrawal (>4 weeks)	0
Challenge	
Same symptoms reoccur upon rechallenge (<4 weeks)	3
Same symptoms reoccur upon rechallenge (4-12 weeks)	1
Statin myalgia clinical index score (total points)	
Probable	9-11
Possible	7-8
Unlikely	<7

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Severe myotoxicity is rare with statin therapy.¹⁴ However, case reports have identified critical DDIs and other factors that predispose patients to muscle-related AEs (TABLE 2).¹⁸ In addition to DDIs, key components commonly involved with severe myotoxicity include medical complexity and advanced age. Other common clinical traits involving SAMS include chronic kidney or hepatic disease, low body mass index (BMI), and underlying musculoskeletal or metabolic conditions.²¹

Statin therapy is associated with an extensive spectrum of muscle complaints, ranging from benign symptoms to rare cases of rhabdomyolysis.¹⁸ Thus, proper clinical assessment is important. However, emerging research demonstrates a strong connection to statins and the nocebo effect among most patients considered statin-intolerant.^{30,31} The nocebo (Latin for "I shall harm") effect can occur when a patient has negative treatment expectations that result in AEs even when the treatment is benign.⁴ Common scenarios may involve a nega-

tive statin news story or purported AEs in a family member, which cause a patient to note a worsening of muscle complaints with their statin or cause a candidate for statin therapy to hesitate in initiating treatment. Many patients will also commonly research medication adverse effects via the Internet; a recent Google search of "statin side effects" yielded more than 9.3 million results. Unfortunately, this may negatively impact patient care as statin adherence and CV events worsen upon patients' hearing a negative statin-related news story. Conversely, positive stories result in adherence and a reduction in CV events.³²

Frequency of statin intolerance

Rates of reported statin intolerance are highly variable and dependent upon the setting.³³ Data from randomized controlled trials (RCTs) demonstrate discontinuation rates and AEs comparable to placebo. A meta-analysis of placebo-controlled RCTs (N > 125,000) with a mean follow-up of 4.1 years was conducted.³⁴ Discontinuation rates for statin users (13.3%) and placebo recipients (13.9%) were not statistically different, nor were differences noted between primary and secondary prevention subgroups. Similar observations were reported for incidence of myopathy (muscle weakness + elevated CK) between treatment and placebo groups. These findings are in sharp contrast to the statin intolerance rate of 29% reported in clinical practice.⁶

Why is there such a gap between study subjects and patients in real-world clinical practice? Differences may be attributed to the study subjects being carefully selected and monitored and willing to begin treatment, which is often not the case for clinic patients.^{14,18} But it needn't be so. High tolerability among study subjects illustrates that avoidance of major DDIs and careful monitoring of clinic patients coupled with explicit counseling on the risks and benefits of statin therapy may result in improved adherence, fewer AEs, and improved clinical outcomes.

Patient education during the shared decision-making process prior to statin initiation is critically important since recent findings strongly suggest that the nocebo effect is responsible for most cases of SAMS. Two trials specifically designed to test the nocebo effect among patients classified as statin-intolerant have been conducted. The SAMSON trial was a double-blind study that evaluated severity of SAMS among patients who previously discontinued statin therapy due to intolerable AEs.³⁰ Subjects were given a total of 12 bottles, with 4 bottles containing atorvastatin 20 mg, 4 bottles containing matching placebo, and 4 empty bottles. Each bottle was used

for 1-month periods in random sequence, with subjects reporting symptom intensity daily. No significant difference ($P=0.39$) in mean symptom scores (0=no symptoms; 100=worst imaginable symptoms) between placebo months and statin months was observed; and interestingly, subjects also reported symptom scores even during the no-tablet months.

Similarly, the Statin Web-based Investigation of Side Effects (StatinWISE) study enrolled 200 subjects with a history of statin intolerance.³¹ Participants were provided atorvastatin 20 mg daily or placebo for 6 double-blind, 2-month treatment periods and asked to rate their muscle symptoms. Overall muscle symptom scores did not differ between the placebo and atorvastatin treatment periods. Also, study withdrawal because of intolerable muscle AEs was similar between groups. Most of the subjects completing the trial reported restarting long-term statin therapy.

DIFFERENCES AMONG STATINS

Muscle complaints with statin therapy are considered a class effect and RCTs evaluating SAMS with individual agents are limited to small trials.¹⁸ Nonetheless, insight regarding statin properties and communications from the US Food and Drug Administration (FDA) provide some prescribing guidance.^{35,36} Statins that undergo extensive cytochrome P450 (CYP) 3A4 metabolism include lovastatin, simvastatin, and, to a lesser extent, atorvastatin.³⁵ Concomitantly administered inhibitors of CYP3A4 (**TABLE 2**) can cause a considerable increase in serum levels of these statins and resultant concentration-dependent AEs. Conversely, CYP metabolism, particularly CYP3A4, plays no/minimal role in the clearance of fluvastatin, pitavastatin, pravastatin, and rosuvastatin.³⁵ Yet like all statins, these agents are implicated in DDIs with concomitant therapies (eg, cyclosporine, gemfibrozil) via other statin metabolic pathways.³⁵

Data also indicate higher rates of SAMS with the more lipophilic statins.^{37,38} Agents such as atorvastatin, lovastatin, and simvastatin are considered lipophilic statins that may be more likely to diffuse into extrahepatic tissue (eg, skeletal muscle) than their hydrophilic counterparts (pravastatin, rosuvastatin).

Finally, theories have been proposed regarding the role of coenzyme Q10 (CoQ10) and the development of SAMS.²¹ Statins typically lower serum levels of CoQ10, and deficiencies of CoQ10 are associated with AEs including myalgia. Theoretically, supplementation with CoQ10 should offset SAMS, or utilizing a statin (ie, pitavastatin) that does not lower serum CoQ10 may limit muscle complaints.^{21,39} Clinical reports support both approaches, yet formal studies assessing the impact on SAMS are limited.

Only small studies have evaluated possible differences between individual statins and SAMS. However, findings

align with the aforementioned factors. Rosuvastatin has demonstrated favorable tolerability at lower daily doses and intermittent dosing (eg, 2-3 times/week).²¹ Pravastatin and fluvastatin, although less potent, appear to be alternatives when patients are unable to tolerate more-potent statins. Finally, 2 studies indicate that ~70% of patients can tolerate pitavastatin^{39,40} and remain on therapy for >12 months when previously reporting statin intolerance.^{40,41}

STATIN OPTIMIZATION STRATEGIES

CASE SCENARIO (CONT'D)

A review of the patient's medication profile shows that he has taken verapamil and gemfibrozil for several years. Both are metabolic inhibitors that potentially elevated serum levels of his previous statins (atorvastatin, simvastatin) severalfold. This DDI would have caused concentration-dependent AEs resulting in his limited ability to climb steps.

This case emphasizes the importance of choosing initial statin therapy carefully and/or modifying concomitant medications as appropriate to avoid major DDIs. Once patients experience SAMS, they frequently become hesitant to initiate or optimize statin therapy. Since the patient was receiving ezetimibe in combination with simvastatin, it, too, might be eliminated from future use because of perceived intolerance. Since the patient case likely illustrates valid SAMS, rechallenging with a noninteracting statin or finding alternative treatments to the interacting medications would be prudent. Counseling the patient that ezetimibe is not a statin and likely did not contribute to his AEs is also imperative. Ultimately, combining the ezetimibe with a statin free of major DDIs would likely be well tolerated and achieve significant LDL-C reduction, possibly avoiding the need for a PCSK9 inhibitor.

True intolerance or nocebo effect?

A key to optimizing statin therapy is differentiating true intolerance from the nocebo effect. Data support that most clinic patients reporting SAMS are experiencing the latter.^{30,31} Utilizing such tools as the NLA's Myalgia Clinical Index Score can help guide the practitioner.¹⁸ In our patient case, the reported symptoms, pattern, and timing associated with statin dechallenge and rechallenge reveal an index score of ~11, indicating a "probable" association. In contrast, those with the nocebo effect have lower index scores because of more-generalized complaints, nonspecific distribution, and timing of symptoms that do not align with the initiation and discontinuation of statin therapy. It is also important to note that most patients considered statin-intolerant can tolerate some level of statin intensity.⁵

Patient engagement and shared decision-making

Engaging the patient and utilizing shared decision-making are critical for managing SAMS. Working through the clinical index score and illustrating to those with the nocebo effect that the reported symptoms do not align with their statin can be an effective strategy for reintroducing or optimizing therapy. Questioning the patient regarding how bothersome their reported AEs are and addressing any concerns or hesitations that may be present further engages and allows the patient to believe their input is part of the solution. Finally, educating the patient on the benefits of statin therapy, including significantly reducing their chances of a major catastrophic vascular event such as a myocardial infarction or stroke, is often very motivational in guiding their decision to initiate or continue statin therapy. The protective effects of statins are durable and consistent across databases, extending beyond 30 years.^{2,14}

Strategies for continuing the statin despite intolerance

Upon reintroduction of statin therapy or a dose increase, a few strategies can be considered to potentially elevate the statin threshold. Limited data suggest that repleting low serum vitamin D levels or initiating the ubiquinol formulation of CoQ10 may improve statin tolerability and/or possibly offset the nocebo effect.^{21,42} Although the data are limited, such therapies are safe and may be clinically justified if supplementation enables patients at high CV risk to receive statin therapy.

Older data indicate that 43% of statin-intolerant patients experience no recurrent symptoms when simply switching statins.⁴³ Yet a more guided approach may produce better results. Instead of randomly switching to another statin, practitioners should consider choosing agents with data supporting improved tolerability and probability of fewer DDIs, including rosuvastatin and pitavastatin. If less LDL-C reduction is needed, fluvastatin and pravastatin are alternatives.^{21,35,38} For patients who are highly statin-intolerant or hesitant to initiate therapy, using conservative, intermittent dosing with gradual titration can be effective. Statins possessing long half-lives (ie, atorvastatin, pitavastatin, rosuvastatin) can achieve significant LDL-C reduction when administered a few times weekly. The intermittent dosing also simplifies determining if an AE is statin-related.²¹ For example, if the patient begins rosuvastatin 10 mg every Sunday and reports muscle complaints later in the week, the timing and pharmacokinetics do not support a correlation to the statin. This can be a key point when counseling patients.

Ongoing assessment

Continued monitoring and reassurance is often needed to maintain statin therapy, especially among patients who are highly statin-intolerant.²¹ Critical to success is educating those experiencing the nocebo effect that reported AEs

TABLE 2. Clinical factors potentially predisposing to statin-associated muscle symptoms²¹

Advanced age
Female gender
Asian ethnicity
Low body mass index (frailty)
Pre-existing muscle/joint/tendon conditions
Chronic pain disorders
Diabetes mellitus
Obesity
Neuromuscular conditions
Chronic renal or hepatic disease
Hypothyroidism
Vitamin D deficiency
Physical exertion
Family history of myalgia (with or without statin therapy)
DDIs via CYP3A4: potentially ↑↑ statin serum levels
Amiodarone
Azole antifungals - multiple agents
Amlodipine
Diltiazem
Verapamil
Macrolide antibiotics - clarithromycin, erythromycin
Protease inhibitors - multiple agents
Excess grapefruit/juice consumption
Other common interacting medications
Cyclosporine
Gemfibrozil

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are not likely statin-related. This may require periodic statin dechallenge and rechallenge for resistant patients. Clinical follow-up of statin-intolerant patients typically follows a few scenarios. First are those patients who are managed by switching to a better-tolerated statin and/or, when able, modifying concomitant medications to avoid subsequent DDIs.²¹ Such patients illustrate the importance of appropriately selecting an initial statin that avoids major DDIs and potential AEs for improved tolerability. For more-intolerant patients, a regimen of vitamin D and ubiquinol (CoQ10) may be considered (although evidence is controversial), followed by conservative and gradual titration of an extended-half-life statin.²¹

Many patients who are highly statin-intolerant can suc-

cessfully utilize a low-dose, intermittent statin regimen with concomitant ezetimibe. Such combination therapy has few third-party payer barriers and can often achieve an LDL-C reduction of ~30% to 40%.²¹ Importantly, titration for those able to tolerate statin therapy to the maximally tolerated dose is essential. A key message from clinical guidelines is to achieve and maintain the maximally tolerated statin and dose. Finally, for the <5% of patients deemed statin-intolerant,⁵ the utilization of non-statin therapies, including ezetimibe, bempedoic acid, and PCSK9 inhibitors, will need to be considered to achieve the required LDL-C reduction.

SUMMARY

Although no definition of statin intolerance has been universally adopted, many major organizations provide guidance to the clinician for identifying and managing statin intolerance. Nonadherence to statin therapy or not optimizing the statin dose is associated with a higher rate of CV events. It remains imperative to involve the patient in shared decision-making, explicitly counseling on the risks and benefits of statin therapy and common misconceptions that can result in statin hesitation or the nocebo effect. Certain statins are less prone to major DDIs and are likely better tolerated. Choosing such agents when reintroducing statin therapy and implementing other strategies are critical to prevent recurrent statin intolerance and ultimately improve long-term adherence and reduce CV events. The number one cause of death in the United States remains heart disease, and statin therapy is one of our core strategies in our ongoing attempts to mitigate this disease.¹⁴ ●

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