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Assessment and management of statin-associated muscle symptoms (SAMS): A clinical perspective from the National Lipid Association

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ABSTRACT: Statin-associated muscle symptoms (SAMS) are the most common form of statin intolerance and are associated with increased risk of cardiovascular events that manifest from statin underutilization and discontinuation. The reported frequencies of SAMS are divergent in the literature. The writing group estimates the prevalence of SAMS, namely all muscle symptoms temporally related to statin use but without regard to causality, to be about 10% (range 5% to 25%), and the prevalence of pharmacological SAMS, specifically muscle symptoms resulting from pharmacological properties of the statin, to be about 1-2% (range 0.5% to 4%). In clinical practice, SAMS are likely to result from a combination of pharmacological and nonpharmacological effects, however this does not make the symptoms any less clinically relevant. Regardless of the etiology, SAMS need to be addressed in accordance with patients' preferences and experiences. This clinical perspective reviews the epidemiology and underlying pathophysiology of SAMS, and the cardiovascular consequences resulting from statin discontinuation. We present patient-centered clinical and communication strategies to mitigate SAMS and improve medication adherence and outcomes among statin users. Treatment strategies include 1) optimizing lifestyle interventions, 2) modulating risk factors that may contribute to muscle symptoms, 3) optimizing statin tolerability by dose reduction, decreased dosing frequency, or use of an alternate statin with more favorable pharmacokinetic properties, and 4) use of non-statins, emphasizing those with evidence for atherosclerotic risk

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reduction, either in combination with or in place of statin therapy depending on the patient's circumstances. The focus of this clinical perspective is sustainable lipoprotein goal achievement, which is important for cardiovascular risk reduction.

Introduction

Treatment to reduce low-density lipoprotein cholesterol (LDL-C) and other atherogenic lipoproteins is a well-established strategy to reduce the occurrence of fatal and nonfatal atherosclerotic events including myocardial infarction, stroke, and coronary revascularization.[1] Statins, as an adjunct to a heart healthy lifestyle, are the preferred initial pharmacotherapy for atherogenic lipoprotein lowering intervention due to their proven efficacy, safety, reduction in atherosclerotic events, and prolongation of life.[2] The authors acknowledge the importance of lowering the concentrations of all atherogenic apolipoprotein B (apoB)-containing lipoproteins for cardiovascular risk reduction, which includes LDL-C, non-high-density lipoprotein cholesterol (non-HDL-C), and apoB.

Statin intolerance is an important cause of medication discontinuation and is associated with increased risk of cardiovascular events.[3] Because more than 40 million individuals in the United States are taking or have been prescribed statins, even a relatively low incidence of statin-associated side effects can affect hundreds of thousands to millions of individuals nationwide and even more worldwide.[4] The safety of statin therapy was extensively reviewed in a Scientific Statement from the American Heart Association (AHA) in 2019 that documented excellent safety with low rates of intolerance.[5] Among statin-associated adverse events, muscle-related symptoms are the predominant reason for medication intolerance and discontinuations.[6]

In 2022 the National Lipid Association (NLA) published an updated Scientific Statement on statin intolerance providing a new definition and key considerations for atherosclerotic cardiovascular disease (ASCVD) risk reduction using both statin and non-statin therapies.[7] This NLA Clinical Perspective is a companion document that provides focused guidance for the management of statin-associated muscle symptoms (SAMS). The purpose of this document is to give clinicians practical suggestions for identification, classification, and management of SAMS using multimodal intervention strategies. In addition, detailed patient-centered clinical and communication strategies that may help mitigate SAMS are presented.

What are statin intolerance and SAMS?

Statin intolerance

In 2014, the NLA was one of the first organizations to define statin intolerance, providing uniform terminology.[8] In 2022, the NLA published an updated and simplified definition of statin intolerance that included:[7]

- One or more adverse effects temporally associated with statin therapy
- Symptoms that resolve or improve with dose reduction or discontinuation
- Classification as either: 1) complete intolerance – the inability to tolerate any dose of a statin; or 2) partial intolerance – the inability to tolerate the dose necessary to achieve the patient-specific therapeutic objective
- Requires exposure to a minimum of two statins, including at least one at the lowest approved daily dosage

Although other definitions of statin intolerance have been proposed by guideline groups from Europe[9,10], Canada[11], and South America[12], they all share common features with the NLA definition, that include symptoms that are reversible upon discontinuation (dechallenge) and reoccur with rechallenge.

SAMS

The most common symptoms that result in statin intolerance or statin discontinuation are muscle-related.[13] The term SAMS refers to all muscle symptoms temporally related to statin use but without regard to causality (see Glossary for terms). The term "pharmacologic SAMS" refers specifically to muscle symptoms that are caused by the statin. "Statin myopathy" was the initial term used to describe a broad spectrum of statin-related muscle symptoms and signs ranging from muscle aches (myalgia), mild to moderate creatine kinase (CK) elevations with and without muscle symptoms, to rhabdomyolysis with renal injury. However, the term statin myopathy as initially employed was overly broad. To capture heterogeneity in muscle-related adverse effects, the NLA Statin Muscle Safety Task Force proposed more precise terminology to account for the full range of statin-related muscle symptoms (Table 1).[13]

An alternative definition of myopathy has been employed in statin clinical trials: adverse muscle symptoms accompanied by CK elevations $\geq$ 10 X upper limit of normal (ULN). By this definition, statin-induced myopathy occurs with a frequency of 1/1000 in randomized controlled trials (RCTs).[14] Of note, there is large variability in baseline CK values with respect to age, gender, and ethnicity as well as by level of physical activity and exercise. Baseline CK is generally higher in Black patients than White patients and is higher in men compared to women.[15,16] The most severe but very rare form of statin-induced myotoxicity is rhabdomyolysis, in which muscle breakdown leads to large elevations in CK,

Table 1 NLA Statin Muscle Symptom Taskforce (2014) Definition of Statin Associated Muscle Symptoms and Estimated Prevalence.

Myalgia (5-25% in observational studies)—unexplained muscle discomfort often described as "flu-like" symptoms with normal CK level. The spectrum of myalgia symptoms includes the following:
Muscle aches
Muscle soreness
Muscle stiffness
Muscle tenderness
Muscle cramps with or shortly after exercise (not nocturnal cramping)
Myopathy (1/1000)—muscle weakness (not attributed to pain; and not necessarily associated with elevated CK)
Myositis—muscle inflammation by skeletal muscle biopsy and/or magnetic resonance imaging
Myonecrosis—CK muscle enzyme elevations
Mild > 3 X baseline or ULN CK adjusted for age, race, and sex
Moderate ≥ 10 X baseline or ULN CK adjusted for age, race, and sex
Severe ≥ 50 X baseline or ULN CK adjusted for age, race, and sex
Clinical rhabdomyolysis (1/10,000)—myonecrosis with myoglobinuria or acute renal injury (increase in creatinine ≥0.5 mg/dL)

Abbreviations: CK creatine kinase; ULN upper limit of normal
Adapted from Rosenson (2014) et al.[13]

myoglobinuria, and can cause acute renal injury. It is estimated to occur in < 1/10,000 individuals treated with a statin over five years, but the risk is higher in patients with risk factors for SAMS (Table 2).[5]

There is no biochemical test or clinical syndrome complex to determine whether muscle symptoms are directly attributable to statin use. Since muscle symptoms ascribed to statins are at least 5-fold more frequent in observational studies than in RCTs (see later analysis), a "nocebo effect" has been proposed. In contrast to the placebo effect in which patients perceive benefit from an inactive treatment, the nocebo effect is characterized by the expectation or anticipation of harm from a particular treatment.[5] Here, the patient misattributes the etiology of their muscle discomfort to the statin instead of other more likely etiologies, such as increased body aches from physical activity. It is likely that a combination of pharmacological effects, nocebo (or psychological) effects, and co-occurrence of muscle symptoms unrelated to statin therapy contribute to SAMS in individual patients.

Importantly, although several lines of evidence indicate that most cases of SAMS are not caused by the statin, it should not be assumed that all cases of SAMS are unrelated to statin treatment. The mechanism by which statins might cause SAMS is not well understood, and interpretation of SAMS is clouded by high background rates of muscle symptoms in the general population who do not take statins. To help identify pharmacologic SAMS, the NLA Statin Muscle Safety Task Force proposed a clinical scoring system, the Statin Myalgia Clinical Index (SMCI), based on the muscle distribution of symptoms, symmetry, and temporal association between statin initiation, statin withdrawal (dechallenge), and statin rechallenge (Table 3).[13] SAMS typically occur bilaterally, but unilateral symptoms can occur if the patient has asymmetrical muscle use. Onset of muscle symptoms is typically within the initial 4-8 weeks of treatment, although they can occur at any time (Figure 1).[17] Even with genetic susceptibility for statin-induced myalgias, symptoms may not occur for up to 4 years.[18] Patients often experience marked improvement in symptoms within 2-4 weeks following statin discontinuation. Once symptoms have resolved, a statin rechallenge is recommended. Pharmacologic SAMS is more likely if recurrent muscle symptoms occur within the first 4 weeks of therapy but does not exclude the possibility of nonpharmacologic SAMS.

The SMCI was developed to help clinicians estimate the probability of statin-induced myalgia categorized as unlikely, possible, or probable.[13] The Index has not been validated prospectively in a clinical trial, but was updated using data from a trial of coenzyme Q10.[19] The revised instrument, called the NLA Statin-Associated Muscle Symptom Clinical Index (SAMS-CI),[20] had a 91% negative predictive value for identifying patients with a low likelihood of having reproducible SAMS on rechallenge.[21] However,

Table 2 Risk factors for SAMS[6,13,22].

Demographics	Genetics	Comorbid conditions	Social	Drugs*
Older age	Family history of SAMS	Hypothyroidism, including post-treatment of hyperthyroidism	New exercise routine	Fibrates (especially gemfibrozil)
Female sex	Known pathogenic variants in genes involved in statin metabolism (testing not routinely recommended)	Vitamin D deficiency	Strenuous exercise	Colchicine
Asian ethnicity**		Musculoskeletal disease	Alcohol use	Immunosuppressants
Low body weight		Immunologic disease	Cocaine and other stimulants	Antiarrhythmics
		Chronic kidney disease		Antivirals
		Organ or electrolyte dysfunction		Antibiotics
				Antifungals
				Antiseizures
				Other inhibitors of statin clearance

*Either through direct myotoxic effects or drug-drug interactions with statins.
**Especially for high dose rosuvastatin.

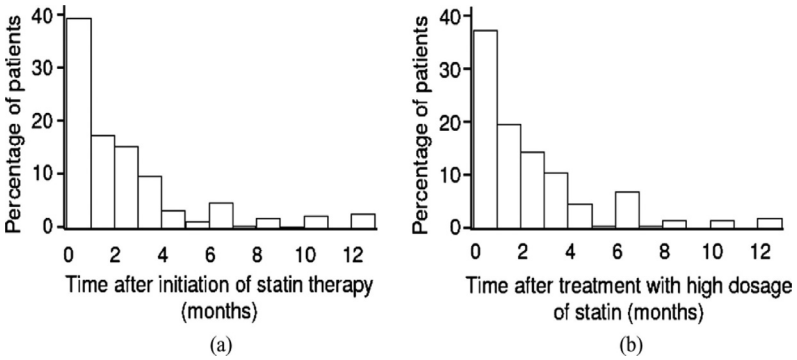

Figure 1 PRIMO Study- Distribution of the time of onset of muscular symptoms following (a) initiation of statin therapy; or (b) titration to high-dosage statin therapy. The median time of onset was 1 month following both initiation of statin therapy, and titration to a high dosage of statin.
Adapted from Bruckert (2005) et al.[17]

Table 3 NLA Statin Myalgia Clinic Index (NLA SMCI).

Clinical symptoms (new or unexplained worsening of previous symptoms)	Score
Local distribution/pattern	
Symmetric pain in hip/thigh flexors	3
Symmetric pain in calf	2
Symmetric pain in the proximal muscles of the upper limbs	2
Asymmetric, non-specific or intermittent pain	1
Temporal pattern	
Symptom onset < 4weeks	3
Symptom onset 4-12weeks	2
Symptom onset > 12weeks	1
Discontinuation	
Improvement with discontinuation (< 2 weeks)	2
Improvement with discontinuation (2-4weeks)	1
Did not improve with discontinuation (>4weeks)	0
Rechallenge	
Similar symptoms occur in rechallenge < 4weeks	3
Similar symptoms occur in rechallenge after 4-12 weeks	1
Similar symptoms occur after 12 weeks or do not reoccur	0
Clinical score of statin-induced myalgia	
Likely	9-11
Possible	7-8
Unlikely	<7

Adapted from Rosenson (2014) et al.[13]

SAMS-CI scores were not sensitive, identifying only 50% of individuals with reproducible statin-induced myalgia. Thus, the updated tool might be used to identify individuals unlikely to have statin-induced myalgia, but further validation is needed.

Additional resources exist to assist clinicians with SAMS identification and management, such as the American College of Cardiology Statin Intolerance Tool (https://www.acc.org/statinintoleranceapp) which provides an online platform for clinical use and incorporates items from the NLA SMCI.

How common are SAMS?

We estimate that SAMS occur in approximately ~10% (range: 5% to 25%) of statin-treated patients in the general population, regardless of causality. Although results from RCTs have been interpreted to show that pharmacologic SAMS occur in < 1% of patients[5,23,24], we estimate the prevalence of pharmacologic SAMS to be about 1-2% (range: 0.5% to 4%). Table 4 presents key frequency estimates in the general population. The earliest estimates from clinical practice, not from pharmaceutical company sponsored trials, were in the range of 5% to 13%.[25,26] The nocebo effect was unlikely to be operative at that time, as it was prior to awareness of SAMS, although patients' caution about a newly prescribed drug may increase symptom reporting. The PRIMO study from French general practice sites, published in 2005, provides the best available estimate for frequency of SAMS in clinical practice, particularly when using statins at high doses.[17] With regard to pharmacologic SAMS, the least biased frequency estimate may derive from the STOMP study with verified SAMS as the primary endpoint.[27] The latest frequency estimate from meta-analyses of large cardiovascular outcome RCTs will be discussed in detail later.

Table 5 shows frequency estimates for pharmacologic SAMS among patients previously diagnosed with SAMS in clinical practice. The rates range from 3.3% to 16.1%.[29-32] The wide variability is attributable to differences in trial design (i.e., patient selection, study endpoints, outcome definition and trial incentives). Results from two N-of-1 trial series (SAMSON and Statin-WISE)[29,32] as well as a meta-analysis of the Cholesterol Treatment Trialists' (CTT) Collaboration[24] suggested that the majority of participants (≥ 90%) had SAMS that were not caused by the statin. Although it is unclear whether these results accurately represent the conditions of real-world use or whether patient self-selection for these trials affected outcomes, the data confirm conclusions from other studies that most patients with SAMS do not have pharmacologic SAMS.

Table 4 Estimates of the frequency of SAMS and pharmacologic SAMS in the general statin-treated population.

Source	Type of evidence	Frequency estimate	Comments
Frequency of SAMS			
Lipid disorders clinic in New Zealand[25] 1991 n=110	First 110 patients treated in the clinic with simvastatin	13.6%	Clinical experience prior to widescale internet use and prior to social media. 15 patients (13.6%) reported muscle aches they attributed to statin therapy. 5 patients (4.5%) withdrew from therapy due to suspected side effects.
Academic clinician estimate (James Shepherd) [26] 1995	Early clinical experience	~5%	Prior to widescale internet use and prior to social media.
PRIMO[17] 2005 n=7,924	Nationwide observational survey of high-dosage statin use	10.5%	Symptoms solicited by questionnaire. 97% of those reporting symptoms had statin treatment adjustment. Results varied by statin, from 5.1% with fluvastatin-XL to 18.2% with simvastatin.
USAGE[28] 2012 n=10,138	Internet survey of a registered consumer panel of current or former statin users	Up to 25%	25% of current statin users reported muscle symptoms with concern for statin side-effects, although only 19% switched or stopped statins due to all side-effect concerns.
Frequency of pharmacologic SAMS*			
STOMP[27] 2013 n=468	Parallel group RCT among statin- naïve subjects, muscle symptoms as primary outcome	4.8%	Endpoint of new unexplained muscle pain regardless of severity, resolved after study drug cessation, and confirmed in additional randomized crossover trial. Marginal significance ($p = 0.05$) for statin effect.
Large scale statin randomized trials[23] 2016 n>150,000	Meta-analysis of tertiary RCT endpoints	Up to 0.5-1.0%	The meta-analysis makes an unstated assumption that statins do not improve muscle symptoms in any patient subset. In addition, recruitment bias may have excluded patients with previous statin myalgia or those more likely to experience muscle symptoms.
CTT Collaboration[24] 2022 n=154,664	Meta-analysis of individual patient level data from 23 RCTs	0.5% 0.7% (year 1)	The same limitations stated above for the 2016 meta-analysis[23] also apply here. Any muscle pain or weakness occurred in 27.1% of statin users versus (vs) 26.6% of those on placebo RR 1.03 (95% CI 1.01-1.06). After one year there was no significant excess of first reported SAMS events. SAMS was more prevalent with higher intensity statin regimens than lesser intensive regimens [RR 1.08 (95% CI 1.04-1.13) vs 1.03 (95% CI 1.00-1.05)] compared with placebo.

PRIMO, Prédiction du Risque Musculaire en Observationnel survey; STOMP, Effect of Statins on Skeletal Muscle Function and Performance trial; USAGE, Understanding Statin Use in America and Gaps in Patient Education survey; CI, confidence interval; CTT, Cholesterol Treatment Trialists'; RCT, randomized controlled trial; RR, relative risk; SAMS, statin-associated muscle symptoms

*Pharmacologic SAMS refers specifically to muscle symptoms that are caused by the statin.

N-of-1 trials have been envisioned as a potential tool for classification of SAMS. The StatinWISE investigators suggested that N-of-1 trial packs could be employed as practical clinical tools to enable patient decision-making on statin resumption.[29] This was recently demonstrated in a small, 73-patient trial that concluded the use of N-of-1 experimentation enhances medication uptake, regardless of patient blinding.[33] If this result is generalizable to the general population, real-world assessment of patients with N-of-1 trials may be clinically meaningful.[29]

Table 6 provides overall estimates for total and pharmacologic SAMS frequencies as well as reasonable ranges posited to emerge from future practice and research. Notably, these estimates are consistent with other reports[17,27,28] which surmise that a large majority of SAMS are not pharmacologically induced. Further research and clinical progress, perhaps the use of clinically targeted N-of-1 trial packs, could help to close the knowledge gap.

We estimate 1-2% of statin-treated patients have pharmacologic SAMS. A previous, widely cited estimate from a 2016 meta-analysis gave a frequency for pharmacologic SAMS no higher than 0.5% to 1.0%[23] (Table 4). The authors stated that they had "shown definitively that almost all of the symptomatic adverse events that are attributed to

Table 5 Estimates of the frequency of pharmacologic SAMS among patients with SAMS.

Source	Type of evidence	Frequency estimate	Comments
GAUSS-3[30] 2016 n=491	Atorvastatin 20 mg vs placebo in the first phase of this crossover RCT*	16.1% 42.6% with muscle symptoms on atorvastatin but not placebo 26.5% with muscle symptoms on placebo but not atorvastatin	Because of 4 possible outcomes in crossover trial, random sorting would produce an estimate of 25%. 16.1% (the absolute difference between 42.6% and 26.5%) represents the proportion of patients with pharmacologic SAMS.
ODYSSEY ALTERNATIVE[31] 2015 n=314	Atorvastatin 20 mg, ezetimibe, alirocumab in parallel group double-blind RCT	13.5% higher rate of muscle adverse events and 6.3% higher muscle-related discontinuations in atorvastatin vs alirocumab groups	Study drug discontinuation rate 22.2% for atorvastatin, 15.9% for alirocumab. Patients aware of future open label alirocumab phase available to all participants.†
SAMSON[32] 2021 n=60	N-of-1 trial series with atorvastatin 20 mg, placebo tablets, or empty pill bottles in random order	≤10%‡	Recruited among those stopping a statin for muscle symptoms within 2 weeks of statin initiation. Due to selection bias in recruitment and participation, this group did not represent all patients with SAMS.
StatinWISE[29] 2021 n=151	N-of-1 trial series with atorvastatin 20 mg vs placebo randomized to 2-month intervals over 1 year	3.3%	SAMS frequency estimated from difference in study drug discontinuations, 11.9% while on statin and 8.6% on placebo. Due to selection bias in recruitment and participation, this group did not represent all patients with SAMS.

*Preliminary phase of GAUSS-3 intended to verify pharmacologic SAMS.

†High discontinuation rate for alirocumab in the blinded trial likely represented statin nocebo effect, since tolerance of alirocumab improved greatly in subsequent open-label phase.

‡By visual inspection of data, 3 to 6 of the 60 patients (5-10%) appear to have confirmed statin-induced SAMS. Estimates of pharmacologic SAMS frequency in SAMSON and StatinWISE are approximations.GAUSS-3, Goal Achievement after Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects Trial-3; SAMSON, Self-Assessment Method for Statin side effects Or Nocebo; RCT, randomized controlled trial; SAMS, statin-associated muscle symptoms; StatinWISE, Statin Web-based Investigation of Side Effects.

Table 6 NLA Clinical Perspective estimates on the frequency of total and pharmacologic SAMS in real-world practice.

	Frequency estimate	Frequency range	Comments
Total SAMS	10%	5% to 25%	SAMS frequency may have increased from earliest estimates due to nocebo effect. Best estimate is from PRIMO,[17] reinforced by USAGE.[28]
Pharmacologic SAMS	1-2%*	0.5% to 4%	Least biased estimates come from earliest reports and STOMP,[27] but patients can tolerate mild symptoms. N-of-1 trials suggest downward adjustment from 4-5%.

*Some reasons to suggest the estimate of ≤ 1% for pharmacologic SAMS from the Lancet meta-analyses of large RCTs[23,24] (Table 5) is too low:• Exclusion and negative self-selection of subjects with higher SAMS risk (including previous experience of SAMS) engendering selective enrollment in clinical trials.• Use of a limited, not general, statistical model in the meta-analysis. Limited model – SAMS counted as occurring or not occurring (0, 0, 1, 0, 1, 0, 0, 0). General model - Statin therapy could act in either direction with regard to muscle symptoms in individual patients (0, 0, 1, 0, -1, 0, 0, 1).• Attention in the 2016 meta-analysis[23] was directed toward the excellent safety record of statins and their efficacy for cardiovascular outcomes, but safety and tolerability were not sufficiently distinguished.• Single-blind statin run-in phase in some trials. Definitions: Total SAMS: refers to all statin-associated muscle symptoms without regard to causality. Pharmacologic SAMS: refers specifically to muscle symptoms that are caused by the statin.

statin therapy in routine practice are not actually caused by it (i.e., they represent misattribution)".[23] A subsequent 2022 meta-analysis of data from 154,664 individual participants in 23 trials from the CTT Collaboration suggested that >90% of SAMS were not pharmacologic, yielding a placebo-corrected prevalence of pharmacologic SAMS of 0.5%.[24] We think that the prevalence estimate could be low for reasons described in an extended footnote in Table 6, but it is still a valid conclusion that most SAMS (>80% by our estimate) are not pharmacologic.

Does it matter whether SAMS are 'real' or not?

It has been hypothesized that the vast majority of SAMS observed in clinical practice are due to "misattribution" and the "nocebo effect,"[34-36] and that it is beneficial to prove the patient has misinterpreted their symptoms. This belief of a nocebo effect is derived partly from results from the SAMSON Trial and StatinWISE study.[29,32] These studies evaluated patients who had recently discontinued (or were planning to discontinue) statin therapy and had symptoms monitored for 12 months, during which time they alternated between no treatment, blinded statin, or placebo (SAMSON) or statin and placebo (StatinWISE).[29,32] In both studies, though some patients were able to accurately differentiate between statin and placebo, symptom intensity/severity of adverse effects did not differ between groups. However, results from these small trials conducted in self-selected patients cannot be generalized to all patients.

Clinicians and researchers who emphasize the presence of nocebo effects explain that patients are primed to monitor and anticipate muscle symptoms based upon the expectation of harm resulting from information obtained from family, friends, researchers, clinicians, and media reports.[34] However, the influence of media reports may be exaggerated. In a study of 674,900 Danish individuals ≥40 years of age who were initiated on statin therapy between 1995 and 2010, the odds ratio for early statin discontinuation vs continued use was 1.09 (95% confidence interval, 1.06–1.12) for exposure to negative statin-related news stories and 0.92 (0.90–0.94) for positive statin-related news stories.[37] Although the difference was statistically significant, the increase or decrease of statin discontinuation in association with media reports was less than 10%. Further, it should be noted that of the 1931 transcripts of identified statin-related news stories, only 110 (< 6%) were graded as negative; 731 (38%) were positive, and 1090 (56%) were neutral. Thus, the assumption that all statin-related media coverage is negative is inaccurate. It must be acknowledged that media reporting and perception may be different in European-based vs U.S.-based societies. Others have argued that statin denial reflects "an internet-driven cult with deadly consequences."[38] It is our position that rather than reproach individuals who create or consume content online, and particularly social media, the responsibility should shift to clinicians to provide non-judgmental and collaborative care and explore ways to educate patients and their families to improve statin tolerability and other outcomes for individual patients.

Our goal is not to disprove the presence of a nocebo effect that likely contributes to SAMS for many patients. Rather, our belief is that the clinical approach should extend beyond tailoring patient expectations for adverse effects and informing them of the potential of nocebo effects, while emphasizing benefits and safety of statin therapy. This may include a discussion of our understanding that stable and mild SAMS are unlikely to be harmful, and if tolerable, do not necessarily warrant a change in treatment. The ultimate goal is to optimize lipid-lowering goal achievement and reduce the risk of ASCVD events, so efforts to prove that patients have misinterpreted their symptoms may be counterproductive and unnecessary.

The patient experience of symptoms while taking statin therapy is real regardless of etiology and needs to be acknowledged and respected. Patient-reported outcomes as defined by the Food and Drug Administration (FDA), such as quality of life and health status, are defined as subjective "reports of the status of a patient's health condition that come directly from the patient, without interpretation of the patient's response by a clinician or anyone else."[39] They are essential to our understanding of cardiovascular health and patient experiences,[40,41] and the phrase, "without interpretation of the patient's response by a clinician," is key in this definition. It is thus essential to avoid minimizing the patient experience of SAMS or any other reported adverse outcomes. As an analogy drawn from cardiology, the field is becoming increasingly aware of the increased risk of depression (and its negative prognostic implications) following diagnosis of and/or treatment for cardiovascular disease.[42] As such, clinicians, patients, and families are now more likely to proactively discuss and monitor for symptoms of depression in order to initiate timely treatment as appropriate. Importantly, for patients with ASCVD who later report depressed mood, we do not attribute this to the power of suggestion.

It is important to understand the myriad reasons why patients choose to continue or discontinue statin therapy. The STatin Adverse Treatment Experience (STATE) survey evaluated 1,500 patients who had taken a statin in the past 2 years and experienced ≥1 statin-associated symptom in the previous 6 months.[43] Of the 1,168 (78%) of patients who continued taking statins, the most commonly-reported reasons were avoiding a heart attack or stroke, lowering cholesterol, and doctor recommendation. For the 332 (22%) patients who discontinued statins, the most common reasons were tolerability issues associated with the medication. Of note, patients who discontinued statins reported higher symptom severity and impact than patients who continued statin therapy.

In addition to patient expectations for adverse effects, other factors may contribute to unexpectedly high rates of SAMS. Whereas baseline psychological functioning was not found to be predictive of SAMS following initiation of statin treatment,[44] the quality of the patient-clinician relationship is likely quite important. Based upon data from the Medical Expenditure Panel Survey 2006-2015, among adults with ASCVD, patients with higher scores on a self-reported measure of shared decision-making were more likely to report statin use.[45] In an internet survey of over 10,000 current (88%) and former (12%) statin users, former users were less satisfied with physician-led discussions of the importance of cholesterol levels for their heart health (65% vs 83%) and more likely to report muscle-related symptoms (60% vs 25%).[28] In addition, it recognized that nocebo effects may contribute to and reinforce racial and ethnic inequities in clinical settings and outcomes.[46] Past experiences, poor communication, medical mistrust, perceived discrimination, and racial discordance may all contribute to nocebo effects and

suboptimal and inequitable outcomes.[46] Strategies to improve empirical research to evaluate and mitigate placebo and nocebo effects in clinical care within a health equity framework have been proposed.[46]

How is patient-clinician communication relevant to statin adherence?

Although strategies to improve adherence and outcomes among statin users experiencing SAMS are the focus of this clinical perspective, most of the strategies listed below are generalizable to other medications, and importantly, irrespective of a nocebo effect. Optimization of medication adherence requires a multi-faceted approach that includes assessment of illness perceptions, perceived need for the medication, background beliefs, affordability, and concerns about medication adverse effects.[47] Contextual issues, including health literacy, past medication experiences, previous interactions with clinicians, and the impact of racism and other forms of discrimination must also be considered.[47]

Both patient- and clinician-directed approaches to improve adherence to statin therapy have been studied, and have yielded mixed results.[48] Patient-level approaches include shared decision-making, discussing the importance of cardiovascular risk reduction, and reducing medication burden (i.e., single pill combination therapies, injectable therapies).[48] Clinician-level approaches include development of multidisciplinary care with involvement of a clinically trained lipid specialist, implementation of strategies to recognize and address SAMS, and allowance of time to counsel patients on the importance of reducing cardiovascular disease risk.[48] The clinical lipid specialist may serve an important role in this endeavor, as they typically have specialized training and experience managing hyperlipidemia treatment and SAMS.[49-51]

Shared decision-making is rightly lauded as a strategy to improve patient experiences and outcomes. At a minimum, it includes the exchange of factual information between a patient and their clinician, a determination of patient preferences, and agreement upon the optimal treatment strategy.[52] However, it also extends beyond presentation and discussion of scientific evidence. A framework of genuine shared decision-making includes addressing patient and family health literacy and creating a supportive clinical environment and trusting patient-clinician relationship in which patients can openly share concerns, ask questions, and express preferences, with the goals of improving clinical outcomes, limiting adverse effects, and optimizing patient experiences. We believe that rather than focusing our clinical attention on attempting to determine the presence and/or intensity of a nocebo effect, efforts are better directed toward understanding patient-reported outcomes (from the perspective of the patient, as intended), improving patient-clinician communication, and working toward shared goals of optimal health outcomes and quality of life. In Boxes 1 and 2, we provide detailed strategies for effective communication with patients when introducing statins and during follow-up clinic visits. Recommendations are also provided for effective and respectful clinical documentation (Box 3).

What are the clinical consequences of statin discontinuation?

The occurrence of SAMS generally prompts a re-evaluation by patient and clinician about risks and benefits of continuation of statin therapy. Since many patients discontinue statin therapy in response to SAMS or other adverse effects, observational studies have been performed to determine the frequency of cardiovascular events or mortality in people who either continue to take a statin as prescribed, take the statin with suboptimal adherence or discontinue the statin.

In 2014, De Vera and colleagues published a systematic review of real-world observational studies assessing the impact of statin adherence and discontinuation on cardiovascular events and mortality.[53] The results demonstrated increased cardiovascular events for statin nonadherence or early discontinuation, with a risk ratio of 1.22 to 1.39 if patients who discontinued therapy within the first year of initiation are excluded. [53] The relative mortality risk for statin nonadherence or withdrawal was greater than the risk of increased cardiovascular events, approaching or exceeding a 2-fold increase in various settings. However, some of the mortality risk could relate to conditions that led to statin nonadherence rather than nonadherence itself.[53] Several other studies have demonstrated similar results,[54,55] with one study of patients with SAMS showing that individuals who continued statin therapy despite having an adverse reaction had significantly lower risk of ASCVD events and all-cause mortality compared to those who discontinued statin therapy, which was apparent within the first year and progressively increased during up to 8 years of follow-up (figure 2A and 2B).[3]

What characteristics related to statin metabolism, pharmacokinetics, or drug-drug interactions influence the occurrence of SAMS?

It is important to consider how other medications might interact with the pharmacokinetics of a statin when selecting which statin to use. Figure 3 displays potential routes of statin biotransformation and areas of potential interaction.[56] For example, medications that are strong inhibitors of cytochrome P450 or important drug transporters, such as organic anion transport protein 1B1 (OATP1B1), or P-glycoprotein 1 (P-gp), will increase the plasma concentration of certain statins and potentially increase the risk for SAMS (Table 7).[9,57] A recent review by Hirota T *et al.* provides an overview of pharmacokinetic drug interactions and pharmacogenetics of statins and clinician recommendations for statin dosing.[57] For example, lovastatin and simvastatin,

Box 1 Strategies for initial conversations when introducing statins.

Patient education

- Provide clear information about the rationale for statin therapy *for that individual patient*.
- Determine whether the patient prefers "the big picture" or very detailed information.
- Recognize that repeated information sessions may be indicated, particularly because anxiety at the time of diagnosis might interfere with learning.
- Include family members/caregivers as appropriate and as per patient preference. Ask: "Who else would you like to have in the room to talk about this new medication?"
- Provide patient education in verbal as well as written formats. Written materials should be prepared with a focus on health literacy (8th grade reading level). Be mindful of the increased risk of cognitive dysfunction in patients with advanced cardiovascular disease.
- Direct patients to trusted websites with accurate information about statins (i.e., www.cardiosmart.org/topics/high-cholesterol and lipid.org/patient-tear-sheets).
- Accept responsibility for patient comprehension. Instead of "Do you understand this information?" ask "Am I explaining this clearly?"

Respectful inquiry

- Inquire about relevant past experiences with health care, clinicians, and medications, as well as illness perceptions.
- Employ motivational interviewing strategies: Inquire about readiness to begin treatment, acknowledge ambivalence, and facilitate problem solving.
- Acknowledge that taking a statin might be one of several heart-healthy behavior changes asked of patients. Work with patients to prioritize behavioral changes; taking a statin may or may not be where the patient wishes to begin.
- Learn why optimal health outcomes are important *for that individual patient*. This includes understanding values and priorities and what is important for quality of life.

Language considerations

- Consider patient language and culture. Professional interpreters are usually preferable to, or in addition to, family members.
- Use open-ended language (rather than yes or no questions) to encourage questions and the disclosure of concerns. Ask: "What questions or concerns do you have?"
- Ask patients to communicate when they agree and disagree with treatment plans.
- Employ active listening and incorporate teach-back language: "In your own words, please describe the medication plan that we talked about during today's visit. I'd like to make sure we are both on the same page."

Box 2 Strategies to engage patients during follow-up visits.

Respectful inquiry

- Offer direct inquiry into adherence and adverse effects with non-judgmental questioning. For example: "Many people have trouble taking their medications every day. In the last two weeks, how many days have you missed taking your cholesterol pill? Was it because of forgetting or another reason?"
- If patients report SAMS, request description in specific terms (e.g., severity, frequency, duration, aggravating factors, impact on activities or functional status).
- Inquire about patient and family concerns regarding medications, adverse effects, options, and outcomes.

Positive verbal reinforcement

- Provide positive verbal reinforcement for honest disclosure of non-adherence.
- Provide positive verbal acknowledgement for positive heart-healthy behavioral changes made by the patient, no matter the size.

Shared decision-making

- When discussing options to change to a different statin, dosage, and/or dosing schedule, frame this as an opportunity to collaborate to determine the best approach. Consider asking, "Can we try an experiment together?"
- Provide reassurance, if clinically appropriate, that the presence of muscle symptoms, *regardless of etiology*, does not automatically indicate that cessation of statin treatment is warranted. Rather, individualized discussions should include the tolerability of symptoms within the context of the cardioprotective effects of statins.
- Determine an appropriate re-evaluation interval to assess statin tolerability to support patients and maintain clinical follow-up.
- Consider whether to propose that patients take short (i.e., 1-2 week) 'drug holidays' if symptoms reach unacceptable levels. It can be helpful for patients to notify clinicians when pausing therapy, and also when restarting, to clarify the specifics of symptoms and obtain an accurate timeline of symptom patterns.

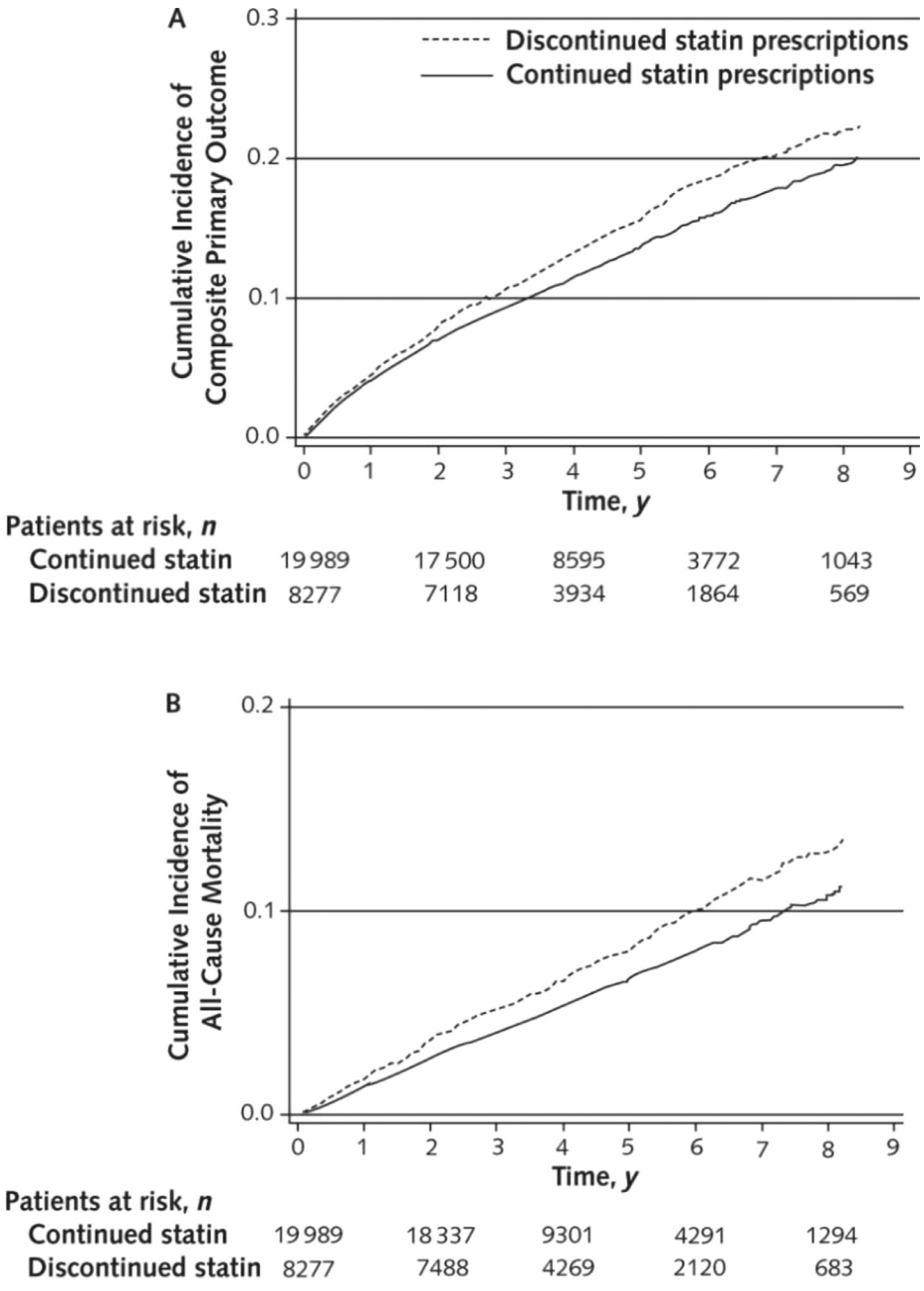

Figure 2 A. Cumulative incidence of major adverse cardiovascular events after discontinuation or continuation of statin therapy after an adverse reaction. B. Cumulative incidence of all-cause mortality after discontinuation or continuation of statin therapy after an adverse reaction Adapted from Zhang (2017) et al.[3].

and to a lesser extent atorvastatin, are metabolized by the CYP3A4 pathway and can have significant interactions with drugs that inhibit this process, including amiodarone, azole antifungals, macrolide antibiotics, cyclosporine, among others (Table 8).[22] For a more exhaustive list of clinically relevant drug-drug interactions, please refer to the AHA Scientific Statements.[22,58] It is important to note that pravastatin and pitavastatin are the only statins that do not undergo significant cytochrome P450 metabolism and, therefore, may be reasonable choices in patients prescribed multiple drugs that pose a risk for this interaction. Statins like atorvastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin, which use the OATP1B1 pathway, are likely to interact with strong inhibitors, such as carbamazepine, clarithromycin, cyclosporine, and others.[22]

It has been theorized that the lipophilicity of statins may have a role in SAMS. Lipophilic statins, which encompasses most statins except pravastatin and rosuvastatin, have been hypothesized to have greater residence time in tissue such as myocytes.[6] This has been suggested to possibly increase risk of SAMS, but is unproven, and all statins can cause pharmacologic SAMS and even rhabdomyolysis.[6] Additionally, how

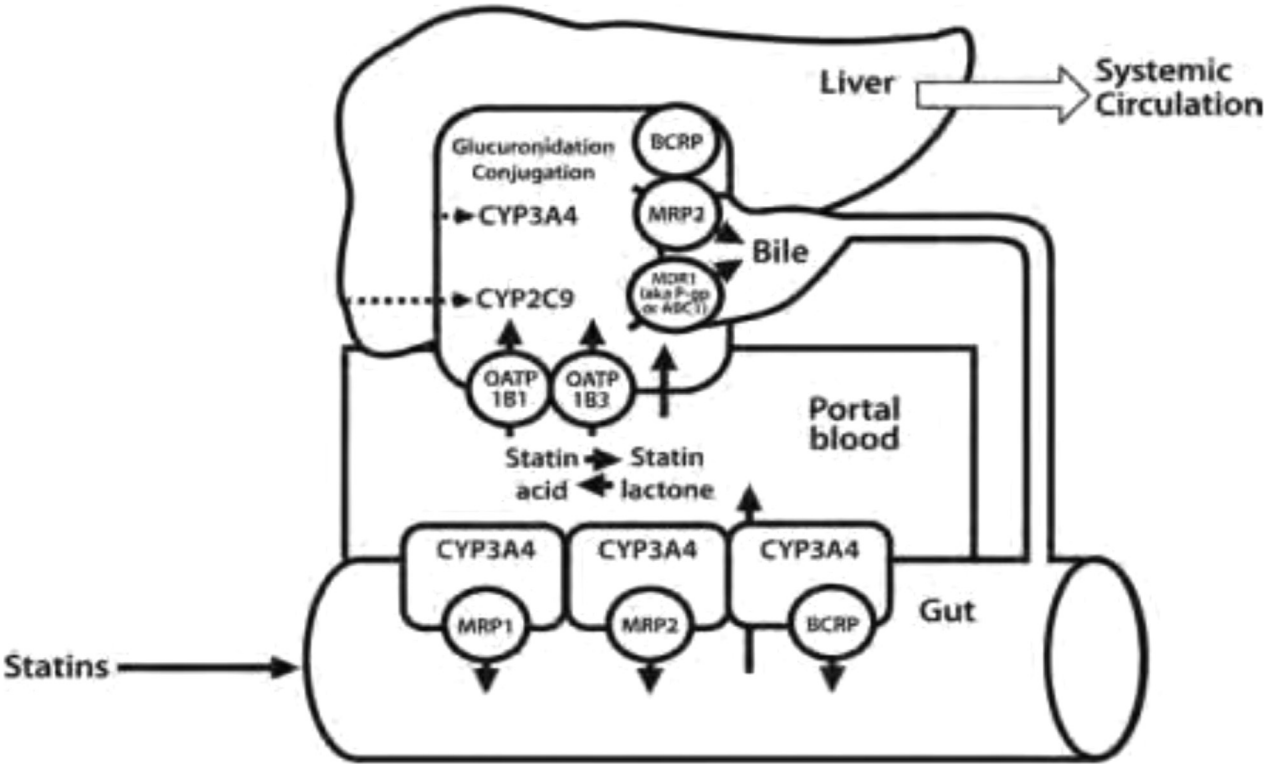

Figure 3 Potential routes of statin biotransformation and areas of potential interaction.
Adapted from Kellick (2014) at al.[56]
BCRP, breast cancer-resistant protein; CYP, cytochrome P450; MDR1, multidrug-resistant protein 1, MDR2, multidrug-resistant protein 2; OATP1B1, organic anion transporter protein 1B1; OATP1B3, organic anion transporter protein 1B3; P-gp, P-glycoprotein

Box 3 Strategies for accurate and respectful documentation.

- Rather than describing a patient as "non-compliant" or "non-adherent," be specific about the behaviors and/or reasoning. Examples include "they stopped taking the medication due to leg cramping that interfered with job tasks" or "as of January 1st, they were unable to obtain the medication due to unaffordable co-pays."
- Use "reported" or "described" instead of "complained of" when documenting SAMS as well as other patient-reported outcomes.
- Document medication treatment plans in sufficient and clear detail to inform other clinicians as well as patients who review their clinic notes.

the statin is eliminated can have important implications for risk of SAMS. All statins are renally eliminated to a small extent, ranging from <2% (atorvastatin) to upwards of 20% (pravastatin).[22] This is clinically important as most statins require consideration of dose limits with renal impairment, with the exception of atorvastatin (Table 7).

Thus, it is important when selecting alternative statins for SAMS patients that the pharmacokinetic properties of each statin are considered and that different mechanisms are selected. For example, if a patient had adverse drug reactions while taking both atorvastatin and simvastatin, which rely on CYP3A4 and P-gp for biotransformation and are lipophilic, an appropriate alternative for statin rechallenge may be rosuvastatin or pravastatin, which circumvent shared pharmacokinetic properties, metabolizing enzymes (avoid CYP3A4), and transporters (avoid P-gp) compared to atorvastatin and simvastatin.

Is genetic testing for variants associated with SAMS phenotypes warranted?

Genetic testing is usually not indicated. Table 9 provides a list of genetic variants potentially associated with the SAMS phenotype.[60] The *SLCO1B1* rs4149056 variant, coding for a weaker OATP1B1 transporter, has the most evidence supporting its association with the SAMS phenotype, but has not been routinely measured in clinical care.[61] Genetic testing has not become standard of care because some patients with pharmacologic SAMS may have no identifiable causative variants and other patients with known causative variants never develop SAMS. Although genetic testing is not often indicated, obtaining a family history of intolerance of specific statins is clinically useful because it could be a sign of a potentially heritable cause of statin intolerance, which may encourage avoidance of statins with similar pharmacokinetic properties. Similarly, patients may be more receptive to taking a statin that is well tolerated by relatives.

Table 7 Select pharmacokinetic properties for currently used statins.

Drug	Lipophilicity	Cytochrome P450 Enzymes	Transporters	Half-life (hours)	Renal excretion (%)
Atorvastatin	Lipophilic	CYP3A4	OATP1B1, BCRP, P-gp	14	<2
Fluvastatin	Lipophilic	CYP2C9 (CYP2C8 and CYP3A4 minor)	OATP1B1, 1B3, 2B1, BCRP	3	5
Lovastatin	Lipophilic	CYP3A4	OATP1B1, P-gp	2-3	10
Pitavastatin	Lipophilic	CYP2C9 marginal (CYP2C8 minor)	OATP1B1, 1B3, BRCP, P-gp	12	15
Pravastatin	Hydrophilic	none	OATP1B1, 1B3, 2B1, BCRP, OAT3	1.8	20
Rosuvastatin	Hydrophilic	CYP2C9	OATP1B1, BCRP, P-gp, OATP1A2, 1B3, 2B1, OAT3	19	10
Simvastatin	Lipophilic	CYP3A4	BCRP, P-gp, OATP1B1	2	13

BCRP, breast cancer resistance protein; CYP, cytochrome P450; OATP, organic anion-transporting polypeptide; OAT, organic anion transporters; P-gp, P-glycoprotein

Adapted from Myles Turner (2019) et al.[59] and Wiggins (2016) et al.[22]

Table 8 Pathway for clinically relevant drug-drug interactions involving statins.

Enzyme / transporter	Statin	Examples of inhibitors	Examples of inducers
CYP3A4	atorvastatin (to a lesser degree), lovastatin, simvastatin	amiodarone, azole antifungals (i.e., ketoconazole), calcineurin inhibitors (i.e., cyclosporine), macrolide antibiotics (i.e., clarithromycin), protease inhibitors (i.e., ritonavir))	carbamazepine, phenytoin, phenobarbital, rifampin, St. Johns wort
CYP2C9	fluvastatin, pitavastatin (marginal), rosuvastatin	amiodarone, fluvoxamine, azole antifungals (i.e., ketoconazole)	carbamazepine, phenobarbital, phenytoin rifampin
P-gp	atorvastatin, lovastatin, pitavastatin, rosuvastatin, simvastatin	amiodarone, azole antifungals (i.e., ketoconazole), calcineurin inhibitors (i.e., cyclosporine), macrolide antibiotics (i.e., clarithromycin), protease inhibitors (i.e., ritonavir), tyrosine kinase inhibitors (i.e., lapatinib), ranolazine	carbamazepine, doxorubicin, phenytoin rifampin, St. Johns wort
OATP1B1	atorvastatin, fluvastatin, lovastatin, pravastatin, pitavastatin, rosuvastatin, simvastatin	bempedoic acid, calcineurin inhibitors (i.e., cyclosporine), gemfibrozil, macrolide antibiotics (i.e., clarithromycin), protease inhibitors (i.e., ritonavir)	unknown
OATP1B3	fluvastatin, pitavastatin, pravastatin, rosuvastatin	bempedoic acid, calcineurin inhibitors (i.e., cyclosporine), gemfibrozil, macrolide antibiotics (i.e., clarithromycin), protease inhibitors (i.e., ritonavir)	unknown

CYP, cytochrome P450; OATP, organic anion-transporting polypeptide; P-gp, P-glycoprotein

Adapted from Wiggins (2016) et al.[22] and Beavers (2022) et al.[58]

Table 9 Gene variants associated with SAMS.

Gene	Variant	Statin
SLCO1B1	rs4149056	Atorvastatin, rosuvastatin, simvastatin
COQ2	rs4693075	Atorvastatin, rosuvastatin
HTR7	rs1935349	Atorvastatin, pravastatin, simvastatin
GATM	rs9806699	Simvastatin
CYP3A4	rs2740574	Atorvastatin, simvastatin

Adapted from Brunham (2018) et al.[60]

Is laboratory testing helpful in the evaluation of SAMS?

Clinical laboratory tests are not typically helpful in evaluating SAMS, but may be appropriate in certain circumstances. The literature on the impact that statins have on CK has been mixed. Most patients with SAMS do not have elevated CK. Moreover, CK can be increased in asymptomatic individuals on statin therapy or can be elevated for other reasons (i.e., increased physical activity or exercise,

hypothyroidism, drug abuse (cocaine, alcohol), medications (daptomycin)).[62] Some clinicians choose to measure a CK prior to initiating statin therapy as this may be particularly helpful in different ethnicities as normative ranges may vary. Having a baseline CK for comparison could be helpful. Those who may benefit from a pretreatment CK include those with a high risk of muscle symptoms: 1) significant drug-drug interactions (Tables 2 and 8), 2) certain underlying chronic diseases (i.e., muscle disorders, chronic kidney disease, hypothyroidism), and 3) prior severe statin myopathy (i.e., rhabdomyolysis, CK >5x ULN). Prior NLA guidance suggests withholding statin therapy for CK levels >3 times ULN[13] and the ACC/AHA guidelines recommends withholding statin therapy for CK levels >5 x ULN.[63] Post-treatment CK measurements may be useful in some patients with SAMS, but are particularly important in the evaluation of suspected myopathy or rhabdomyolysis.

Measurement of anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) antibodies, electromyography, muscle strength testing, and muscle biopsy are neither pragmatic for clinical practice nor routinely recommended. These tests may be ordered by a neurologist or a clinical lipid specialist for evaluation of persistent weakness, chronic CK elevations, or muscle pain or tenderness that does not remit with statin withdrawal.[13] Measurement of levels of hepatic aminotransferase, alkaline phosphatase, and bilirubin are helpful to exclude severe hepatic impairment and measurements of blood urea nitrogen and creatinine are helpful to exclude renal dysfunction, both of which can impair statin metabolism and aggravate statin intolerance. Hypothyroidism is an important secondary cause of myalgia/myopathy that should be ruled out. Vitamin D levels can also be measured and supplemented if deficient. Refer to the vitamin D supplementation section for more details.

What management strategies are helpful to address SAMS?

A multifaceted approach is necessary after a patient experiences a perceived threat to well-being, quality of life, and/or functional status related to SAMS. Utilization of effective communication strategies is vital to establish a trusting patient-clinician relationship and optimize outcomes in patients with SAMS.[63] It is also important to validate and acknowledge patient-reported SAMS, while also emphasizing the risk of cardiovascular morbidity and mortality that may manifest without the use of statin treatment. This individualized approach takes time and commitment from both patient and clinician and should emphasize patient-specific management strategies that will optimize identification of an efficacious and tolerable lipid-lowering regimen.

The results of several studies suggest that approximately 60-80% of patients with SAMS are eventually able to tolerate some statin regimen.[64,65] It is important to first rule out potential risk factors that may cause or aggravate the patient's muscle symptoms and mitigate those that are modifiable (table 2). Additionally, employing healthy strategies such as optimizing lifestyle interventions – adequate hydration, heart healthy nutrition, regular stretching and physical activity, warm–up/cool-down activities before/after exercise, adequate sleep, and possibly use of certain supplements may help to maximize medication tolerance.

Efforts to understand the patient's prior experience with statins and their viewpoints provides the clinician with a foundation for future recommendations. This includes a detailed discussion of prior statin usage and a thorough review of medical records to clarify dates of use, dose, duration, and adverse effects with a timeline for symptom onset and resolution, as well as rechallenges with the medication. Management strategies consists of 1) same statin but lower dose, 2) different statin, 3) supplementation, and/or 4) non-statins (Figure 4). This section will focus on optimizing statin therapy (Table 10), but early implementation of non-statin therapies can help facilitate atherogenic lipoprotein goal achievement in parallel with efforts to enable the patient to stay on statin therapy.

Utilizing a lower dose statin. Continuing the same statin but at a lower dose is often an effective strategy because SAMS are typically dose-related. Partial dose tolerance allows for individual treatment plans utilizing statins. LDL-C-lowering efficacy with statins is greatest with the lowest daily dose which may achieve 2/3 of its maximum LDL-C lowering effect with an additional 5-6% reduction from baseline with each doubling of dose. Therefore, even at the statin's lowest daily dose, many patients will achieve substantial LDL-C lowering while improving tolerability. Starting with the lowest daily dose of a high potency statin (i.e., atorvastatin 10 mg or rosuvastatin 5 mg) offers a moderate intensity response, which can result in an impressive 33-45% reduction in LDL-C (Table 11). Over 50% reduction in LDL-C can be achieved, even when a high dose statin is not tolerated, by adding either ezetimibe or other non-statin pharmacotherapies in combination with low to moderate-intensity statin treatment (Figure 5). The results of the RACING study demonstrated that compared to treatment with rosuvastatin 20 mg daily, open label treatment with low dose rosuvastatin 10 mg daily in combination with ezetimibe 10 mg daily was associated with a lower rate of drug discontinuation (4.8% combination vs 8.2% monotherapy, $p<0.0001$) and greater achievement of LDL-C < 70 mg/dL at years 1, 2, and 3 (73%, 75%, and 72% combination vs 55%, 60%, and 58% monotherapy, respectively, all $p<0.0001$).[66]

In cases of persistent intolerance during low-dose statin therapy, utilization of an intermittent statin dosing regimen (non-daily statin dosing) may be needed to facilitate patient tolerability. In these circumstances, it is recommended to use statins with a longer half-life (i.e., atorvastatin and rosuvastatin as evidenced in the literature but likely also pitavastatin based on its pharmacokinetic properties) to ensure plasma and hepatic levels are sufficiently sustained to induce meaningful LDL-C lowering. Though limited data exist, there are accounts of 20-40% LDL-C lowering depending on the dose and dosing interval.[65] To optimize medication adherence,

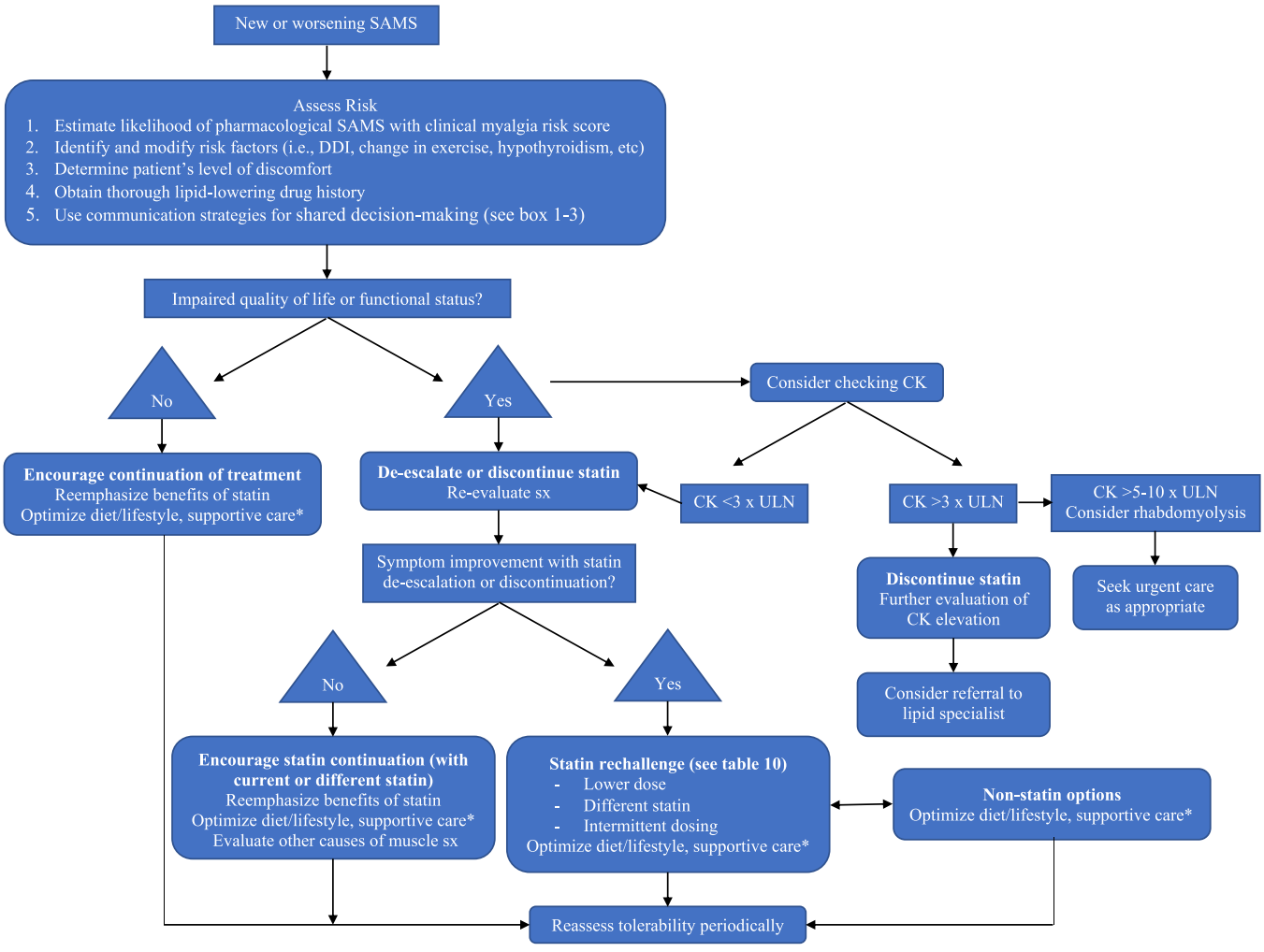

Figure 4 Potential strategies for managing SAMS
Abbreviations; CK, creatine kinase; DDI, drug to drug interactions; SAMS, statin-associated muscle symptoms; Sx, symptoms; ULN, upper limit of normal
*Supportive care measures: stretch, hydrate, sleep, consider washout / drug holiday

which is a concern with this dosing strategy, it is recommended to choose a specific dosing schedule (such as Monday, Wednesday, and Friday) instead of every other day.

Switching statins. All seven FDA-approved statins are pharmacologically unique, with differences in biotransformation pathways, half-life, elimination routes, and lipophilicity (Table 7). Switching to a statin that is metabolized by a different enzyme system, avoids various transporters, or is less lipophilic may improve drug tolerability. Additionally, there are data from the PRIMO study that fluvastatin and pravastatin are better tolerated as compared to atorvastatin and simvastatin[17], but this may be related in part to their lower LDL-C lowering efficacy. The low milligram amount with pitavastatin dosing (1, 2, or 4 mg) may be more psychologically appealing to patients who prefer the "lowest milligram strength".

When discussing statin rechallenge in patients with SAMS, it can be helpful to frame expectations regarding tolerability. Tolerability discussions provide a helpful perspective for the patient to reflect on functional status and quality of life rather than an expectation for completely symptom-free therapy. An individual could experience mild tolerable muscle symptoms for the first 2-4 weeks, which later resolve. It is important to emphasize that statin rechallenge may not cause the same symptoms, particularly after a dose reduction or change to another statin. Setting the stage for positive but realistic expectations may facilitate improved patient outcomes.

Do dietary supplements prevent and/or manage SAMS?

In an attempt to circumvent adverse drug reactions and prevent discontinuation of treatment due to SAMS, both clinicians and patients have considered use of supplementation as a potential amelioration strategy. Though several substances have been hypothesized as possible treatment

Table 10 Statin dosing strategies to optimize tolerability in patients with SAMS.

Strategy*	Rationale / Example
Lower dose	SAMS are dose-related Consider using the lowest daily dose which will provide the majority of the statin's LDL-C lowering capacity i.e., patient with SAMS on atorvastatin 80 mg daily may tolerate atorvastatin 10 mg daily
Different statin	Use statins that utilize either a different metabolic pathway (CYP3A4, CYP2C8, CYP2C9) or a different mode of biotransformation Select an agent with a pharmacokinetic profile different from the offending agent (see Table 7) i.e., patient with SAMS on atorvastatin 80 mg daily may tolerate pravastatin, rosuvastatin, fluvastatin-XL, or pitavastatin better as these avoid CYP3A4 and P-gp
Intermittent dosing	Reserved for more severe cases where patients cannot tolerate even the lowest dose of a daily statin Recommend utilizing statins with longer half-lives and greater potency (atorvastatin or rosuvastatin) i.e., patient with SAMS on atorvastatin 10-80 mg daily may tolerate rosuvastatin 5 mg given three times per week (Monday, Wednesday, Friday)
Evidence-based	Some patients may be more accepting of statins that have been shown to have reduced rates of SAMS in clinical trials i.e., consider use of fluvastatin-XL, or pravastatin instead of simvastatin
Naturally derived statin	Some patients may be more accepting of using a naturally derived statin medication. i.e., lovastatin is a natural fungal-derived product that is FDA-approved for cholesterol lowering while the dietary supplement red yeast rice is not
Lowest milligram strength	Some patients may be more accepting of using a drug with a lower milligram dosing i.e., recommend using pitavastatin which is available as 1 mg, 2 mg, and 4 mg, as opposed to 10 to 80 mg for other statins
Washout period	Some patients may benefit from a washout period or drug holiday to alleviate or prevent symptoms Holding the statin for a few days to a few weeks and then restarting treatment again may improve persistence rates i.e., patient taking rosuvastatin 20 mg daily takes a 1-2 week drug holiday in preparation for a strenuous physical event such as running a marathon

CYP, cytochrome P450; FDA, Food and Drug Administration; LDL-C, low-density lipoprotein cholesterol; mg, milligram; SAMS, statin-associated muscle symptoms; XL, extended release.

*Although the focus of this table is centered on statin dosing strategies to improve tolerability, a foundational emphasis on optimizing dietary and lifestyle interventions is recommended for all patients to improve cardiovascular risk profile and potentially enable use of lower statin doses.

Table 11 Approximate LDL-C lowering by statin and dose

Drug	Percent LDL Lowering						
	20-25%	26-32%	33-40%	41-45%	46-51%	52-55%	55-58%
Rosuvastatin			2.5 mg	5 mg	10 mg	20 mg	40 mg
Atorvastatin			10 mg	20 mg	40 mg	80 mg	
Simvastatin	5 mg	10 mg	20 mg	40 mg			
Pitavastatin		1 mg	2 mg	4 mg			
Lovastatin	10 mg	20 mg	40 mg	80 mg			
Pravastatin	10 mg	20 mg	40 mg	80 mg			
Fluvastatin	20 mg	40 mg	80 mg				

approaches for mitigation of SAMS, only a few have been investigated sufficiently and utilized in practice to warrant discussion in this clinical perspective.

Insufficient vitamin D stores are associated with muscle discomfort and have been associated with SAMS,[67,68] but a causal relationship is unproven. Several mechanistic hypotheses exist, including: 1) shunting of cytochrome P450 (specifically CYP3A4) from statin metabolism to vitamin D hydroxylation in vitamin D deficient states, 2) statin-induced reduction in vitamin D plasma levels (lipoproteins act as carriers for vitamin D), and 3) reduction in vitamin D mediated gene transcription and protein synthesis required for muscle repair.[69] Data investigating a link between vitamin D levels and SAMS, as well as supplementation with vitamin D to treat SAMS represents low level evidence with several limitations. The majority of data suggest an association between low vitamin D and SAMS, with risk increasing at vitamin D plasma levels <30 ng/mL and more strongly at <20 ng/mL.[69] In studies using vitamin D supplementation to ameliorate SAMS the dosage has varied but most utilized

higher doses (50,000-100,000 units per week) aiming for on-treatment levels of 50-80 ng/mL, and pretreating with vitamin D supplementation prior to re-challenging with statin therapy. However, to date there has not been evidence from RCT that vitamin D supplementation either prevents SAMS or reduces the severity of muscle symptoms. Although it may be reasonable to check vitamin D levels in patients with SAMS and initiate supplementation if deficiency is identified, a well-designed RCT is still needed before any recommendations can be made about either routine measurement of vitamin D levels in those with SAMS as well as any treatment recommendation in those with SAMS and low vitamin D levels.

Another controversial supplement for the treatment of SAMS is Coenzyme Q_{10} (CoQ_{10}), a naturally occurring byproduct of the mevalonate pathway, and integral to mitochondrial function and cellular energy production.[70] Its use seems plausible from a physiological role in patients with SAMS as its endogenous production, and resultant plasma and tissue concentrations, are reduced with statin treatment, but steady-state mitochondrial levels may not be substantially reduced during long-term statin treatment. Additionally, oral administration with CoQ_{10} has been demonstrated to dose-dependently increase plasma CoQ_{10} levels, reaching peak effects after 2 weeks, but this may not alter mitochondrial function.[71] RCTs and meta-analyses evaluating CoQ_{10} in doses ranging from 100 to 600 mg daily, have produced discordant results regarding improvement in pain scores and results did not seem to vary by CoQ_{10} dose.[72,73] One analysis failed to show an increase in statin adherence with CoQ_{10}

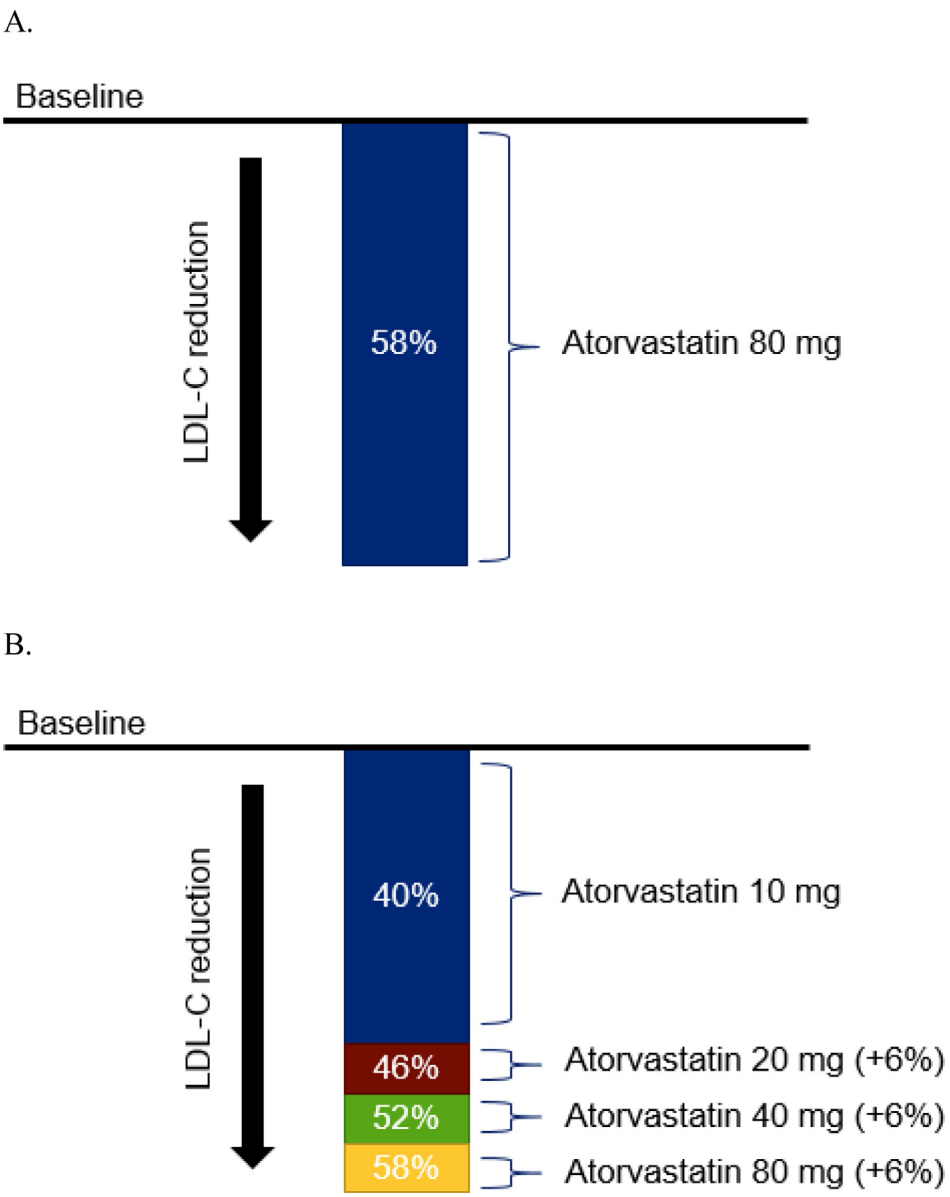

Figure 5 Approaches to achieving high-intensity statin LDL-C lowering in a patient with SAMS.
A. LDL-C lowering with the high-intensity statin – atorvastatin, B. LDL-C lowering across all atorvastatin dosing ranges, C. LDL-C lowering with low dose atorvastatin plus ezetimibe which equates to a high-intensity statin

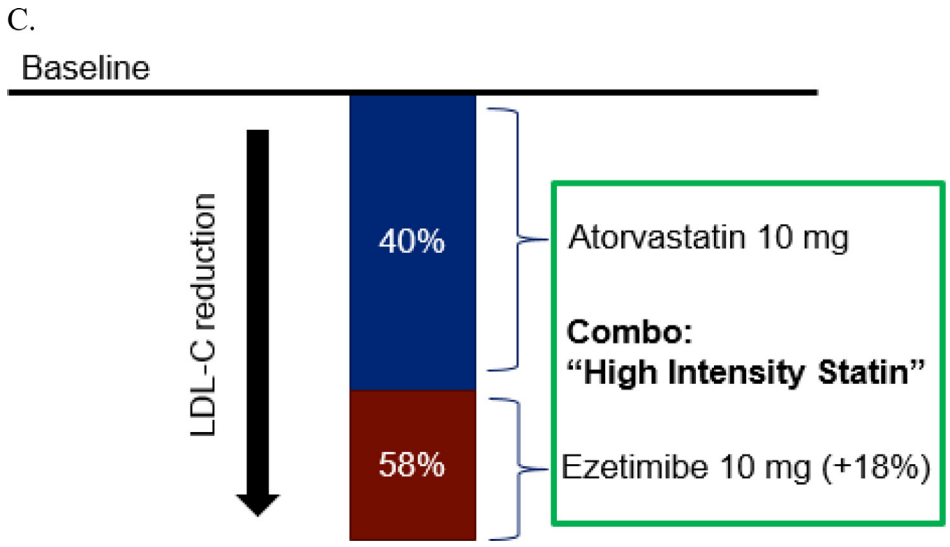

Figure 5 Continued

supplementation, which is perhaps a more important outcome measure than pain score improvement.[73] Use of CoQ_{10} is not supported by most guideline recommendations for mitigation of SAMS.[9,13,63] However, others have suggested that given the hypothetical possibility of a clinical benefit, coupled with anecdotal reports of effectiveness from some clinicians and patients, a trial of CoQ_{10} might seem reasonable as a last line strategy in certain patients with SAMS. Until a well-designed RCT is completed in those with SAMS and low levels of CoQ_{10}, such a strategy cannot be currently recommended.

Another question that arises during discussion of supplementation is the role of nutraceuticals in statin-intolerant patients. Nutraceuticals should not be promoted to replace pharmaceutical grade, evidenced-based, lipid-lowering therapies, however, they may have a niche role as complementary to statins and non-statins in some statin intolerant patients.

What can be done if my patient cannot tolerate any statins, or is unable to achieve lipid goals on statin therapy?

Despite a concerted effort on the part of the patient and clinician, some patients are unable to tolerate any dose of any of the seven FDA-approved statins that are clinically available. Inability to tolerate low doses of 3-4 statins, or not achieving lipid goals on suboptimal statin dosing, is often sufficient to justify initiation of treatment with non-statin therapies. Fortunately, several classes of non-statin drugs are available that can facilitate reductions in LDL-C and non-HDL-C in patients not on statin therapy (Table 12). Other non-statin drugs have been proven to reduce cardiovascular events as either monotherapy (cholestyramine[74], niacin[75], gemfibrozil[76,77]) or in combination with a statin (ezetimibe[78], alirocumab[79], evolocumab[80]). In some patients treatment with fenofibrate may produce modest LDL-C lowering, but fibrates are primarily indicated for triglyceride-lowering and lack solid evidence of cardiovascular benefit. For patients with familial hypercholesterolemia (FH) and ASCVD, treatment with lipoprotein apheresis may be a viable option after exploring available non-statin drug therapies. For patients with homozygous FH, the specialty drugs lomitapide and evinacumab can be very efficacious, but these drugs are restricted to use only in patients with homozygous FH.

Among these options, ezetimibe and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibiting monoclonal antibodies are proven to reduce ASCVD events.[81] In addition, niacin monotherapy reduced ASCVD events in men with ASCVD[75], but not in combination with statins.[82,83] The LDL-C-lowering efficacy is modest, but cholestyramine monotherapy is also proven to reduce the risk of cardiovascular events.[74] It is important to maintain the focus on achieving LDL-C and non-HDL-C goals while sequentially adding non-statin therapies. Many patients with medication intolerance may become weary of undergoing trials of new medications, or resist trying new medications, but the consequences of not achieving lipid goals are progression of ASCVD and occurrence of cardiovascular events. Accordingly, the patient's treatment is incomplete until appropriate lipid goals have been achieved.

Among patients with FH and ASCVD who are unable to achieve sufficient LDL-C lowering on non-statin pharmacologic therapy, treatment with lipoprotein apheresis is FDA-approved if the LDL-C concentration is $>$ 100 mg/dl on maximal tolerable lipid-lowering therapy.[84,85] This procedure is available only at specialized treatment centers and involves extracorporeal removal of apo B-containing lipoproteins from plasma. The LDL-C concentration can be acutely lowered by 75-85% during a 3-4 hour procedure performed every 1-2 weeks.[84,85]

Table 12 Nonstatin LDL-C-lowering drug options.

Drug	Mechanism of Action	LDL-C lowering capacity	Proven to Prevent ASCVD Events?	Comments
Ezetimibe	Cholesterol absorption inhibitor	18-20%	Yes, as combination therapy with a statin	Well tolerated
Alirocumab, Evolocumab	Monoclonal antibody that sequesters PCSK9	50-60%	Yes, as combination therapy with a statin	Injectable (SubQ)
Colesevelam, cholestyramine, colestipol	Bile acid sequestrant	14-18% (up to 20-30% with higher doses)	Yes, for cholestyramine as monotherapy	Timing of administration is important to maximize efficacy and reduce DDI
Niacin	Multiple effects	10-25%	Yes, for niacin as monotherapy but not in combination with a statin	Many side effects
Bempedoic acid	ATP citrate lyase inhibitor	15-30%*	No	Clinical outcomes trial in progress
Inclisiran	Small interfering RNA blocks PCSK9 translation	50%	No	Clinical outcomes trial in progress
Fenofibrate, gemfibrozil	PPAR alpha modulator	10-15%	Yes, for gemfibrozil as monotherapy No, for fenofibrate as monotherapy or in combination with a statin	DDI with gemfibrozil and statins
Lomitapide	Microsomal transfer protein inhibitor	20-50%	No	Restricted to homozygous FH REMS drug Monitor for DDI
Evinacumab	Monoclonal antibody that sequesters ANGPTL3	49%	No	Restricted to homozygous FH Injectable (IV)

*Greater LDL-C lowering efficacy in the absence of statin therapy.ANGPTL3, angiopoietin-like protein 3; ATP, adenosine triphosphate; DDI, drug-drug interaction; FH, familial hypercholesterolemia; IV, intravenous; PCSK9, proprotein convertase subtilisin/kexin type 9; REMS, Risk Evaluation and Mitigation Strategy program; SubQ, subcutaneous

Summary and conclusions

SAMS is the most common cause of statin intolerance and the rates documented in clinical trials differ significantly than those reported in clinical practice. The consequences of SAMS include implications for statin adherence and persistence and ultimately a heightened risk for atherosclerotic events and mortality if statin treatment is not optimized or is discontinued. There are many multifaceted approaches to managing SAMS that must first center around a communicative and compassionate patient-clinician relationship. Most patients with SAMS can tolerate some dose of a statin through interventions that focus on lifestyle, risk factor modulation, and statin pharmacology optimization. The adjunctive use of non-statins can facilitate a tolerable and efficacious regimen, allowing patients to achieve further LDL-C and non-HDL-C lowering and reduction in risk of cardiovascular sequelae.

Key Take-Home Messages

- Statin-associated muscle symptoms (SAMS) are the most common form of statin intolerance.
- The prevalence of SAMS, regardless of causality, is estimated to be about 10% (range 5% to 25%).
- The prevalence of pharmacological SAMS (muscle symptoms resulting from pharmacological properties of the statin) is estimated to be about 1-2% (range 0.5% to 4%).
- Most SAMS are attributable to non-pharmacological factors (e.g., increased body aches from physical activity), not direct pharmacological effects of statin on muscle tissue, but are still clinically relevant because they may result in statin discontinuation.
- Discontinuation of statin therapy in patients with SAMS is associated with increased risk of cardiovascular events and total mortality.
- Patient-centered clinical and communication strategies can help mitigate SAMS and improve medication adherence and outcomes among statin users.
- The clinician should extend beyond tailoring patient expectations for adverse effects and informing them of the potential of nocebo effects, while emphasizing benefits and safety of statin therapy.
- Modulation of risk factors for SAMS can improve statin tolerance.
- Optimization of dietary/lifestyle interventions can potentially minimize statin dosing intensity through improvement in cardiovascular/lipid risk.

- Statin tolerability can be further optimized through dose reductions, changing to a different statin, or intermittent dosing with evidence suggesting approximately 60-80% of patients with SAMS are eventually able to tolerate some statin regimen.
- Non-statin therapies need to be used when statin monotherapy is insufficient to achieve LDL-C and non-HDL-C goals, prioritizing therapies with proven cardiovascular benefit.
- Treatment of patients with SAMS is incomplete until LDL-C and non-HDL-C goals have been achieved.

Glossary

Statin intolerance – one or more adverse effects associated with statin therapy, which resolves or improves with dose reduction or discontinuation, and can be classified as complete inability to tolerate any dose of a statin, or partial intolerance with inability to tolerate the dose necessary to achieve the patient-specific therapeutic objective. To classify a patient as having statin intolerance, a minimum of two statins should have been attempted, including at least one at the lowest approved daily dosage.

SAMS (statin-associated muscle symptoms) – Muscle symptoms occurring during statin treatment without regard to causality. This is the most common cause of statin intolerance.

Pharmacological SAMS – SAMS occurring as a direct result of the pharmacological properties of the statin.

Nocebo - adverse effects that result from expectation of harm rather than pharmacological causes.

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