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NONSTATIN DRUGS (L. TOKGOZOGLU AND A.L. CATAPANO, SECTION EDITORS)

A Review of Statin Intolerance: a Focus on Statin-Attributed Muscle Symptoms

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Abstract

Purpose of Review To provide a systematic approach to management of the patient with statin-attributed muscle symptoms.

Recent Findings We examined the prevalence of statin intolerance, the role of the nocebo effect, key findings in the patient's history and laboratory studies, the potential value of coronary calcium scoring, and the importance of shared decision-making in considering statin re-initiation.

Summary Most patients with statin-attributed muscle symptoms can be successfully treated with statins or a combination of statins and non-statins to achieve successful ASCVD risk reduction.

Keywords Statin intolerance · Statin-associated muscle symptoms · Nocebo effect

Introduction

Multiple large-scale randomized controlled trials (RCTs) and meta-analyses have shown that statin therapy is associated with consistent atherosclerotic cardiovascular disease (ASCVD) risk reduction in both secondary and primary prevention studies in women and men [1], those at low ASCVD risk [2], people with diabetes [3], severe hypercholesterolemia [4], and older adults up to 75 years of age [5]. In addition, a legacy risk reduction effect of statins that continues for at least 3 years after completion of a placebo-controlled RCT was demonstrated in intermediate-risk primary prevention subjects [6]. Despite these benefits, statin discontinuation is common in clinical practice and has been associated with adverse consequences, particularly in those with established ASCVD. Although there have been rare reports of neurocognitive disorders, hepatotoxicity, hemorrhagic stroke, and renal toxicity, a causal relationship has been confirmed only for statin-associated muscle symptoms (SAMS), temporary elevation in transaminases, and newly noted diabetes. This article will focus on statin intolerance attributed to muscle symptoms.

Diagnostic Criteria for SAMS

The lack of specific biomarkers makes the diagnosis of true SAMS difficult. Stakeholder organizations have suggested a variety of criteria to diagnose SAMS (Table 1). A point system has also been proposed to classify muscle symptoms as unlikely, possibly or probably due to statin therapy (Fig. 1) [12]. In clinical practice, SAMS are most often reported within weeks after initiation or increase in intensity of therapy, are more likely to occur in physically active individuals, affect proximal large muscle groups, and generally resolve within several weeks to as long as 8 weeks after discontinuation. When similar symptoms recur after re-challenge with an alternate statin, particularly in the starting dose, and resolve within weeks upon drug discontinuation, the diagnosis of statin-associated muscle symptoms is more likely [13].

While some experts have suggested that the incidence of SAMS reported in meta-analyses of large RCTs largely

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Table 1 Comparison of guideline definitions of statin intolerance (for the purpose of this review, statin intolerance refers to adverse events attributed to muscle symptoms)

Guideline	Publication year	Definition
International Lipid Expert Panel [7]	2022	Based upon **FOUR** criteria: • The inability of the patient to tolerate at least two different statins at the lowest available dose • Intolerance associated with confirmed statin-related AEs or significant biomarker abnormalities (e.g., elevated CK) • Improvement of symptoms or resolution of upon dose decrease or discontinuation of statins • The exclusion of predisposing factors such as drug–drug interactions, thyroid disorders, vitamin D deficiency, and pre-existing neuromuscular disorders
National Lipid Association [8]	2014	The inability to tolerate at least two statins: one statin at the lowest starting daily dose and another statin at any daily dose, due to either objectionable symptoms (real or perceived) or abnormal laboratory determinations, which are temporally related to statin treatment and reversible upon statin discontinuation
European Atherosclerosis Society [9]	2015	The assessment of SAMS includes the nature of muscle symptoms (e.g., pain, weakness, or cramps which are symmetrical and proximal, occurring 4–6 weeks after starting therapy), increased creatine kinase levels and their temporal association with initiation of therapy with statin, and statin therapy suspension and rechallenge
Canadian Consensus Working Group [10]	2016	A clinical syndrome characterized by significant symptoms and/or biomarker abnormalities that: • Prevent long-term use of and adherence to indicated use of statins as • Documented by challenge/de-challenge/rechallenge, when appropriate, using at least 2 statins, including atorvastatin and rosuvastatin, that is • Not due to drug-drug interactions or untreated risk factors for intolerance (e.g., untreated hypothyroidism), and leading to • Failure to maintain therapeutic goals as defined by national guidelines
Luso-Latin American Consortium [11]	2017	Pharmacologic: • The inability to tolerate at least two statins at any dose, **OR** inability to tolerate doses higher than 5 mg of rosuvastatin; 10 mg atorvastatin; 20 mg of simvastatin; 20 mg of pravastatin; 20 mg of lovastatin; 40 mg of fluvastatin; or 2 mg of pitavastatin, **AND** • Symptoms or CK changes NOT attributable to established drug–drug interactions and recognized conditions increasing the risk of statin intolerance Symptomatic: • Intolerable muscle symptoms (muscle pain, weakness or cramps, even with normal or mildly changed CK) **OR** severe myopathy Etiologic: • Plausible time relationship (0–12 weeks) with the introduction of statin, dose increase or introduction of a drug competing for the same metabolic pathway, **AND/OR** • Resolution or improvement of symptoms after discontinuation of statin (usually in 2–4 weeks), **AND** with worsening in less than 4 weeks after the new exposure (rechallenge)

represent misattribution [14], observational studies and a large web-based survey have reported muscle symptoms in 10 to 25% of studied subjects [15, 16]. More recently, a random effects meta-analysis including 176 studies (112 RCTs and 64 cohort studies) with 4,143,517 subjects reported that the incidence of statin intolerance was 9.1% (95% confidence interval (CI) 8.01–10%) [17••].

A major impediment to the determination of whether muscle complaints are truly statin-related is the nocebo affect, pre-existing patient belief that symptoms that occur while taking a medicine are due to that medicine [18]. The GAUSS-3 (Goal Achievement After Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects 3) trial was a 2-stage RCT, the purpose of which was to initially identify subjects with statin-induced muscle symptoms during a placebo-rechallenge procedure and then to compare the low-density lipoprotein cholesterol (LDL-C) lowering efficacy and tolerability of ezetimibe versus evolocumab at weeks 22 and 24 of treatment. During the randomization phase of this trial, 491 subjects with a history of intolerable muscle symptoms while taking each of

two or more statins entered a double-blind phase in which 246 received placebo for 10 weeks and 245 atorvastatin, 20 mg daily, followed by cross-over to the alternate treatment group. During this phase, 26.5% of patients had muscle symptoms while taking placebo but not atorvastatin, and 42.6% had symptoms while taking atorvastatin but not placebo [19]. This study supported the observation that muscle symptoms, at least in some patients, are statin related.

Another way of studying whether muscle symptoms are actually due to the statin is to employ *N* of 1 trials, RCTs in which an individual patient serves as their own control during blinded administration of statin or placebo [20, 21]. Two such trials examined patient populations from England. In one study, 200 individuals, who were either considering statin discontinuation or stopped statin therapy during the previous year because of muscle symptoms, were treated with atorvastatin 20 mg daily or placebo over six 2-month randomly assigned treatment periods. The authors, using a muscle score symptoms methodology, reported no differences in the mean muscle symptom score between the statin and placebo periods (mean difference statin minus placebo − 0.11). By the end of the trial, 88% of subjects felt that the trial had been helpful in their decision-making about whether to restart a statin, and 66% reported readiness or intention to reinitiate statin therapy [22].

A second double blind *N* of 1 trial enrolled 60 subjects who had discontinued statins because of side effects reported within 2 weeks of initiating therapy. The purpose of the trial was to determine whether symptoms would be induced by atorvastatin 20 mg daily or placebo. Each patient received four bottles of atorvastatin 20 mg, placebo, or empty bottles, and they were asked to take the content of each bottle for one month and to use a smartphone app to report symptom intensity on a scale from 0 to 100. In this cohort, the mean symptom intensity was 8.0 during no-tablet months, 15.4 during placebo months compared to no-tablet months, and 16.3 with atorvastatin administration compared to no-tablet months. Six months after completion of the trial, 50% agreed to restart statin therapy. The authors observed that among those who had discontinued therapy because of side effects, 90% of reported symptoms attributed to statin therapy were also reported while taking the placebo [23]. The Understanding Statin Use in America and Gaps in Education (USAGE) survey assessed the practices of current and former statin users.in 10,138 individuals. Muscle-related side effects were reported by 60% of former users, which was the primary reason for discontinuation. Patients not satisfied with physician discussion were more likely to discontinue statins highlighting the importance of shared decision making [16]. However, selection bias among those agreeing to participate and lack of demographic and racial diversity limit the generalizability of these findings.

Factors Associated with Increased Risk for Statin-Associated Muscle Symptoms

Statin use is associated with variability in the risk of SAMS in different racial populations [24]. The SLCO1B1*15 allelic variant, which occurs primarily in Japanese individuals, results in reduced function of the organic anion transporter that regulates the hepatic uptake of simvastatin, leading to higher serum levels and a higher rate of myopathy in Japanese subjects [25, 26]. Similarly, the 421C > A polymorphism in the drug efflux transporter, ATP binding cassette G2 gene (ABCG2), results in a plasma concentration of rosuvastatin that is twice as high as in those without this variant [27]. Higher plasma levels of statins and their active metabolites increases the risk of myopathy or rhabdomyolysis [28•].

Among major guidelines, hypothyroidism, vigorous muscular exercise, vitamin D deficiency, preexisting muscle disease, renal impairment, drug-drug interactions, female sex, and East Asian ethnicity are recognized as risk factors for SAMS [7–9, 28•]. Polypharmacy is a common cause and should be questioned. Increased use of grapefruit juice in those taking statins metabolized by CYP P450 3A4, including lovastatin, simvastatin, and atorvastatin may have higher statin blood levels [29], but this effect should be balanced against the cardioprotective effects of higher intensity statin therapy. Alcohol consumption should be assessed. Although there is no evidence of an interaction between statins and alcohol, alcohol intake may affect liver function and predispose to hepatotoxicity.

The most recent and largest meta-analysis of studies of statin intolerance identified increased odds with older age (odds ratio (OR) 1.33, 95% CI: 1.26 to 1.42), female sex (OR 1.48, 95% CI: 1.39 to 1.54), Asian race (OR 1.25, 95% CI: 1.20 to 1.41), Black race (OR 1.29, 95% CI: 1.21 to 1.45), obesity (OR 1.31, 95% CI: 1.20 to 1.56), diabetes mellitus (OR 1.27, 95% CI:1.19 to 1.47), renal impairment (OR 1.25, 95% CI: 1.18 to 1.48), chronic liver failure (OR 1.24, 95% CI: 1.18 to 1.54), alcohol use (OR 1.22, 95% CI:1.10 to1.54), calcium channel blocker use (OR 1.31, 95% CI: 1.12 to 1.49), antiarrhythmic agent use (OR 1.36, 95% CI: 1.21 to 1.63), and increased statin dose (OR 1.38, 95% CI: 1.25 to 1.56) [17••]. These results should be interpreted with caution as details including the under-representation of Hispanic and Black races, the quantity of alcohol consumption, control of diabetes mellitus and severity of chronic liver or kidney disease were not reported. In addition, the contribution of the nocebo effect could not be determined.

Statin-Associated Muscle Symptom Clinical Index (SAMS-CI)

Instructions:

- Use with patients who have had muscle symptoms that were **new or increased** after starting a statin regimen.
- A **statin regimen** includes any statin at any dose or frequency, including a statin the patient has used previously, at the same or a different dose.
- **Muscle symptoms** may include aches, cramps, heaviness, discomfort, weakness, or stiffness.
- Interpret overall score in light of **other possible causes** of the muscle symptoms, such as:

Recent physical exertion	Hypothyroidism	Concurrent illness
Changes in exercise patterns	Drug interaction with statin	Underlying muscle disease

- **See reverse** for Frequently Asked Questions

How many statin regimens has the patient had that involved new or increased muscle symptoms?

One
Complete the questions on the left side of this page.

Two or more
Complete the questions on the right side of this page.

Regarding this statin regimen:

A. Location and pattern of muscle symptoms
(If more than one category applies, record the highest number.)

		Enter score:
Symmetric, hip flexors or thighs	3	
Symmetric, calves	2	
Symmetric, proximal upper extremity	2	
Asymmetric, intermittent, or not specific to any area	1	

B. Timing of muscle symptom onset in relation to starting statin regimen

<4 weeks	3	
4–12 weeks	2	
>12 weeks	1	

C. Timing of muscle symptom improvement after withdrawal of statin
(If patient is still taking statin, stop regimen and monitor symptoms.)

<2 weeks	2	
2–4 weeks	1	
No improvement after 4 weeks	0	

Rechallenge the patient with a statin regimen,
(even if same statin compound or regimen as above)
then complete final question:

D. Timing of recurrence of similar muscle symptoms in relation to starting second regimen

<4 weeks	3	
4–12 weeks	1	
>12 weeks or similar symptoms did not reoccur	0	

Total:
All four scores above must be entered before totaling

Regarding the statin regimen *before* the most recent regimen:

A. Location and pattern of muscle symptoms
(If more than one category applies, record the highest number.)

		Enter score:
Symmetric, hip flexors or thighs	3	
Symmetric, calves	2	
Symmetric, proximal upper extremity	2	
Asymmetric, intermittent, or not specific to any area	1	

B. Timing of muscle symptom onset in relation to starting statin regimen

<4 weeks	3	
4–12 weeks	2	
>12 weeks	1	

C. Timing of muscle symptom improvement after withdrawal of statin

<2 weeks	2	
2–4 weeks	1	
No improvement after 4 weeks	0	

Regarding the *most recent* statin regimen:
(even if same statin compound as above)

D. Timing of recurrence of similar muscle symptoms in relation to starting regimen

<4 weeks	3	
4–12 weeks	1	
>12 weeks or similar symptoms did not reoccur	0	

Total:
All four scores above must be entered before totaling

Interpretation

Total score:	2–6	7–8	9–11
Likelihood that the patient's muscle symptoms are due to statin use:	Unlikely	Possible	Probable

10 Oct 2016. Based on Rosenson et al. An assessment by the Statin Muscle Safety Task Force: 2014 update. *J Clin Lipidol.* 2014 May–Jun;8(3 Suppl):S58–71.

◂**Fig. 1** An example of the Statin-Associated Muscle Symptom Clinical Index (SAMS-CI) for assessing the likelihood that patient's muscle symptoms were caused or worsened by statin use. Adapted from Rosenson, R.S., et al. Cardiovasc Drugs Ther 31, 179–186 (2017). https://doi.org/10.1007/s10557-017-6723-4. Published on April 18th, 2017, with permission from Springer Nature [12]

Should Statin Therapy Be Restarted in Patients with Statin-Attributed Muscle Symptoms?

Statin intolerance is associated with recurrent myocardial infarction and coronary events, particularly in patients with proven ASCVD [30]. A study of 105,329 Medicare beneficiaries who began a moderate- or high-intensity statin after hospitalization for a myocardial infarction between 2007 and 2013 were followed up for a median follow-up of 1.9–2.3 years. The multivariate-adjusted hazard ratios (HR) comparing those with statin intolerance versus those with high adherence were 1.50 (95% confidence interval [CI]: 1.30 to 1.73) for recurrent myocardial infarctions, 1.51 (95% CI: 1.34 to 1.70) for coronary heart disease events, and 0.96 (95% CI: 0.87 to 1.06) for all-cause mortality. Thus, statin intolerance was, in this population, associated with recurrent myocardial infarction and coronary events, but not all-cause mortality [30]. Because of the established benefit of statins in such patients, the re-initiation of therapy should be attempted whenever possible.

While sub-optimal statin adherence is associated with worsened ASCVD outcomes in secondary prevention cohorts, the data remain less clear for primary prevention [31]. Based on the primary prevention MESA (Multi-Ethnic Study of Atherosclerosis) cohort, 49% [32] of borderline- or intermediate-risk adults who are prescribed statins based upon their Pooled Cohort Equations estimated 10-year ASCVD risk have a coronary artery calcium (CAC) score of 0 [33]. Such individuals derive minimal ASCVD risk reduction from statin initiation [34, 35]. An algorithm that incorporates CAC scoring into clinical decision-making about statin re-initiation in statin intolerant patients has been proposed and provides a practical approach to the use of this technology in such patients (Fig. 2) [36].

Statin therapy is generally well-tolerated by patients when rechallenged. In a large US retrospective cohort study, 11,124 of 107,835 subjects (10%) discontinued statin treatment because of adverse events considered to be statin related. Among these individuals, 6579 (59%) were rechallenged and statin treatment was able to be reinitiated in > 90% of cases. At 12 months, only 515 (7.8%) of the 6579 rechallenged patients were not taking a statin [37].

How Should We Manage SAMS?

The traditional approach to the management of SAMS includes an evaluation of risk factors that predispose to musculoskeletal symptoms, including recent onset muscular activities, hypothyroidism, underlying metabolic, musculoskeletal or rheumatologic disorders, severe vitamin D deficiency or the initiation of drugs that alter statin metabolism [13]. The European Atherosclerosis Society statement on statin-associated muscle symptoms recommended that when muscle symptoms are present, creatine kinase (CK) levels should be measured, and if greater than 4 times the upper limit of normal, the statin should be discontinued for 2–4 weeks before re-challenge [9]. Various complementary therapies to overcome SAMS such as CoQ10 and vitamin D have been proposed but none are supported by randomized controlled trial evidence.

Alternative strategies for LDL-C lowering in such patients include the initiation of a vegan diet, the use of lower or starting doses of the same or other statins, less-than-daily long-acting statins [38, 39], ezetimibe or bempedoic acid monotherapy [40], ezetimibe/bempedoic acid combination therapy [41], either of these drugs in combination with less-than-daily long-acting statins, or in high or very high risk patients, the use of proprotein convertase subtilisin/kexin 9 (PCSK9) monoclonal antibodies [19, 42]. Inclisiran, a small interfering RNA targeting hepatic PCSK9 synthesis is another non-statin approved both by the European Medicines Agency and the U.S. Food and Drug Administration for LDL-C reduction, [43, 44] but has not been studied specifically in this patient population. The use of nutraceuticals with LDL-C lowering properties for treatment of statin intolerant patients has been proposed as an additional strategy in a position statement of the International Lipid Expert Panel, although with few exceptions, subject enrollment in such studies was small [45].

The National Lipid Association defines severe myonecrosis as a greater than or equal to 50 fold increase in creatine kinase above baseline levels or normative upper limit, adjusted for age, race and sex [46]. Clinical rhabdomyolysis is defined as myonecrosis with myoglobinuria or acute renal failure (increase in serum creatine of at least 0.5 mg/dL over baseline values) [46]. Most cases of rhabdomyolysis are due to non-statin related etiologies (trauma, exogenous toxins, alcohol and illicit drugs) [47]. Serious muscle toxicity attributed to statin therapy is rare [28•]. Risk factors for statin-associated myotoxicity include older age, hypertension, diabetes mellitus and the concomitant use of a variety of drugs associated with myotoxicity [48].

Statin drug-drug interactions (DDIs) are most often mediated by the cytochrome P450 enzyme system (CYP450) and the permeability glycoprotein (p-gp). The main role of

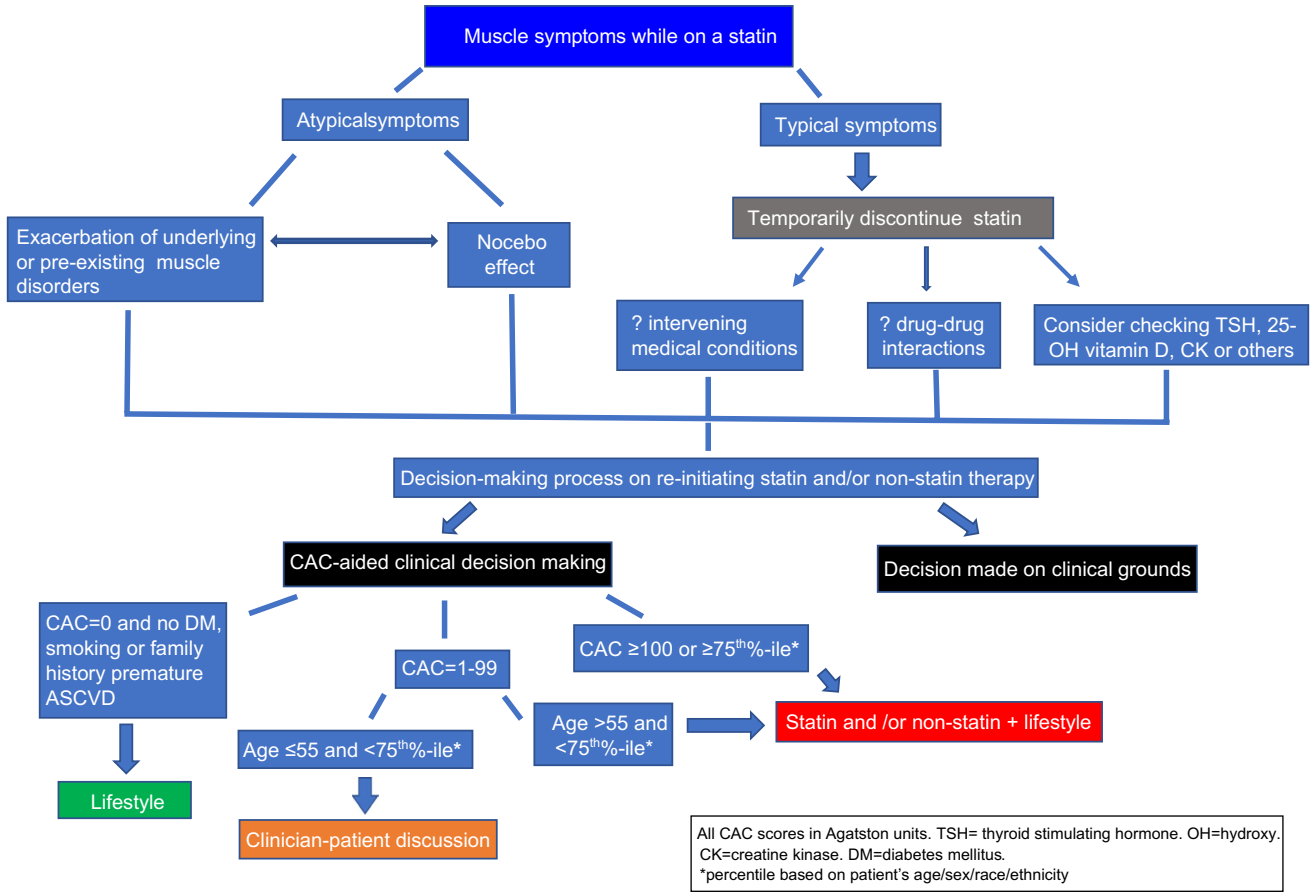

Fig. 2 The role of CAC scoring to aid clinical decision-making in those with statin-attributed muscle symptoms. This article was published in J Clin Lipidol, Vol 15, Orringer CE et al. Coronary artery calcium scoring in patients with statin associated muscle symptoms: prescribing statins for those most likely to benefit, P782-788, Copyright Elsevier (2021) [36]

CYP450, which is mainly expressed in the liver, but also in the gastrointestinal tract, kidney and other sites, is to detoxify medications and facilitate their elimination from the body. P-gp expression, localized primarily in the gastrointestinal tract and in hepatic, renal, and brain tissue, plays an important role in drug disposition by promoting secretion of substrates into the urine and bile. The American Heart Association published a scientific statement providing recommendations on the management of clinically significant DDIs with statins and select agents used in patients with cardiovascular disease [49]. Commonly used drugs in this category include amiodarone, amlodipine, colchicine, conivaptan, cyclosporine/tacrolimus/everolimus/sirolimus, diltiazem, dronedarone, gemfibrozil, ranolazine, ticagrelor, and verapamil [49]. Clinician awareness of these DDI will help to mitigate the risk of serious myotoxicity in individuals receiving statin therapy.

Initial treatment of statin-induced rhabdomyolysis involves prompt cessation of statin therapy and hydration, generally resulting in rapid reversal of clinical symptoms and laboratory abnormalities [28•]. Given the low incidence of statin-associated rhabdomyolysis, data on statin re-initiation are limited. A study of 54 patients with statin-induced muscle injury (3 cases of rhabdomyolysis) over a 5-year follow-up, suggested that statin therapy can be safely and effectively restarted after full resolution of symptoms and normalization of creatine kinase levels [50]. The decision to restart statin therapy in persons with statin-induced rhabdomyolysis should be individualized based on ASCVD risk, concomitant medical conditions, required drug therapy, and the potential for use of non-statin agents. If statin therapy is to be reinitiated, the starting dose should be utilized.

Statin-induced necrotizing autoimmune myopathy was initially described in 2007 in a case series of 8 patients who had progressive weakness and high creatine kinase levels that persisted long after statin discontinuation [51]. This rare disorder, with an estimated incidence of 1 in 100,000 statin users [52], is characterized by proximal muscle weakness, markedly elevated creatine kinase levels persisting after drug discontinuation, the presence of antibodies to HMG-CoA (3-hydroxy-3-methylglutaryl coenzyme A) reductase and the finding of myonecrosis with few inflammatory

cells on muscle biopsy [53, 54]. Therapy for this disorder includes oral or intravenous corticosteroids [55], intravenous immunoglobulin [56] and in some cases azathioprine, methotrexate or rituximab. While statin therapy should not be re-started in such patients, the use of alternate non-statin lipid lowering therapies may be considered [55].

Conclusions

The management of patients who develop statin-attributed muscle symptoms remains a challenge in clinical practice. The first step is to determine the patient's absolute risk and then to consider statin re-initiation. In those in whom the complaints appear to be a result of the nocebo effect, a caring clinician-patient discussion is warranted. A careful evaluation of factors that may increase the risk of statin-attributed muscle symptoms should be undertaken and when present, these risk factors should be addressed. For secondary prevention patients, every effort should be made to restart statin therapy or if not feasible, to consider non-statins to maximally lower LDL-C. For primary prevention, careful reassessment of the need for a statin should be done. In all cases, the benefit of an open and collaborative clinician-patient discussion will help to determine the most appropriate clinical management strategy.

Declarations

Conflict of Interest Dr. Orringer and Grant have no conflicts or competing interests relevant to this manuscript. Dr. Tokgozoglu reports participation in a Data Safety Monitoring Board or Advisory Board for Abbott, Amgen, Novartis, Sanofi, Daiichi-Sankyo, Mylan, Pfizer. She also reports payment/honoraria from Abbott, Amgen, Daiichi Sankyo, MSD, Mylan, Novartis, Novo Nordisk, Sanofi, Servier, Pfizer, and Recordati, as well as consulting fees from Abbott, Amgen, Bayer, MSD, Novartis, Sanofi, Novo Nordisk, and Daiichi Sankyo, and she reports being the Past President of the European Atherosclerosis Society and the Past President of the Turkish Society of Cardiology.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance

1. Cholesterol Treatment Trialists C, Fulcher J, O'Connell R, et al. Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174,000 participants in 27 randomised trials. Lancet. 2015;385(9976):1397–405.
2. Cholesterol Treatment Trialists C, Mihaylova B, Emberson J, et al. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. Lancet. 2012;380(9841):581–90.
3. Colhoun HM, Betteridge DJ, Durrington PN, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet. 2004;364(9435):685–96.
4. Vallejo-Vaz AJ, Robertson M, Catapano AL, et al. Low-density lipoprotein cholesterol lowering for the primary prevention of cardiovascular disease among men with primary elevations of low-density lipoprotein cholesterol levels of 190 mg/dL or above: analyses from the WOSCOPS (West of Scotland Coronary Prevention Study) 5-year randomized trial and 20-year observational follow-up. Circulation. 2017;136(20):1878–91.
5. Cholesterol Treatment Trialists C. Efficacy and safety of statin therapy in older people: a meta-analysis of individual participant data from 28 randomised controlled trials. Lancet. 2019;393(10170):407–15.
6. Boersma E, Kardys I. The legacy of HOPE-3. Eur Heart J. 2021;42(31):3008–10.
7. Penson PE, Bruckert E, Marais D, et al. Step-by-step diagnosis and management of the nocebo/drucebo effect in statin-associated muscle symptoms patients: a position paper from the International Lipid Expert Panel (ILEP). J Cachexia Sarcopenia Muscle. 2022;13(3):1596–622. https://doi.org/10.1002/jcsm.12960.
8. Jacobson TA, Ito MK, Maki KC, et al. National lipid association recommendations for patient-centered management of dyslipidemia: part 1–full report. J Clin Lipidol. 2015;9(2):129–69.
9. Stroes ES, Thompson PD, Corsini A, et al. Statin-associated muscle symptoms: impact on statin therapy-European Atherosclerosis Society Consensus Panel Statement on Assessment, Aetiology and Management. Eur Heart J. 2015;36(17):1012–22.
10. Mancini GBJ, Baker S, Bergeron J, et al. Diagnosis, prevention, and management of statin adverse effects and intolerance: Canadian Consensus Working Group Update (2016). Can J Cardiol. 2016;32(7, Supplement):S35–65.
11. Sposito AC, FariaNeto JR, Carvalho LS, et al. Statin-associated muscle symptoms: position paper from the Luso-Latin American Consortium. Curr Med Res Opin. 2017;33(2):239–51.
12. Rosenson RS, Miller K, Bayliss M, et al. The Statin-Associated Muscle Symptom Clinical Index (SAMS-CI): revision for clinical use, content validation, and inter-rater reliability. Cardiovasc Drugs Ther. 2017;31(2):179–86.
13. Thompson PD, Panza G, Zaleski A, Taylor B. Statin-associated side effects. J Am Coll Cardiol. 2016;67(20):2395–410.
14. Collins R, Reith C, Emberson J, et al. Interpretation of the evidence for the efficacy and safety of statin therapy. Lancet. 2016;388(10059):2532–61.
15. Bruckert E, Hayem G, Dejager S, Yau C, Begaud B. Mild to moderate muscular symptoms with high-dosage statin therapy in hyperlipidemic patients–the PRIMO study. Cardiovasc Drugs Ther. 2005;19(6):403–14.
16. Cohen JD, Brinton EA, Ito MK, Jacobson TA. Understanding Statin Use in America and Gaps in Patient Education (USAGE): an internet-based survey of 10,138 current and former statin users. J Clin Lipidol. 2012;6(3):208–15.
17•• Bytyci I, Penson PE, Mikhailidis DP, et al. Prevalence of statin intolerance: a meta-analysis. Eur Heart J. 2022;ehac015. https://doi.org/10.1093/eurheartj/ehac015. **This meta-analysis**

estimates the prevalence of statin intolerance, employing major stakeholder diagnostic criteria, and identifies risk factors and conditions that are associated with increased the risk of statin-associated muscle symptoms.

18. Barsky AJ, Saintfort R, Rogers MP, Borus JF. Nonspecific medication side effects and the nocebo phenomenon. J Am Med Assoc. 2002;287(5):622–7.
19. Nissen SE, Stroes E, Dent-Acosta RE, et al. Efficacy and tolerability of evolocumab vs ezetimibe in patients with muscle-related statin intolerance: the GAUSS-3 randomized clinical trial. JAMA. 2016;315(15):1580–90.
20. Barsky AJ, Saintfort R, Rogers MP, Borus JF. Nonspecific medication side effects and the nocebo phenomenon. JAMA. 2002;287(5):622–7.
21 Banach M, Rizzo M, Toth PP, et al. Statin intolerance - an attempt at a unified definition. Position paper from an International Lipid Expert Panel. Arch Med Sci. 2015;11(1):1–23.
22. Herrett E, Williamson E, Brack K, et al. Statin treatment and muscle symptoms: series of randomised, placebo controlled n-of-1 trials. BMJ. 2021;372:n135. https://doi.org/10.1136/bmj.n135.
23. Wood FA, Howard JP, Finegold JA, et al. N-of-1 Trial of a statin, placebo, or no treatment to assess side effects. N Engl J Med. 2020;383(22):2182–4.
24. Kalra DK. Bridging the racial disparity gap in lipid-lowering therapy. J Am Heart Assoc. 2021;10(1): e019533.
25. Voora D, Shah SH, Spasojevic I, et al. The SLCO1B1*5 genetic variant is associated with statin-induced side effects. J Am Coll Cardiol. 2009;54(17):1609–16.
26. Link E, Parish S, Armitage J, et al. SLCO1B1 variants and statin-induced myopathy–a genomewide study. N Engl J Med. 2008;359(8):789–99.
27. Naito R, Miyauchi K, Daida H. Racial differences in the cholesterol-lowering effect of statin. J Atheroscler Thromb. 2017;24(1):19–25.
28.• Newman CB, Preiss D, Tobert JA, et al. Statin safety and associated adverse events: a scientific statement from the American Heart Association. Arterioscler Thromb Vasc Biol. 2019;39(2):e38–81. **This scientific statement from the American Heart Association provides a comprehensive overview of statin safety and statin associated adverse events in multiple population groups and in individuals with a variety of chronic disease states.**
29. Lee JW, Morris JK, Wald NJ. Grapefruit Juice and Statins. Am J Med. 2016;129(1):26–9.
30. Serban MC, Colantonio LD, Manthripragada AD, et al. Statin intolerance and risk of coronary heart events and all-cause mortality following myocardial infarction. J Am Coll Cardiol. 2017;69(11):1386–95.
31. Chowdhury R, Khan H, Heydon E, et al. Adherence to cardiovascular therapy: a meta-analysis of prevalence and clinical consequences. Eur Heart J. 2013;34(38):2940–8.
32. Nasir K, Bittencourt MS, Blaha MJ, et al. Implications of coronary artery calcium testing among statin candidates according to American College of Cardiology/American Heart Association Cholesterol Management Guidelines: MESA (Multi-Ethnic Study of Atherosclerosis). J Am Coll Cardiol. 2015;66(15):1657–68.
33. Grundy SM, Stone NJ. 2018 American Heart Association/American College of Cardiology/Multisociety guideline on the management of blood cholesterol-secondary prevention. JAMA Cardiol. 2019;4(6):589–91.
34. Blaha MJ, Budoff MJ, DeFilippis AP, et al. Associations between C-reactive protein, coronary artery calcium, and cardiovascular events: implications for the JUPITER population from MESA, a population-based cohort study. The Lancet. 2011;378(9792):684–92.
35. Orringer CE, Maki KC. HOPE for rational statin allocation for primary prevention: a coronary artery calcium picture is worth 1000 words. Mayo Clin Proc. 2020;95(8):1740–9.
36. Orringer CE, Blaha MJ, Stone NJ. Coronary artery calcium scoring in patients with statin associated muscle symptoms: prescribing statins for those most likely to benefit. J Clin Lipidol. 2021;15(6):782–8.
37. Zhang H, Plutzky J, Skentzos S, et al. Discontinuation of statins in routine care settings: a cohort study. Ann Intern Med. 2013;158(7):526–34.
38. Juszczyk MA, Seip RL, Thompson PD. Decreasing LDL cholesterol and medication cost with every-other-day statin therapy. Prev Cardiol. 2005;8(4):197–9.
39. Gadarla M, Kearns AK, Thompson PD. Efficacy of rosuvastatin (5 mg and 10 mg) twice a week in patients intolerant to daily statins. Am J Cardiol. 2008;101(12):1747–8.
40. Laufs U, Banach M, Mancini GBJ, et al. Efficacy and safety of bempedoic acid in patients with hypercholesterolemia and statin intolerance. J Am Heart Assoc. 2019;8(7): e011662.
41. Ballantyne CM, Banach M, Mancini GBJ, et al. Efficacy and safety of bempedoic acid added to ezetimibe in statin-intolerant patients with hypercholesterolemia: a randomized, placebo-controlled study. Atherosclerosis. 2018;277:195–203.
42. Moriarty PM, Jacobson TA, Bruckert E, et al. Efficacy and safety of alirocumab, a monoclonal antibody to PCSK9, in statin-intolerant patients: design and rationale of ODYSSEY ALTERNATIVE, a randomized phase 3 trial. J Clin Lipidol. 2014;8(6):554–61.
43. Raal FJ, Kallend D, Ray KK, et al. Inclisiran for the treatment of heterozygous familial hypercholesterolemia. N Engl J Med. 2020;382(16):1520–30.
44. Ray KK, Wright RS, Kallend D, et al. Two phase 3 trials of inclisiran in patients with elevated LDL cholesterol. N Engl J Med. 2020;382(16):1507–19.
45. Banach M, Patti AM, Giglio RV, et al. The role of nutraceuticals in statin intolerant patients. J Am Coll Cardiol. 2018;72(1):96–118.
46 Rosenson RS, Baker SK, Jacobson TA, Kopecky SL, Parker BA. The National Lipid Association's Muscle Safety Expert P. An assessment by the Statin Muscle Safety Task Force: 2014 update. J Clin Lipidol. 2014;8(3 Suppl):S58-71.
47. McMahon GM, Zeng X, Waikar SS. A risk prediction score for kidney failure or mortality in rhabdomyolysis. JAMA Intern Med. 2013;173(19):1821–8.
48. Antons KA, Williams CD, Baker SK, Phillips PS. Clinical perspectives of statin-induced rhabdomyolysis. Am J Med. 2006;119(5):400–9.
49. Wiggins BS, Saseen JJ, Page RL, et al. Recommendations for management of clinically significant drug-drug interactions with statins and select agents used in patients with cardiovascular disease: a scientific statement from the American Heart Association. Circulation. 2016;134(21):e468–95.
50. Blaier O, Lishner M, Elis A. Managing statin-induced muscle toxicity in a lipid clinic. J Clin Pharm Ther. 2011;36(3):336–41.
51. Needham M, Fabian VA, Knezevic W, Panegyres PK, Zilko PJ, Mastaglia FL. Progressive myopathy with up-regulation of MHC-I associated with statin therapy. Neuromuscul Disord. 2007;17:194–200.
52. Mammen AL, Chung T, Christopher-Stine L, et al. Autoantibodies against 3-hydroxy-3-methylglutaryl-coenzyme A reductase in patients with statin-associated autoimmune myopathy. Arthritis Rheum. 2011;63(3):713–21.

53. Allenbach Y, Benveniste O, Stenzel W, Boyer O. Immune-mediated necrotizing myopathy: clinical features and pathogenesis. Nat Rev Rheumatol. 2020;16(12):689–701.
54. Thompson PD, Panza G, Zaleski A, Taylor B. Statin-associated side effects. J Am Coll Cardiol. 2016;67(20):2395–410.
55. Allenbach Y, Mammen AL, Benveniste O, et al. 224th ENMC International Workshop: Clinico-sero-pathological classification of immune-mediated necrotizing myopathies Zandvoort, The Netherlands, 14–16 October 2016. Neuromuscul Disord. 2018;28(1):87–99.
56. Mammen AL, Tiniakou E. Intravenous immune globulin for statin-triggered autoimmune myopathy. N Engl J Med. 2015;373(17):1680–2.