Statin-associated muscle symptoms (SAMS) are a commonly reported problem in patients who use or start to use statins. This Heartbeat will provide a guide for clinicians by detailing a structured approach that is based on published data as well as expert opinion.

**Statin Benefits:** The cardiovascular (CV) benefits of statins are backed by a vast database, and statins have a favorable benefit/risk profile. Treatment with moderate- and high-intensity statins reduces the risk of CVD in the setting of high-risk primary and secondary prevention.¹,² For every 18mg/dl reduction in low-density lipoprotein-cholesterol (LDL-C), CVD events are reduced by 21% after one year of treatment with moderate- or high-intensity statins.³ The reduction in ASCVD increases with long-term statin use.⁴

**Problem:** However, many patients taking statins report SAMS that prevent the use of guideline-recommended doses, even though randomized clinical trials (RCTs) indicate that statins have a side-effect profile almost indistinguishable from placebo or comparative drugs, particularly when used in low dosages.⁵ But “real world” data obtained from surveys, registries and insurance claims suggest that side effects of statins are common, especially at higher doses.⁶ Many patients are unwilling to continue with guideline-recommended statin doses after experiencing side effects.⁷

**Consequences:** Patients who stop statins have a higher risk for recurrent myocardial infarction and stroke.⁸ This in turn leads to higher healthcare costs.⁹

**The Challenge of SAMS:** What makes this a more difficult problem is the overriding “nocebo effect.” Muscle symptoms are common in the middle-aged population taking statins. The difference between the muscle symptom data from observational studies and data from RCTs is due to the nocebo effect. The nocebo effect—opposite of placebo—(Latin for “I do harm”) explains why some patients misattribute symptoms to their exposure to statins. In the context of SAMS (without significantly elevated creatine phosphokinase [CK] muscle enzyme) or other adverse events, the nocebo effect is strengthened by exaggerated reports readily available online about the dangers of taking statins and by warnings appropriately communicated by physicians and patient information leaflets about myopathy/rhabdomyolysis.
In some cases, the patient becomes more conscious of background aches and pains when learning about the adverse effects of statins; in other cases, new muscle symptoms arise. Because a placebo-controlled rechallenge is not possible in the clinic, the return of symptoms upon rechallenge with the same or a different statin may well also be a nocebo effect.

**Plan:** Techniques to minimize the nocebo effect in patients starting statins may help prevent statin intolerance. We should:

- Avoid communications that create negative expectations about statins.
- Emphasize the benefits of statins in reducing CV disease and indicate that serious muscle side effects are very unlikely and are easily detected with a blood test (CK).
- Remind patients that muscle aches and pains are common in middle age and older, and usually are due to other causes.

**Management of SAMS**

*Whatever the etiology, these muscle symptoms are real to the patient and must be carefully addressed by the physician in order to keep the patient on a statin.*

An excellent expert opinion piece from this month’s *JACC* presenting a clinical approach is summarized in the illustration below.10

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**How can we diagnose SAMS?** Statin discontinuation and rechallenge is the primary strategy for confirming the presence of statin intolerance secondary to SAMS.

**SAMS Unlikely:**

1. Symptoms start immediately after initiation and/or resolve within minutes to hours upon cessation
2. Symptoms that do not improve or disappear within 12 weeks after statin discontinuation (four weeks often enough)
3. Symptom onset that is present after protracted use (> 12 weeks) without changes in any other apparent patient status
4. Symptoms that occur with other classes of lipid-lowering agents

Asymmetric, intermittent or non-specific symptoms to a particular area also make SAMS less likely.

**Treatment of SAMS**

We need to:

(a) Be convinced of the benefits of statins to convince the patient to take one

(b) Listen to the patient when he/she reports symptoms, assess severity of muscle symptoms and individualize treatment accordingly. If the patient’s symptoms do not interfere with activities of daily living and/or post-exercise symptoms generally abate with rest and occasional acetaminophen, I encourage the patient to hang in there, and emphasize how important the statin is to preventing heart attacks and strokes. When a patient tells me his/her symptoms are unbearable, I’m concerned about rhabdomyolysis and immediately stop the statin if the patient hasn’t already done so, and use the laboratory to further evaluate the patient.

(c) Educate the patient regarding benefits of a statin

(d) Let the patient decide (*buy in*) among several recommended approaches:

1. Lower the dose.
2. Change the dose to every other day with high-dose atorvastatin or rosuvastatin in our highest-risk patients (both have long half-lives and are as efficacious as daily dosing in reducing LDL-C, though efficacy on ASCVD outcomes has not been established).
3. Try pitavastatin or pravastatin, which have less toxic effects because of different pharmacokinetic properties.
4. Discontinue and rechallenge.

All of these have been shown to improve patient adherence to treatment in medical practice. Our favorite among those most refractory is rosuvastatin one to three times per week.

**Lifestyle**

Therapeutic lifestyle changes (TLC) should be considered first-line therapy for lowering LDL-C and reducing CVD risk. Several non-pharmacological approaches are effective in lowering LDL-C and CVD risk, including consumption of a heart-healthy diet, maintaining a normal weight, avoidance of tobacco products and regular exercise. TLC is particularly important for patients with SAMS who cannot tolerate statin therapy. Beyond statin rechallenge, working with patients to help them achieve a healthy lifestyle is an essential component of treating those with SAMS.

**Non-Statin Therapies**

Consideration should be given to adding non-statin agents to prevent ASCVD events among patients unable to tolerate statin therapy or able to tolerate only low doses or intermittent dosing. Our first choice is ezetimibe, usually well tolerated and generally lowering LDL-C by 15% to 25%, as an add-on to attempt to get your patient to acceptable LDL-C levels. A PCSK9 inhibitor should be considered to lower LDL-C in high-risk patients who cannot tolerate any statin. Bile acid sequestrants, fenofibrates and niacin may also be considered, but efficacy on ASCVD outcomes is not convincing.

**Conclusions**

SAMS are the most common cause for statin discontinuation or dose reduction. Most of the muscle symptoms reported in patients taking statins are not due to a statin-induced myopathy and can be overcome with an individualized approach to management. We should avoid statin discontinuation, which results in increased ASCVD risk, especially in high-risk patients.

When a patient presents with SAMS, we should verify that the patient truly cannot tolerate statin therapy. These efforts involve evaluation of symptoms after drug withdrawal and assessment of symptoms upon re-initiation with an alternative statin or lower doses of the same or a different statin.

**Correction**

Last month’s *Heartbeat*, “Heart of a Woman,” was based on a study from JACC called “Knowledge, Attitudes and Beliefs Regarding CVD.” In the study, the authors reported that heart disease in women was a top concern for only 39% of primary care doctors. After publication, the study authors issued a correction. In fact, 76% of doctors gave heart disease a concern score of 4 or 5 on a scale of 1 to 5, with 5 being “extremely concerned.”

**“Oh, I do love a mystery.”**

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