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Discussion

Statin-associated muscle symptoms EAS Consensus Panel paper focuses on this neglected patient group

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Statins are the cornerstone for lowering low-density lipoprotein cholesterol (LDL-C) for cardiovascular disease (CVD) prevention. Moreover, as reported recently, the benefits of statin therapy extend similarly to men and women [1]. While statins are safe and well tolerated, like all treatments, a proportion of patients report side effects.

Muscle symptoms are the most prevalent side effects reported with statin therapy, and one of the main reasons for non-adherence or discontinuation of treatment. While it is recognised that statins do cause a rare side effect known as myositis, defined as muscle symptoms in association with a substantially elevated serum creatine kinase [CK] concentration, most statin-associated muscle symptoms (SAMS) are not accompanied by marked CK elevation. Until recently, the issue of SAMS has been largely neglected. Increasing calls to focus international attention on this important clinical problem prompted the European Atherosclerosis Society (EAS) Consensus Panel to address this contentious issue, and, importantly, review what is known to date about the underlying pathophysiology.

According to lead author, Professor Erik Stroes, Department of Vascular Medicine, Academic Medical Center, Amsterdam, the Netherlands: 'While there has been tremendous progress in cardiovascular prevention using statin therapy, the persistently high cardiovascular risk in patients failing to adhere to statins due muscle symptoms has been overlooked. This EAS Consensus Paper has addressed this important unmet clinical need. The probability of SAMS being caused by statins is based on the nature of symptoms and their temporal relationship with statin initiation, discontinuation, and repetitive re-challenge. Optimal therapy for patients who have SAMS should combine a maximally tolerated, or even non-daily statin dose, together with non-statin-based lipid-lowering therapies in order to achieve LDL-C targets and optimise CVD benefit.'

The EAS Consensus Panel Statement is available to read at this link [http://eurheartj.oxfordjournals.org/content/early/2015/02/18/eurheartj.ehv043].

1. How common are SAMS?

Data from patient registries, as well as clinical experience, indicate that 7–29% of patients complain of SAMS [2–6]. In contrast, the proportion of patients reporting muscle symptoms in blinded randomised controlled trials has been lower, with myalgia rates similar in those on statin or placebo [7–9].

As far as the Panel is aware, the Effects of Statins on Muscle Performance (STOMP) study [10] is the only randomised, double-blind, placebo-controlled study that was specifically designed to examine the effect of statins on skeletal muscle symptoms and performance. Among the 420 statin-naïve subjects randomised to atorvastatin 80 mg daily or placebo for 6 months, 9.4% of the statin-treated and 4.6% of control subjects met the study definition of myalgia ($p = 0.054$). Yet even with this lower incidence of muscle complaints (compared with observational studies), a substantial

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number of patients will experience SAMS, given the widespread use of statins.

2. What is their typical presentation?

SAMS are typically characterised by muscle pain, weakness and aches, usually symmetrical and proximal, generally affecting large muscle groups including the thighs, buttocks, calves and back muscles. While these tend to occur early (within 4–6 weeks after starting a statin [10]), SAMS have been reported after many years of treatment. Symptoms may occur with an increase in statin dose or initiation of an interacting drug, and are often more common in physically active individuals [2]. SAMS often appear more promptly when patients are re-challenged with the same statin.

In most patients, SAMS are not accompanied by marked CK elevation [11,12].

3. Which patients are at risk?

Risk factors for SAMS are summarised in Table 1 [13]. Other factors that increase statin blood levels can increase the likelihood of developing SAMS [14]. These may include the use of high-dose statin therapy, polypharmacy, and drug–drug interactions, such as those involving gemfibrozil, macrolides, azole antifungal agents, protease inhibitors and immunosuppressive drugs), as well as inhibitors of cytochrome P450 isoenzymes, organic anion transport protein 1B1 [OATP 1B1], or P-glycoprotein 1 [P-gp] [15].

Note that the presence of an increasing number of factors is associated with greater risk for SAMS [14–16].

4. How can clinicians best diagnose SAMS?

Definitive diagnosis of SAMS is difficult because symptoms are subjective and there is no “gold standard” diagnostic test and no validated muscle symptom questionnaire.

The EAS Consensus Panel proposes a **clinical definition for the probability of SAMS**, based on the nature of the muscle symptoms (i.e. muscle pain or aching), and their temporal association with statin initiation, discontinuation, and response to repetitive statin re-challenge.

5. How can clinicians best manage SAMS?

If a patient complains of muscle symptoms, the EAS Consensus Panel proposes the following initial course of action:

- Evaluate risk factors which can predispose to statin-associated myopathy (see Table 1)
- Exclude secondary causes (especially hypothyroidism and other common myopathies such as polymyalgia rheumatica, or increased physical activity) (see Table 1)
- Consider concomitant medication: other commonly prescribed drugs may also cause muscle-related side effects; consider also drug–drug interactions that may increase statin blood levels and risk for SAMS (see Table 1)
- Review the indication for statin use.

Management of SAMS depends on the level of CK elevation, and the patient's CVD risk (see Table 2). Note that most patients who complain of muscle symptoms have normal or mild to moderately elevated CK levels (<4 X ULN) [17].

6. What are the therapeutic options?

Treatment options include both statin and non-statin based therapy, as summarised in Table 3 and Fig. 1.

Novel treatments, PCSK9 inhibitors and cholesteryl ester transfer protein (CETP) inhibitors, may offer future potential.

7. What insights do we have into the underlying pathophysiology of statin myopathy?

A number of mechanisms have been proposed (see Fig. 2) [25]. These include:

- reduced levels of non-cholesterol end-products of the mevalonate pathway
- reduced sarcolemmal and/or sarcoplasmic reticular cholesterol
- increased myocellular fat and/or sterols
- inhibition of production of prenylated proteins or guanosine triphosphate (GTP)ases

Table 1
Risk factors for SAMS.

- Patient factors: very elderly (>80 years), female, low body mass index, Asian descent
- Other predisposing factors: History of CK elevation or unexplained muscle/joint/tendon pain, inflammatory or inherited metabolic, neuromuscular/muscle defects, previous statin-induced myotoxicity, myopathy on other lipid-lowering therapy
- Diet/lifestyle: excessive physical activity, overconsumption of grapefruit or cranberry juice, alcohol or drug abuse
- Concurrent conditions: acute infection, impaired renal or hepatic function, diabetes, HIV (both the condition and HIV medications such as protease inhibitors), vitamin D deficiency, organ transplant recipients, severe trauma, biliary tree obstruction
- Surgery with high metabolic demands
- Genetic factors (see below)

Table 2
Management strategies for SAMS.

Patients with muscle symptoms and CK < 4 X ULN	
At low CVD risk	• Consider the benefits of therapeutic lifestyle changes versus risk of continuing the statin
At high CVD risk	• Consider the benefits of ongoing statin therapy versus the burden of muscle symptoms • Withdrawal of statin therapy followed by one or more re-challenges (after a washout) may help in determining causality • Consider an alternative statin, a statin at lowest dose, intermittent (i.e. non-daily) dosing of a highly efficacious statin, or the use of other lipid lowering medications
Patients with muscle symptoms and CK > 4 X ULN	
In patients at high CVD risk	• If CK is < 10 X ULN; continue the statin while monitoring CK. • If CK is > 10 X ULN and there is no secondary cause, stop the statin. • If CK levels subsequently decrease, consider re-starting statin at a lower dose, or start a lower dose of an alternative statin, while monitoring symptoms and CK. • If CK elevation persists, consider referral to a neuromuscular specialist for investigation of an underlying myopathy. • If rhabdomyolysis is suspected, do not re-start statin. These patients, and those with very high CK levels (e.g. > 40 X ULN), should be referred for assessment of renal damage. Non-statin LDL-lowering therapy may be considered.