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Statin-Associated Muscle Symptoms

Challenges and recommendations for diagnosis and management

Statin therapy is a cornerstone for the prevention and treatment of cardiovascular disease (CVD)[1]

However, SAMS or statin myositis are serious side-effects of statin use and often lead to discontinuation of statin therapy[1]

SAMS are marked by significant muscle damage and elevated serum creatine kinase (CK) concentrations[1]

Clinical presentations of SAMS[1,4]

Overall prevalence in 9.1% (8.0–10%) of the patients

High discontinuation rates (≤75%) within 2 years of stain therapy initiation

Negative impact on CVD treatment

Persistent muscle stiffness, ache, tenderness, or cramps

Factors that influence risk of SAMS[1]

Anthropometric factors[1]

- Age >80 years
- Female gender
- Low body mass index
- Asian descent

Concurrent conditions[1]

- Hypothyroidism
- Impaired renal/hepatic function
- Biliary tree obstruction
- Organ transplant
- Severe trauma
- HIV infection
- Diabetes mellitus
- Vitamin D deficiency

Related history[1]

- History of CK elevation or myopathy
- History of pre-existing or unexplained muscle/joint/tendon pain
- Neuromuscular/muscle defects

Surgery[1]

- Surgery with high metabolic demands

Additional factors[1]

- Excessive physical activity
- Dietary effects
- Excessive alcohol use
- Drug abuse

Genetics[1]

- Polymorphisms in genes encoding cytochrome P450 isoenzymes or drug transporters

Key points about SAMS for clinicians[1]

What are SAMS?

- Muscle pain, weakness, and aches that affect the thighs, buttocks, calves, and back muscles

When do SAMS occur?

- They occur early (within 4–6 weeks of initiation), after an increase in statin dose, or if initiated with another interacting drug

What determines the management of SAMS?

- The magnitude of CK elevation and the patient's global cardiovascular risk

Who is at risk of SAMS?

- Individuals who are very elderly (>80 years), female, or of Asian descent; individuals with a low body mass index, a history of muscle disorders or comorbidities (e.g., acute infection, impaired renal or hepatic function, diabetes, HIV), or concomitant interacting medications

How does the EAS Consensus Panel define SAMS?

- Based on the nature of muscle symptoms, their association with statin initiation, discontinuation, and response to periodic statin re-challenge

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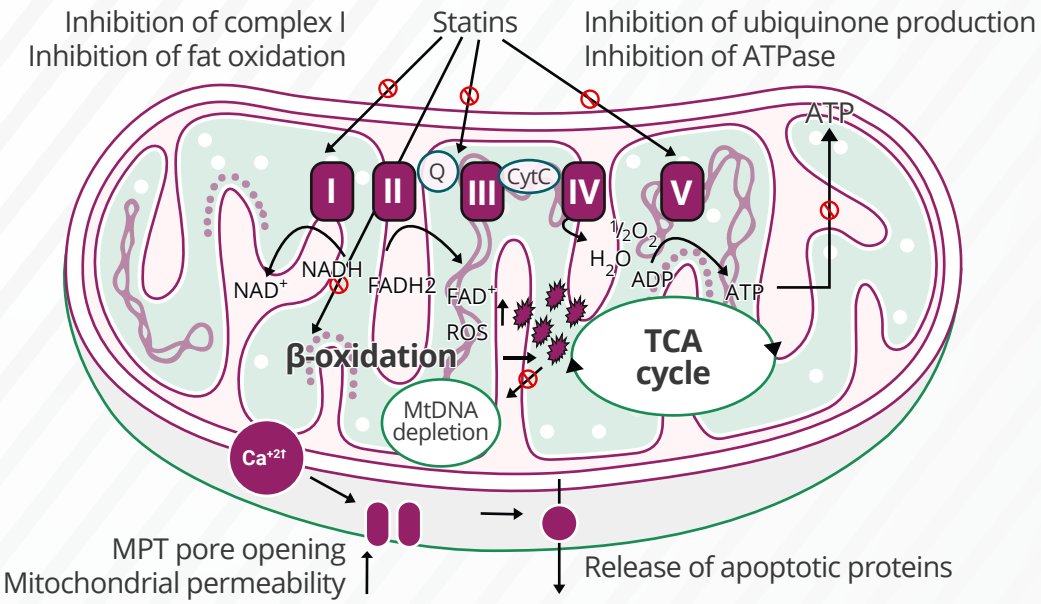
Abnormal mitochondrial function has been reported in various statin users with and without symptoms of myopathy[1]

Possible mechanism and role of mitochondria in the pathophysiology of statin induced myopathy[1]



The statin-muscle mitochondrial interaction may result in[1]

- Reduced production of prenylated proteins, including ubiquinone → Attenuation of electron transfer between electron transport chain complexes I, III, and II
- Subnormal levels of farnesyl pyrophosphate and geranylgeranyl pyrophosphate → Impaired cell growth
- Low membrane cholesterol content → Negative impact on membrane fluidity and ion channels
- Triggered calcium release from the sarcoplasmic reticulum → Impaired calcium signalling

How are SAMS diagnosed?

Definitive diagnosis of SAMS is difficult due to the subjective nature of symptoms[1]

Definitions of SAMS proposed by the European Atherosclerosis Society consensus panel for diagnosis[1]

Symptom	Biomarker	Comment
Muscle symptoms	Normal CK	Myalgia may or may not be related to statin therapy → Causality uncertain
Muscle symptoms	CK>ULN<4X ULN CK>4<10X ULN	Minor CK elevations due to increased physical activity or statin use → Increased risk of severe underlying muscle problems
Muscle symptoms	CK>10X ULN	Myopathy or pain usually generalised and proximal with muscle tenderness/weakness → Association with underlying muscle disease likely
Muscle symptoms	CK>40X ULN	Defined as "rhabdomyolysis" when associated with renal impairment and/or myoglobinuria
None	CK>ULN<4X ULN	Raised CK may be related to statin therapy or exercise → Evaluation of thyroid function recommended
None	CK>4X ULN	Clinical significance unclear if CK increase is persistent

ULN: upper limit of the normal range

Methodology proposed by the National Lipid Association Statin Muscle Safety Task Force to assess the likelihood that a patient's myalgia is associated with statin use[3]

Statin-Associated Muscle Symptom Clinical Index (SAMS-CI) includes ratings on[3]

- Location and patterns of muscle symptoms
- Timing of symptoms related to
  - Starting
  - Stopping
  - Rechallenging

of statins

Advantages[3]

- Easily interpreted scores and proven inter-rater reliability
- Efficient detection of SAMS in clinical practice
- Optimised treatment
- Useful tool for clinical research

SAMS-CI check list for clinicians[3]

Instructions

- Use this checklist to treat 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 previously used statin, at the same or a different dose
- Muscle symptoms may include aches, cramps, heaviness, discomfort, weakness, or stiffness

Interpret overall score considering 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

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, enter record the highest number)

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

Enter score ☐

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

<4 weeks	3
4–12 weeks	2
>12 weeks	1

Enter score ☐

C. Timing 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

Enter score ☐

Rechallenge the patient with a statin regimen (even if same statin compound or regimen as above) **and complete final question**

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

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

Enter score ☐

All four scores above must be entered before totaling

Total ☐

Regarding the statin regimen before the most recent regimen

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

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

Enter score ☐

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

<4 weeks	3
4–12 weeks	2
>12 weeks	1

Enter score ☐

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

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

Enter score ☐

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 week	1
>12 weeks or similar symptoms did not reoccur	0

Enter score ☐

All four scores above must be entered before totaling

Total ☐

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

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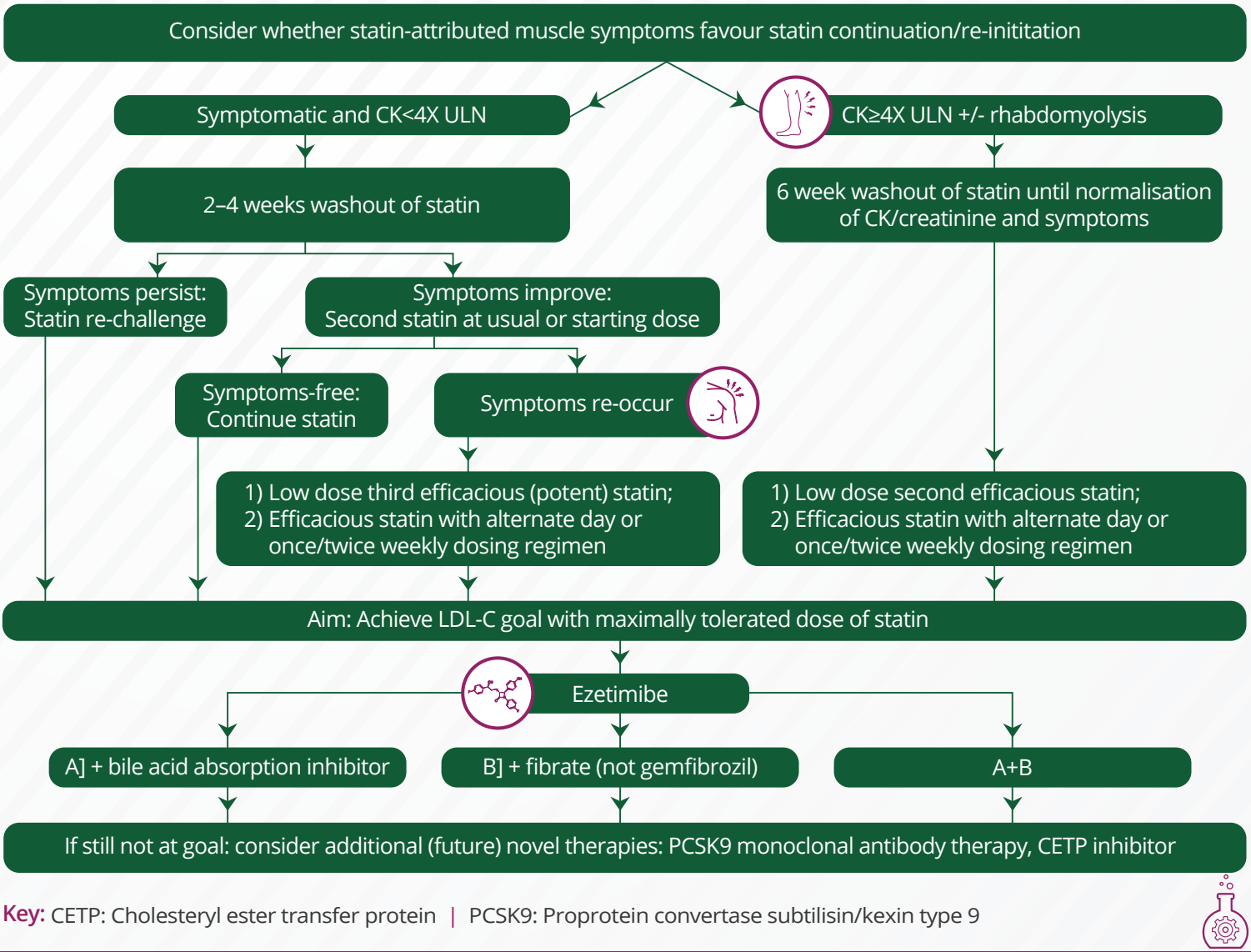
Management of patients with SAMS[1]



Key: CETP: Cholesteryl ester transfer protein | PCSK9: Proprotein convertase subtilisin/kexin type 9

Take-home messages

- Statin therapy offers vast health benefits that far outweigh the corresponding risks, such as a significant reduction in the risk of first and recurrent CVD events in patients with and without diabetes, stroke, and coronary atheroma
- Statin therapy triggers SAMS in many patients, but the manifesting side effects are clinically manageable
- Effective clinical management of SAMS is necessary to decrease patient non-adherence
- SAMS-CI provides better clinical insights for statin therapy management with high efficacy

References

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3. Rosenson, R. S., Miller, K., Bayliss, M., Sanchez, R. J., Baccara-Dinet, M. T., Chibedi-De-Roche, D., … & Jacobson T.A. (2017). The Statin-Associated Muscle Symptom Clinical Index (SAMS-CI): Revision for Clinical Use, Content Validation, and Inter-rater Reliability. *Cardiovasc Drugs and Therapy, 31*(2), 179–186.
4. Bytyci, I., Bajraktari, G., Sahebkar, A., Penson, P. E., Rysz, R., & Banach, M. Y. (2021). The prevalence of statin intolerance worldwide: a systematic review and meta-analysis with 4,143,517 patients. *European Heart Journal, 42*(1).

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