# 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)

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

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

## Clinical presentations of SAMS

- Overall prevalence in 9.1% (8.0–10%) of the patients
- High discontinuation rates (≤75%) within 2 years of statin therapy initiation
- Persistent muscle stiffness, ache, tenderness, or cramps
- Negative impact on CVD treatment

## Factors that influence risk of SAMS

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

### Concurrent conditions
- Hypothyroidism
- Impaired renal/hepatic function
- Biliary tree obstruction
- Organ transplant

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

### Surgery
- Surgery with high metabolic demands

### Additional factors
- Excessive physical activity
- Dietary effects
- Excessive alcohol use
- Drug abuse

### Genetics
- Polymorphisms in genes encoding cytochrome P450 isoenzymes or drug transporters

## Key points about SAMS for clinicians

### 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\(^1\)**

- Inhibition of complex I  
- Inhibition of fat oxidation  
- Statins  
- Inhibition of ubiquinone production  
- Inhibition of ATPase

**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**

- **Low membrane cholesterol content**  
  → **Negative impact on membrane fluidity and ion channels**

- **Subnormal levels of farnesyl pyrophosphate and geranylgeranyl pyrophosphate**  
  → **Impaired cell growth**

- **Triggered calcium release from the sarcoplasmic reticulum**  
  → **Impaired calcium signalling**

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**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\(^1\)**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Biomarker</th>
<th>Comment</th>
</tr>
</thead>
</table>
| 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

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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.

**Statin-Associated Muscle Symptom Clinical Index (SAMS-CI)** includes ratings on:
- Location and patterns of muscle symptoms
- Timing of symptoms related to:
  - Starting
  - Stopping
  - Rechallenging of statins

### SAMS-CI check list for clinicians

**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?**

<table>
<thead>
<tr>
<th>One</th>
<th>Two or more</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete the questions on the left side of this page</td>
<td>Complete the questions on the right side of this page</td>
</tr>
</tbody>
</table>

#### Regarding this statin regimen

<table>
<thead>
<tr>
<th>A. Location and pattern of muscle symptoms (If more than one category applies, enter record the highest number)</th>
<th>Enter score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symmetric, hip flexors or thighs</td>
<td>3</td>
</tr>
<tr>
<td>Symmetric, calves</td>
<td>2</td>
</tr>
<tr>
<td>Symmetric, proximal upper extremity</td>
<td>2</td>
</tr>
<tr>
<td>Asymmetric, intermittent, or not specific to any area</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B. Timing of muscle symptom onset in relation to starting statin regimen</th>
<th>Enter score</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;4 weeks</td>
<td>3</td>
</tr>
<tr>
<td>4–12 weeks</td>
<td>2</td>
</tr>
<tr>
<td>&gt;12 weeks</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>C. Timing muscle symptom improvement after withdrawal of statin (If patient is still taking statin, stop regimen and monitor symptoms)</th>
<th>Enter score</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2 weeks</td>
<td>2</td>
</tr>
<tr>
<td>2–4 weeks</td>
<td>1</td>
</tr>
<tr>
<td>No improvement after 4 weeks</td>
<td>0</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>D. Timing of recurrence of similar muscle symptoms in relation to starting regimen</th>
<th>Enter score</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;4 weeks</td>
<td>3</td>
</tr>
<tr>
<td>4–12 week</td>
<td>1</td>
</tr>
<tr>
<td>&gt;12 weeks or similar symptoms did not reoccur</td>
<td>0</td>
</tr>
</tbody>
</table>

**All four scores above must be entered before totaling**

<table>
<thead>
<tr>
<th>Total score</th>
<th>2–6</th>
<th>7–8</th>
<th>9–11</th>
</tr>
</thead>
<tbody>
<tr>
<td>Likelihood that the patient's muscle symptoms are due to statin use</td>
<td>Unlikely</td>
<td>Possible</td>
<td>Probable</td>
</tr>
</tbody>
</table>

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Management of patients with SAMS

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**


**Key**

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

**Take-home messages**

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