Statin-Associated Muscle Symptoms (SAMS): Impact on Statin Therapy

European Atherosclerosis Society Consensus Panel Statement on Assessment, Aetiology and Management

Stroes ES et al. Eur Heart J 2015;36:1012-1022
Clinical update

Statin-associated muscle symptoms: impact on statin therapy—European Atherosclerosis Society Consensus Panel Statement on Assessment, Aetiology and Management

Statin intolerance: 
A major cause of poor adherence which impacts the cardiovascular benefits of statins
Poor statin adherence increases mortality

>3-fold increase in all-cause mortality

>4-fold increase in cardiac mortality

Kim MC et al. Am J Cardiol 2015;115:1-7
• Statin associated muscle symptoms (SAMS): One of the main reasons for statin non-adherence or discontinuation
RCT: No difference in myalgia rates

35 trials; 74,000 patients; 17 months mean follow-up

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Trials</th>
<th>Statin *</th>
<th>Placebo</th>
<th>HR</th>
<th>( &amp; 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myalgia</td>
<td>21</td>
<td>15.4%</td>
<td>18.7%</td>
<td>0.99</td>
<td>(0.96-1.03)</td>
</tr>
<tr>
<td>CK elevation</td>
<td>16</td>
<td>0.9%</td>
<td>0.4%</td>
<td>1.18</td>
<td>(0.89-1.56)</td>
</tr>
<tr>
<td>Rhabdomyolysis</td>
<td>20</td>
<td>0.17%</td>
<td>0.12%</td>
<td>1.09</td>
<td>(0.65-1.83)</td>
</tr>
</tbody>
</table>

*Atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin, but excluding cerivastatin

Kashani A et al. Circulation 2006;114:2788-97
PRIMO: Observational, retrospective study

<table>
<thead>
<tr>
<th>Statin</th>
<th>Dose (mg/d)</th>
<th>% with muscle symptoms</th>
<th>Odds ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pravastatin</td>
<td>40</td>
<td>10.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>40-80</td>
<td>14.9</td>
<td>1.28 [1.02–1.60]</td>
<td>0.035</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>40-80</td>
<td>18.2</td>
<td>1.78 [1.39–2.29]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>80</td>
<td>5.1</td>
<td>0.33 [0.26–0.42]</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

7924 patients treated with high dose statin for >3 months before the study or discontinued/modified high dose statin due to muscular side effects in last 3 months

**Overall 10.5% reported muscle symptoms**

Why the discrepancy between RCT and Observational Studies?

RCT:
- Exclusion of patients unlikely to adhere or using interacting drugs?
- Lack of dedicated questionnaires into muscle complaints?

Observational studies:
- Patients aware of muscle symptoms with statin use due to package inserts / doctors warning / media attention?
- *But lack of placebo for comparison*
Incidence of SAMS using a RCT design

Statins on Skeletal Muscle Function and Performance (STOMP)

Subjects (n=440)
- Men and women
- >20 years
- No prior statin use

Design
- Randomised, double blind
- 80 mg atorvastatin vs. placebo for 6 months

Muscle function
- Handgrip strength
- Elbow flexor/extensor
- Knee flexor/extensor

Aerobic performance (VO₂Max)
Physical activity (accelerometer)
Muscle symptoms - called twice monthly

Parker BA et al. Circulation 2013; 127:96-103
Assessment made before and after atorvastatin 80 mg or placebo, administered for 6 months to 420 healthy, statin-naive subjects.

Parker BA et al. Circulation 2013; 127:96-103
How to identify SAMS
### Defining SAMS

- There is no “gold standard” diagnostic test

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>CK</th>
<th>When to consider SAMS?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle symptoms</td>
<td>Normal</td>
<td>Often called myalgia; may be statin-related</td>
</tr>
<tr>
<td>Muscle symptoms</td>
<td>&gt; ULN and &lt;4 x ULN</td>
<td>Consider increased exercise; may be statin-related</td>
</tr>
<tr>
<td>Muscle symptoms</td>
<td>&gt;4 &lt;10 X ULN</td>
<td></td>
</tr>
<tr>
<td>Muscle symptoms</td>
<td>&gt;10 X ULN</td>
<td>Often called myositis or ‘myopathy’ even in the absence of a muscle biopsy;</td>
</tr>
<tr>
<td>Muscle symptoms</td>
<td>&gt;40 X ULN</td>
<td>Associated with statin or underlying muscle disease</td>
</tr>
<tr>
<td>None</td>
<td>&gt; ULN and &lt;4 X ULN</td>
<td>May be statin related</td>
</tr>
<tr>
<td>None</td>
<td>&gt;4 X ULN</td>
<td>Clinical significance unknown</td>
</tr>
</tbody>
</table>

Stroes ES et al. Eur Heart J 2015;36:1012-1022
Assessing SAMS

• Usually symmetrical and proximal

• Affect large muscle groups (thighs, buttocks, calves and back muscles)

• Usually occur early (within 4–6 weeks) of starting statin; but can occur after many years of treatment.

• May occur with an increase in statin dose, initiation of an interacting drug, or increase in physical activity

• May appear more rapidly if patient is re-challenged with a statin

Stroes ES et al. Eur Heart J 2015;36:1012-1022
Consider risk factors for SAMS

- >80 years, female, low BMI, Asian descent
- Excess physical activity
- Excess alcohol or grapefruit or cranberry juice
- Acute infection, hypothyroidism, impaired renal or hepatic function, organ transplant recipient, trauma, HIV, diabetes
- Vitamin D deficiency
- Surgery with high metabolic demands
- History of CK elevation or unexplained muscle/joint/tendon pain, or myopathy on another lipid-lowering therapy
- Inflammatory or inherited metabolic, neuromuscular/muscle disorders
- Polymorphisms in cyt P450 isoenzymes or drug transporters

Stroes ES et al. Eur Heart J 2015;36:1012-1022
Consider factors that influence statin pharmacokinetics

- Pre-existing risk factors and co-morbidities
- High-dose statin therapy
- Polypharmacy
- Drug-drug interactions (e.g. gemfibrozil, macrolides, azole antifungal agents, protease inhibitors and immunosuppressive drugs, inhibitors of CYP450 isoenzymes, OATP 1B1, or P-gp)
- Pharmacogenetics

Stroes ES et al. Eur Heart J 2015;36:1012-1022
How to manage SAMS
Step 1: Counsel for benefit/harm

Allow sufficient time to:

• Counsel the patient about the cardiovascular benefit of statins

• Re-emphasise the long-term safety and absence of ‘organ damage’ with statins, even when discomfort/pain is present

• Explain the high likelihood of successful re-challenge with statin

Stroes ES et al. Eur Heart J 2015;36:1012-1022
Step 2: Use a standardised approach

Consider if statin-attributed muscle symptoms favour statin continuation / reinitiation

Symptomatic & CK <4 X ULN

- 2-4 weeks washout of statin
  - Symptoms persist: statin re-challenge
  - Symptoms improve: Second statin at usual or starting dose

  - Symptom-free: Continue statin
  - Symptoms re-occur
    - 1) Low dose third efficacious (potent) statin;
    - 2) Efficacious statin with alternate day or once/twice weekly dosing regimen

CK ≥4 X ULN +/- rhabdomyolysis

- 6 week washout of statin until normalisation of CK/creatinine and symptoms

Aim: achieve LDL-C goal* with maximally tolerated dose of statin

Ezetimibe

- A] + bile acid absorption inhibitor
- B] + fibrate (not gemfibrozil)
- A + B

If still not at goal: consider additional (future) novel therapies: PCSK9 monoclonal antibody therapy, CETP inhibitor

Stroes ES et al. Eur Heart J 2015;36:1012-1022
Management of SAMS
Muscle symptoms and CK < 4 X ULN

<table>
<thead>
<tr>
<th>CVD risk</th>
<th>Management strategies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>• Consider therapeutic lifestyle changes vs. risk of continuing statin</td>
</tr>
</tbody>
</table>
| High     | • Consider benefits of ongoing statin therapy vs. burden of muscle symptoms  
          | • Withdraw statin, followed by one or more re-challenges (after a washout)  
          | • 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 |

Stroes ES et al. Eur Heart J 2015 ;36:1012-1022
**Management of SAMS**
**Muscle symptoms and CK > 4 X ULN**

<table>
<thead>
<tr>
<th>Patients at high CVD risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>CK &lt; 10 X ULN</td>
</tr>
<tr>
<td>CK &gt; 10 X ULN and no secondary cause, stop the statin</td>
</tr>
<tr>
<td>• If CK levels decrease, consider re-starting statin at a lower dose, or start a lower dose of an alternative statin. Monitor symptoms and CK</td>
</tr>
<tr>
<td>• If CK elevation persists, consider referral to a neuromuscular specialist for investigation of an underlying myopathy</td>
</tr>
<tr>
<td>• If rhabdomyolysis is suspected, do not re-start statin; refer for assessment of renal damage</td>
</tr>
</tbody>
</table>

Stroes ES et al. Eur Heart J 2015 ;36:1012-1022
Treatment options in SAMS

Statin

Non statin

- First choice: ezetimibe
- Bile acid sequestrants or fibrates in combination with ezetimibe

Nutraceuticals

- Viscous fibre (mainly psyllium, 10 g daily) and foods with added plant sterols/stanols

Stroes ES et al. Eur Heart J 2015;36:1012-1022
What role for complementary therapies?

- Various complementary therapies have been suggested, including **coenzyme Q10 (ubiquinone)**, and **vitamin D supplements**
- None are supported by RCT evidence

- **Red yeast rice (Monascus purpureus)** has been shown to reduce LDL-C levels by 20-30%.
- However, in the absence of robust evidence for long-term efficacy and tolerability, and the lack of standardisation of current preparations, this is currently not recommended.
- Red yeast rice can also induce SAMS due to the statin-like content (**monacolin K**, similar to **lovastatin**)

Stroes ES et al. Eur Heart J 2015;36:1012-1022
Step 3: Rechallenge the patient

Most patients rechallenged can tolerate statins long-term

- Retrospective cohort study in 107,835 patients
- 18,778 (17.4%) patients had statin-related events. Statins were discontinued at least temporarily by 11,124 of these patients

- On re-challenge:
  - 92.2% were still on a statin >12 months later
  - 47.6% were on the same statin to which they had the statin-related adverse event

Pathophysiology of SAMS
Effects potentially involved in statin-related muscle injury/symptoms

Role of mitochondrion
Possible targets of statins in the mitochondrion with deleterious effects on muscle function

Stroes ES et al. Eur Heart J 2015;36:1012-1022
Potential mechanisms implicated in mitochondrial toxicity

Effect of statins on mitochondria

- Ubiquinone attenuates electron transfer complex I-III
- Prenylation ETC proteins
- Farnesyl/geranylgeranyl-PP leading to impaired growth / autophagy
- Membrane cholesterol affecting membrane fluidity and ion channels
- Calcium release from s. reticulum leading to impaired calcium signalling

Needham M et al. Neuromuscul Disord. 2014;24(1):4-15
Stroes E et al. Eur Heart J 2015;36:1012-1022
Summary

SAMS is a major reason for ‘referral’

- Leading to statin non-adherence / discontinuation
- Contributing to decreased CVD-benefit from statins

‘Golden’ principles in management of SAMS

- Always strive to continue ‘maximally-tolerated’ statin therapy
- Always apply repetitive de-/re-challenges