Statin Intolerance Pathway

Person at high CVD risk reports potential intolerance to recommended high intensity statin treatment

Consider other potential side effects for statins
• Be aware of Statin Reluctance and Nocebo Effect
• See ‘Person Centred Care’ box at page 2

Muscular symptoms not related to statins
Non SRM: Consider other causes e.g. PMR, Vit D deficiency. Check bone profile, Vit D, CRP.

Tolerable symptoms
No clinical concern
CK < 4x ULN

Improvement within 2 weeks
Resolved within 6 weeks
Patient happy to continue

Non-SRM. Consider other causes
Wait for 2 weeks before rechallenge

Reassess and restart with lower dose / alternative statin (see page 2 - ‘Statin-based Approaches’)
Offer low or moderate dose of a higher intensity statin (Atorvastatin 10 or 20 mg OD, or Rosuvastatin 5 or 10mg OD)

No recurrence of muscle symptoms
Titrate at 8 weeks intervals to achieve appropriate targets

Symptoms tolerable
Treatment effective, goals achieved
Patient happy to continue

New onset or worsening of muscle symptoms since starting statins? (pain, tenderness or weakness)

Symptoms typical for Statin Related Muscle toxicity (SRM)*?

Measure Creatine Kinase (CK)
Assess severity of symptoms +/- repeat baseline assessment**

Intolerable symptoms
and/or clinical concern
and/or CK > 4x and < 10x ULN

Stop statin for 4-6 weeks
Document time to symptom onset and time to resolution

Has CK normalised?

Yes

Renal function stable/normal eGFR

No

Consider Statin induced necrotizing autoimmune myopathy (SINAM)

CK > 10x and < 50x ULN

CK > 50x ULN

Stop statin and consider Rhabdomyolysis

Seek specialist advice and consider PCSK9i (NICE TA 393, 394)

Consider
Statin induced necrotizing autoimmune myopathy (SINAM)

Intolerable symptoms
and/or clinical concern
and/or CK > 4x and < 10x ULN

No recurrence of muscle symptoms
Titrate at 8 weeks intervals to achieve appropriate targets

Recurrence of muscle symptoms
Short time to onset
Symptoms intolerable

Consider further options
For example commence ezetimibe, or ezetimibe with bempedoic acid or inclisiran or PCSK9i as required, depending on eligibility (TA694, TA733, TA 393, TA394) see page 2 - ‘Statin-based Approaches’

If not effective

This resource relates to NICE guidance:
CG181, CG71, TA385, TA393/394, TA694, TA733, QS100

**Consider other causes if new onset of muscle symptoms of >2 weeks duration in a person previously tolerant of statin therapy for > 3months

Abbreviations
CK = Creatine Kinase
CRP = C-Reactive protein
eGFR = Estimated glomerular filtration rate
PMR = Polymyalgia rheumatica
SINAM = Statin induced necrotizing autoimmune myopathy
SRM = Statin related muscle toxicity
ULN = Upper Limit of Normal Range
Vit D = Vitamin D

Please refer to page 2 for more details
**Introduction**

- Statins are the cornerstone for prevention and treatment of cardiovascular (CV) disease with a substantial evidence of reduction of morbidity and mortality. Refer to Lipid Management Pathway and related NICE guidelines (CG181, CG71) for guidance on initiation, titration and monitoring of statin therapy.
- In clinical trials, statins were found to be largely well tolerated (often with a similar adverse effect [AE] profile to placebo), however this is not reflected in clinical practice where up to 75% of people started on a statin will discontinue treatment within 2 years.
- Stopping statin therapy is associated with an increased risk of major CV events and there is growing concern that clinicians are labelling patients as ‘statin intolerant’ too quickly. Indeed statin discontinuation is significantly associated with negative media coverage.

**Definition of Statin Intolerance**

- Intolerance to initial statin therapy is defined by NICE as the presence of clinically significant adverse effects that represent an unacceptable risk to the patient or that may reduce compliance with therapy.
- Other definition: any adverse event (AEs) considered unacceptable by the patient, and/or some laboratory abnormalities, both attributed to statin treatment and leading to its discontinuation.

**Statin-associated muscle symptoms (SAMS)**

- SAMS are one of the principal reasons for statin non-adherence and/or discontinuation. However, not all such symptoms should lead to a label of ‘statin intolerance’ as they may not be truly statin related muscle toxicity (SRM) as demonstrated by resolution on de-challenge and recurrence with re-challenge.

**Non-SRM related musculoskeletal symptoms (Non SRM)**

- If patients report symptoms that are not typical of SRM (e.g. asymmetric distribution, failure to resolve with de-challenge despite normal CK) consider other musculoskeletal disorders, metabolic, degenerative or inflammatory e.g. Vitamin D deficiency, polymyalgia rheumatica. Check Bone profile, Vit D, CRP.

**Considerations when starting a statin to reduce risk of SRM**

- Check baseline thyroid, liver and renal function, any potential drug interactions, and address (e.g. drug interactions).
- Evaluate and identify any risk factors and address (e.g. exercise, reducing weight)
- Listen to the concerns of each patient.
- Reinforce healthy lifestyle habits (e.g. exercise, reducing weight)
- Address any issues/concern.
- Make sure the patient understands the importance of adherence.
- Advise patients to contact you if they experience muscle symptoms
- Be aware of “nocebo effect” and “statin reluctance”
- Reinforce healthy lifestyle habits (e.g. exercise, reducing weight)
- Listen to the concerns of each patient.
- Explain LDL-C targets and strategies to lower LDL-C/non-HDL-C
- Discuss options to reduce LDL-C/ non-HDL-C with pros and cons
- Explain the benefits of statins
- Evaluate and identify any risk factors and address (e.g. drug interactions)
- Work with patients to identify and agree best options and next steps
- Follow up on agreed plan and address any issues/concern.
- Advise patients to contact you if they experience muscle symptoms
- Ongoing patient education and regular review helps addressing concerns around medicine safety and underline the importance of adherence.

**SRM Phenotype Classification (SRM)**

**SRM 0**

- **CK elevation >4x ULN**
- **No muscle symptoms**

**SRM 1**

- **Myalgia, tolerable**
- **190/100,000**
- **Patient-years**
- **0.3-3.3%**
- **Muscle symptoms without CK elevation**

**SRM 2**

- **Myalgia, intolerable**
- **0.2-21/000**
- **Muscle symptoms, CK >4x ULN, complete resolution on dechallenge**

**SRM 3**

- **Myopathy**
- **5/100,000**
- **Patient-years**
- **CK elevation >4x ULN <10x ULN, muscle symptoms, complete resolution on dechallenge**

**SRM 4**

- **Severe myopathy**
- **0.11%**
- **CK elevation >10x ULN <50x ULN, muscle symptoms, complete resolution on dechallenge**

**SRM 5**

- **Rhabdomyolysis**
- **0.1-8.4/100,000**
- **CK elevation >10x ULN with evidence of renal impairment + muscle symptoms or CK >50x ULN**

**SRM 6**

- **Autoimmune-mediated necrotizing myositis (SIMAN)**
- **≥2/million per year**
- **Detection of HMGCR antibodies, HMGCR expression in muscle biopsy showing autoimmune myositis, incomplete resolution on dechallenge**

**SRM Phenotype Incidence Definition**

- **SRM 0**
  - CK elevation >4x ULN
  - No muscle symptoms

- **SRM 1**
  - Myalgia, tolerable
  - 190/100,000 Patient-years
  - 0.3-3.3%
  - Muscle symptoms without CK elevation

- **SRM 2**
  - Myalgia, intolerable
  - 0.2-21/000
  - Muscle symptoms, CK >4x ULN, complete resolution on dechallenge

- **SRM 3**
  - Myopathy
  - 5/100,000 Patient-years
  - CK elevation >4x ULN <10x ULN, muscle symptoms, complete resolution on dechallenge

- **SRM 4**
  - Severe myopathy
  - 0.11%
  - CK elevation >10x ULN <50x ULN, muscle symptoms, complete resolution on dechallenge

- **SRM 5**
  - Rhabdomyolysis
  - 0.1-8.4/100,000
  - CK elevation >10x ULN with evidence of renal impairment + muscle symptoms or CK >50x ULN

- **SRM 6**
  - Autoimmune-mediated necrotizing myositis (SIMAN)
  - ≥2/million per year
  - Detection of HMGCR antibodies, HMGCR expression in muscle biopsy showing autoimmune myositis, incomplete resolution on dechallenge

**Non-muscle related statin side effects**

May vary between different statins. In clinical trials some side effects often associated with statins are not statistically different from placebo.

**Most commonly reported**

- Gastrointestinal disturbance and asymptomatic increases in hepatic transaminases (ALT or AST). May affect up to 1 in 10 statin users.
- Rarer side effects include: Hepatotoxicity, new onset Type 2 Diabetes (benefits outweigh risk, do not stop statin), Renal insufficiency, proteinuria, Neurocognitive and neurological impairments (no apparent link from RCTs), Intracranial haemorrhage (conflicting evidence, benefit outweigh possible harm), Intestinal lung disease, Pancreatitis, Skin disorders including alopecia, Lupus-like reactions, Sleep disturbance, Headache, dizziness, depression, sexual dysfunction.

**Management:** If symptoms appear statin related, consider de-challenge and re-challenge or change to a different statin (e.g. hydrophilic instead of lipophilic).

- Liver enzyme abnormalities - minor increases in liver enzymes (<2x ULN) may be seen within the first three months of statin therapy (temporary discontinuation and further assessment is warranted if levels exceed 3x ULN).

**Recommendations:**

- Advise patients to contact you if they experience muscle symptoms
- Ongoing patient education and regular review helps addressing concerns around medicine safety and underline the importance of adherence.

**References:**

- AFMC 
- Pathway endorsed by NICE Dec 2021. Please refer to the Lipid Management Pathway and Full List of References (click here)

**Person-centred approach to address statin intolerance**

- **Initial Consultation**
  - Be aware of “nocebo effect” and “statin reluctance”
  - Reinforce healthy lifestyle habits (e.g. exercise, reducing weight)
  - Listen to the concerns of each patient.
  - Explain LDL-C targets and strategies to lower LDL-C/non-HDL-C
  - Discuss options to reduce LDL-C/ non-HDL-C with pros and cons
  - Explain the benefits of statins
  - Evaluate and identify any risk factors and address (e.g. drug interactions)
  - Work with patients to identify and agree best options and next steps

- **Follow up**
  - Follow up on agreed plan and address any issues/concern.
  - Advise patients to contact you if they experience muscle symptoms
  - Ongoing patient education and regular review helps addressing concerns around medicine safety and underline the importance of adherence.

**Statin-based approaches to manage muscle symptoms**

- **Adopt person-centred approach as described above**
- **Therapy with a lower dose statin is preferred to no statin**
- **Apply a repetitive “De-Challenge” – “Re-Challenge” approach to establish if symptoms are caused by a statin(s) and the best statin regimen for each patient.**
- **Switch to a different statin or re-challenge with the same statin using a lower dose or frequency (interruption of statin dosing)**
- **Patients who do not tolerate statins on a daily basis, alternate day or twice-weekly dosing is a good option.**
- **Rovastatin and atorvastatin have longer half-lives, permitting their use on a non-daily regime.**
- **Adding ezetimibe to a lower dose statin may be better tolerated with reduced risk of LDL-C/ non-HDL-C.**
- **Once a new regime is tolerated, dose / frequency can be up-titrated slowly to achieve LDL-C / non-HDL-C goals with minimal or no muscle complaints.**
  - It is important to note that cardiovascular benefits have not been proven for all the above approaches but any reduction of LDL-C / non-HDL-C is beneficial.

**References:**

- Refer to the ACC Lipid Management Algorithm. (click here)
- Consider ezetimibe. (NICE TA 385) therapy as per algorithm
- Consider ezetimibe combined with bempedoic acid (NICE TA 694) as per algorithm
- Consider inclisiran if eligible for treatment according to NICE TA 733
- Consider PCSK9i if eligible for treatment according to NICE TA 393, 394