SUFFOLK AND NORTH EAST ESSEX: STATIN INTOLERANCE PATHWAY

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

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

New onset or worsening of muscle symptoms since starting Statins? (Pain, tenderness, or weakness)

NO → Consider other potential side effects for statins
- Be aware of **Statin Reluctance** and **Nocebo Effect**
- See '***Person Centred Care***' *b*ox at page 2

YES

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

NO → Muscular symptoms not related to Statins → Non SRM: Consider other causes e.g. PMR, Vitamin D Deficiency. Check bone profile,

*Symmetrical pain and/or weakness in large proximal muscle groups, worsened by exercise

YES

Measure Creatinine Kinase (CK) and renal function
Assess severity of symptoms
+/- repeat baseline assessment**

Tolerable symptoms
No clinical concern
CK < 4x ULN

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

NO → **Stop statin for 4-6 weeks**
Document time to symptom onset and time to resolution monitoring over 48-72 hours. **Seek specialist advice via email**

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

Has CK normalised?

NO → Consider **Statin induced necrotizing autoimmune myopathy (SINAM)** → **Seek specialist advice and consider** PCSK9i (NICE TA 393, 394)

Have symptoms resolved?

NO → Non-SRM. **Consider other causes**

Has the patient been **symptom free for at least 2 weeks?**

NO → Wait 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

Symptoms tolerable.
Treatment effective, goals achieved.
Patient happy to continue.

Recurrence of muscle symptoms.
Short time onset.
Symptoms intolerable.

NO → **Consider further options.**
(For example add ezemtimibe, or give as monotherapy and if needed add bempedoic acid) see **page 2- 'Statin-based approaches'**

If not effective → **Seek specialist advice and consider** PCSK9i (NICE TA 393, 394)

CK ≥ 10x and < 50x ULN

YES → **Withhold statin**
Check Renal function
stable/normal eGFR

NO → Stop statin and consider **Rhabdomyolysis**

CK ≥ 50x ULN

Urgently
- **Primary care or outpatients**: Refer patient to MAU via consultant on-call.
- **Acute admission**: If admitted as an inpatient, review and seek specialist advice

Abbreviations
CK = Creatinine 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

Suffolk and North East Essex Area Prescribing Committee (SNEE APC)
NHS Ipswich and East Suffolk CCG (IESCCG), NHS North East Essex CCG (NEECCG), NHS West Suffolk CCG (WSCCG)
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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-Statin 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 avoid the highest doses in at risk groups (See "Risk Factors" below).
- Ask the person if they have had persistent generalised unexplained muscle pain, whether associated or not with previous lipid-lowering therapy. If they have, measure CK. If CK levels are > 4x ULN do not start statin - investigation required. Do not measure CK if person is asymptomatic.
- Warn patients about AEs, specifically muscle symptoms. Advise people who are being treated with a statin to seek medical advice if they develop muscle symptoms (pain, tenderness or weakness). If this occurs, measure CK (see page 1).

Risk factors for SRM and statin intolerance

Endogenous factors

- Female gender
- Advanced age (> 75 yrs)
- Frailty (reduced lean body mass) History of muscle disorder or high CK
- Impaired renal or hepatic function Personal or family history of intolerance to lipid-lowering therapies.
- Hypothyroidism

Exogenous Factors

- Excessive alcohol intake
- High intensity exercise
- Dehydration
- Drug interactions with statins (including herbal medicines)
- Vitamin D deficiency

Classification of statin related muscle toxicity (SRM)

Alfirevic A. et. al. Clin Pharm Ther. 2014; 96:470-476

SMR	Phenotype	Incidence	Definition
SMR 0	CK Elevation < 4 x UNL	1.5-26%	No muscle symptoms
SMR 1	Myalgia, tolerable	190/100,000 patient-years; 0.3-33%	Muscle symptoms without CK elevation
SMR 2	Myalgia, intolerable	02.-2/1,000	Muscle symptoms, CK <4x ULN, complete resolution on dechallenge
SMR 3	Myopathy	5/100,000 Patient-years	CK elevation >4x ULN <10x ULN ± muscle symptoms, complete resolution on dechallenge
SMR 4	Severe myopathy	0.11%	CK elevation >10x ULN <50x ULN, muscle symptoms, complete resolution on dechallenge
SMR 5	Rhabdomyolysis	0.1-8.4/100,000	CK elevation >10x ULN with evidence of renal impairment + muscle symptoms or CK >50x ULN
SMR 6	Autoimmune-mediated necrotizing myositis (SINAM)	~2/million per year	Detection of HMGCR antibodies, HMGCR expression in muscle biopsy showing autoimmune myositis, incomplete resolution on dechallenge

HMGCR = 3-hydroxy-3-methylglutaryl coenzyme A reductase ULN = upper limit of normal

- SRM is a spectrum from myalgia to severe myopathy
- SRM 0 - does not preclude statin therapy, consider reducing starting dose
- SRM 1-3 manage according to pathway
- When SRM4 is suspected, without evidence of impaired renal function, discontinue statin therapy immediately and refer for outpatient assessment. Assess and treat possible contributory factors and re-assess the need for a statin. Intensify lifestyle modifications and consider alternative lipid lowering regimens.
- If rhabdomyolysis (SRM5) is suspected, immediately stop statins, urgently refer to inpatient assessment and management including intravenous rehydration as required to preserve renal function. Do not wait for measurement of urinary myoglobin. Post recovery, manage as for SRM4.
- Statin induced necrotizing autoimmune myositis (SINAM) (SRM6) should be suspected in patients with progressive muscle weakness and ongoing CK elevation despite statin withdrawal. Requires immunosuppressive treatment and avoidance of re-exposure to statins. Re-assess the need for lipid lowering therapy - may be eligible for treatment with PCSK9 inhibitor (NICE TA 393, 394).

Person-centred approach to address statin intolerance

Initial Consultation

- Be aware of "nocebo effect"[1] and "statin reluctance"[2]
- 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 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.

(1) Nocebo effect is negative expectations of the patient regarding a treatment leading to reporting more negative effects even if they are prescribed a placebo. (2) Statin reluctance is an attitudinal state of aversion to taking statins (often without prior exposure).

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 (intermittent dosages) • Patients who do not tolerate statins on a daily basis, alternate day or twice-weekly dosing is a good option.
- Rosuvastatin 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 robust reduction 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.

LDL-C lowering options for patients with genuine statin intolerance

- Refer to the AAC 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 PCSK9i if eligible for treatment according to NICE TA 393, 394

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), Interstitial lung disease, Pancreatitis, Skin disorders including alopecia, Lupus-like reaction, Sleep disturbance, headache, dizziness, fatigue, 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. Several studies have confirmed that the cardiovascular benefits of statin treatment in high-risk populations outweigh the rare adverse effects, such as rhabdomyolysis.

Contact for specialist advice

ESNEFT- Ipswich Hospital: lipidclinic@esneft.nhs.uk
This guidance has been adopted from the Accelerated Access Collaborative and NHS England Statin Intolerance Pathway (2nd August 2021) with minor amendments to wording and inclusion of the localised process.