Statin Intolerance

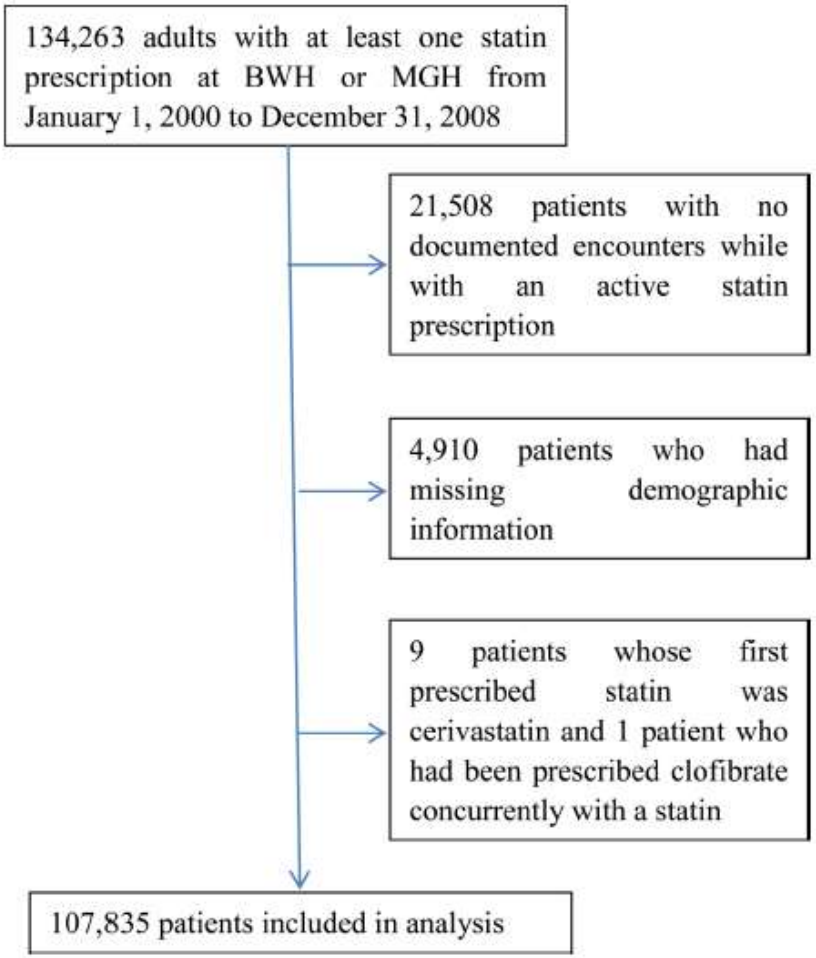
- Managing the problem

Dr RDG Neely

Specialist Adviser on Lipids
Academic Health Sciences Network
North East and North Cumbria

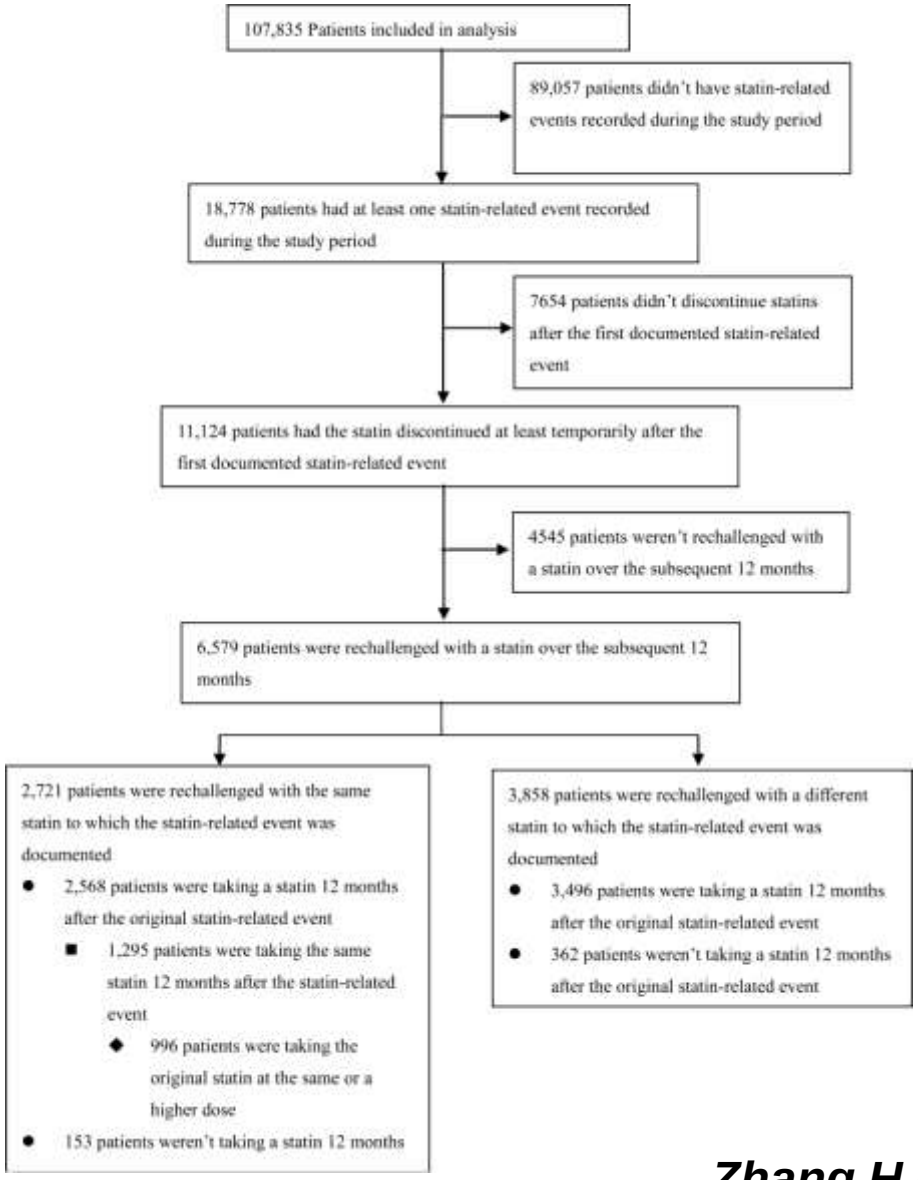
How often are statins discontinued due to AEs?

A large retrospective cohort study in practices affiliated to US hospitals.



Zhang H et al., Ann Intern Med. 2013; 158: 526

How often are statins discontinued due to AEs?



Of 107,835 on statins

18,778 (17.4%) had AE

7,654 (7.1%) continued

11,124 (10.3%) discontinued

6,579 (59%) were rechallenged

2,721 with the same statin

3,858 with a different statin

Of these 6064 (92%) were taking a statin 12 months after SRE

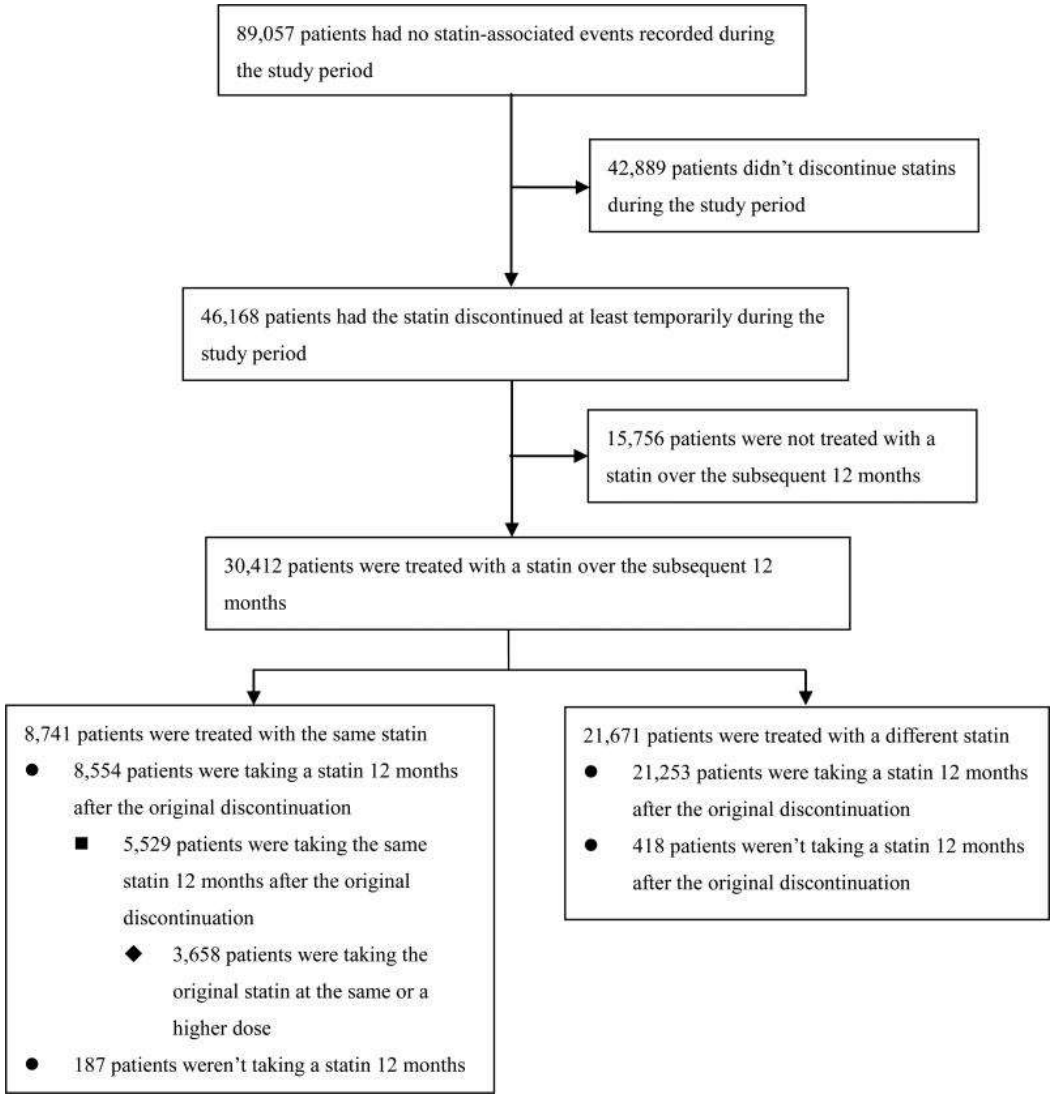
Zhang H et al., Ann Intern Med. 2013; 158: 526

What sort of AEs led to statin discontinuation?

Statin-related event category	Patients (%)
Myalgia or myopathy	5075 (4.7)
Rhabdomyolysis	7 (0.006)
CK 3-10 ULN	992 (0.9)
Musculoskeletal and connective tissue disorders other than myalgia or myopathy	2742 (2.5)
Muscle spasms	882 (0.8)
Pain in extremity	537 (0.5)
Arthralgia	356 (0.3)
Other	967 (0.9)
General disorders and administration site conditions	2493 (2.3)
Pain	1222 (1.1)
Fatigue	313 (0.3)
Asthenia	208 (0.2)
Other	750 (0.7)
Hepatobiliary disorders	2308 (2.1)
Drug intolerant	1827 (1.7)
Gastrointestinal disorders	1681 (1.6)
Nervous system disorders	564 (0.5)
Memory problems	70 (0.06)
Immune system disorders	399 (0.4)
Vascular disorders	399 (0.4)
Psychiatric disorders	333 (0.3)
Unknown	246 (0.2)

Zhang H et al., Ann Intern Med. 2013; 158: 526

How often are statins discontinued but no AEs?



89,057 on statins with no AE

42,889 (48.2%) continued

46,168 (51.8%) discontinued

15,756 (17.7%) weren't retreated

30,412 restarted, 8,741 with the same statin, 21,858 with a different statin

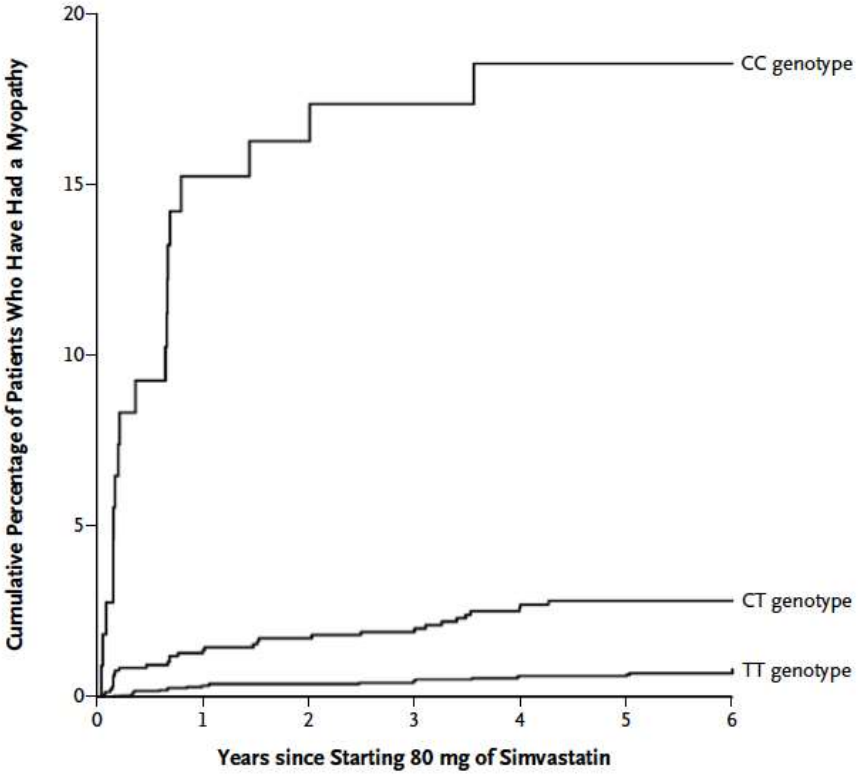
Of these 29,807 (98%) were taking a statin after 12 months

Zhang H et al., Ann Intern Med. 2013; 158: 526

SEARCH – the demise of simvastatin 80mg

SEARCH trial randomly assigned 12,064 participants from the United Kingdom who had had a myocardial infarction to receive either 80 mg or 20 mg of simvastatin daily.

Myopathy (SRM 4-5) occurred in 49 of the 6031 randomised to 80 mg, but only in 2 of 6033 randomised to 20 mg

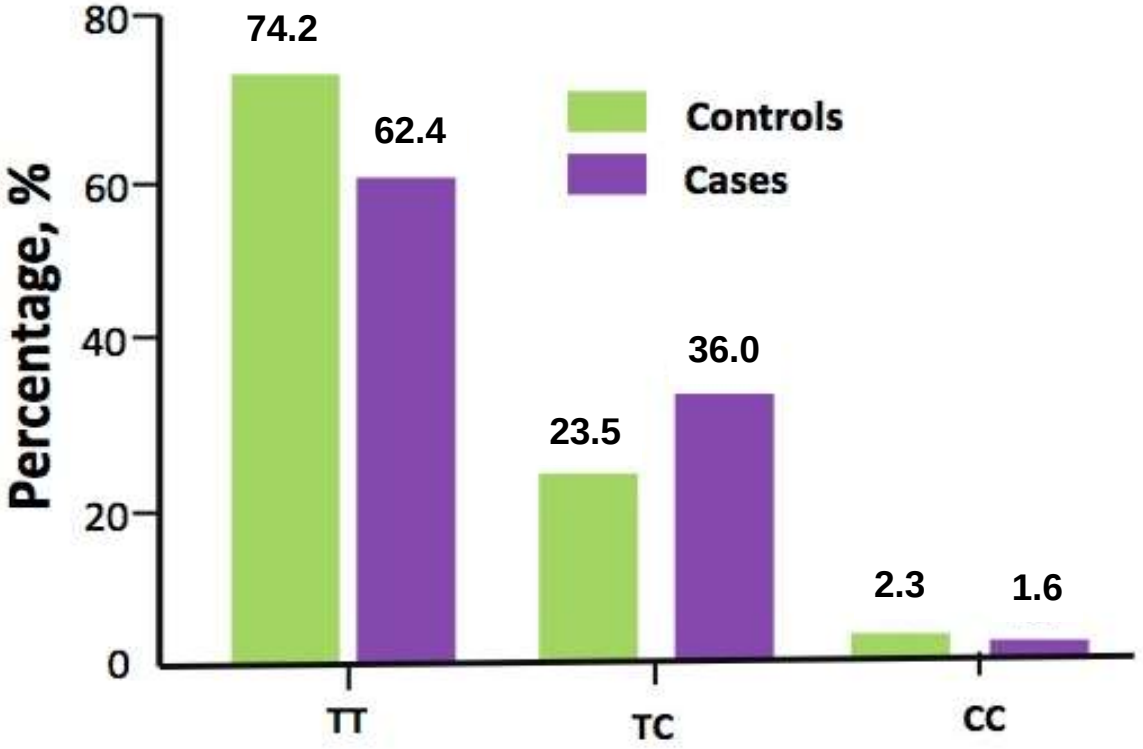


SLCO1B1 rs4149056

Genotype	Population Frequency	Cumulative No. and Percentages with Myopathy							
		Year 1				Year 5			
				Attributable to gentoype				Attributable to gentoype	
		no.	%	*no.*	*% of total*	*no.*	%	*no.*	*% of total*
TT	0.730	12	0.34	0	0	21	0.63	0	0
CT	0.249	17	1.38	12.8	75	32	2.83	24.9	78
CC	0.021	16	15.25	15.6	98	19	18.55	18.4	97
All genotypes	1.000	45	0.91	28.4	63	72	1.56	43.3	60

Link E et al, NEJM (2007) 359: 789

Frequency of *SLCO1B1* rs4149056 C allele carriers in SRM cases (SRM2-3) and controls



There was a higher proportion of carriers of the minor C allele in the case group, irrespective of the type of statin used, compared to the controls; 37.6 % vs 25.8 %

Bakar et al, Clin Pharmacol Ther (2018) 104: 178

The Newcastle upon Tyne Hospitals NHS
NHS Foundation Trust

Newcastle University

Definition of Statin Intolerance

“For the purposes of this guidance, intolerance to initial statin therapy should be defined as the presence of clinically significant adverse effects from statin therapy that are considered to represent an unacceptable risk to the patient or that may result in compliance with therapy being compromised.”

“Adverse effects include evidence of new-onset muscle pain (often associated with levels of muscle enzymes in the blood indicative of muscle damage), significant gastrointestinal disturbance or alterations of liver function tests.”

NICE TA132 2008 – ezetimibe

Statin Intolerance Pathway

ACCELERATED ACCESS COLLABORATIVE

NHS England

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***' box 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, Vit D deficiency. Check bone profile, Vit D, CRP.

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

YES

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

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

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

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)

YES

Have symptoms resolved?

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

YES

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

No → Wait for 2 weeks before **rechallenge**

YES

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 goals achieved
Patient happy to continue

No → **Consider further options**
(For example co-administering ezetimibe or as monotherapy)
see page 2 - '***Statin-based Approaches***'

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

Recurrence of muscle symptoms
Short time to onset
Symptoms intolerable

CK > 10x and < 50x ULN

Yes → **Renal function** stable/normal eGFR

No → Stop statin and consider **Rhabdomyolysis**

CK > 50x ULN → **Urgently** seek specialist advice and inpatient **assessment**

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

Please refer to page 2 for more details

Another Definition of Statin Intolerance

Any adverse event (AEs) considered unacceptable by the patient, and/or some laboratory abnormalities, both attributed to statin treatment and leading to its discontinuation.

AAC Statin Intolerance Pathway 2020

Introduction

- Statins are the cornerstone for prevention and treatment of cardiovascular (CV) disease with a substantial evidence of reduction of morbidity & 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 & 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)

SRM	Phenotype	Incidence	Definition
SRM 0	CK elevation <4x ULN	1.5-26%	No muscle symptoms
SRM 1	Myalgia, tolerable	190/100,000 Patient-years; 0.3-33%	Muscle symptoms without CK elevation
SRM 2	Myalgia, intolerable	0.2-2/1,000	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 (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 & 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.

(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 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.

Authors: Dr Rani Khatib & Dr Dermot Neely on behalf of the AAC Clinical Subgroup. June 2020. Review date: June 2021.
Pathway endorsed by NICE July 2020. Please refer to the Lipid Management Pathway and Full List of References (click here)

ACCELERATED ACCESS COLLABORATIVE

NHS England

Person-centred approach to 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 & 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.

(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).

AAC Statin Intolerance Pathway 2020

Non-muscle related statin side effects

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, dysglycaemia (benefits outweigh risk, do not stop statin), renal insufficiency, proteinuria, neurocognitive impairments (no apparent link from RCTs), 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).

AAC Statin Intolerance Pathway 2020

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 true statin related muscle toxicity (SRM) as demonstrated by resolution on de-challenge and recurrence with re-challenge

AAC Statin Intolerance Pathway 2020

Monitoring for adverse effects - CK

- **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 creatine kinase (CK).**

[NICE CG181 2014] [1.3.34]

- **Do not measure creatine kinase (CK) levels in asymptomatic people who are being treated with a statin.**

[NICE CG67 2008] [1.3.36]

Is it a statin related myopathy?

FACTORS FAVORING STATIN MYOPATHY	FACTORS FAVORING ALTERNATE DIAGNOSIS
History	**History**
Pain or weakness in large, symmetric, proximal muscle groups	Pain or weakness is asymmetric or affects distal muscle groups
Symptoms worsen with exercise	Symptoms are continuous
Symptoms resolve within 2 weeks of statin cessation	Symptoms continue 2 weeks after statin cessation
Symptoms return within 2 weeks of statin rechallenge	Symptoms do not return with statin rechallenge
Physical examination	**Physical examination**
Diffuse, proximal muscle weakness	Focal or asymmetric muscle weakness
Mild hyporeflexia	Hyperreflexia
Normal pain, vibration, and position sense	Abnormal pain, vibration, or position sense
Laboratory values	**Laboratory values**
Normal creatine kinase	Elevated creatine kinase
Normal thyroid-stimulating hormone	Elevated thyroid-stimulating hormone
Normal sedimentation rate or C-reactive protein	Increased sedimentation rate or C-reactive protein
Normal vitamin D	Possibly low vitamin D

Fernandez G et al., Cleve Clin J Med (2011) 78: 393

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

Statin-related myotoxicity (SRM) phenotype classification

SRM classification	Phenotype	Incidence	Definition
SRM 0	CK elevation <4× ULN	1.5–26%	No muscle symptoms
SRM 1	Myalgia, tolerable	190/100,000 Patient-years; 0.3–33%	Muscle symptoms without CK elevation
SRM 2	Myalgia, intolerable	0.2–2/1,000	Muscle symptoms, CK <4× ULN, complete resolution on dechallenge
SRM 3	Myopathy	5/100,000 Patient-years	CK elevation >4× ULN <10× ULN ± muscle symptoms, complete resolution on dechallenge
SRM 4	Severe myopathy	0.11%	CK elevation >10× ULN <50× ULN, muscle symptoms, complete resolution on dechallenge
SRM 5	Rhabdomyolysis	0.1–8.4/100,000 Patient-years	CK elevation >10× ULN with evidence of renal impairment + muscle symptoms or CK >50× ULN
SRM 6	Autoimmune-mediated necrotizing myositis	~2/million per year	HMGCR antibodies, HMGCR expression in muscle biopsy, incomplete resolution on dechallenge

Alfirevic A Clin Ther Pharmacol (2014) 96:470

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

AAC Statin Intolerance Pathway 2020

Precautions to prevent Statin Related Myopathy (SRM)

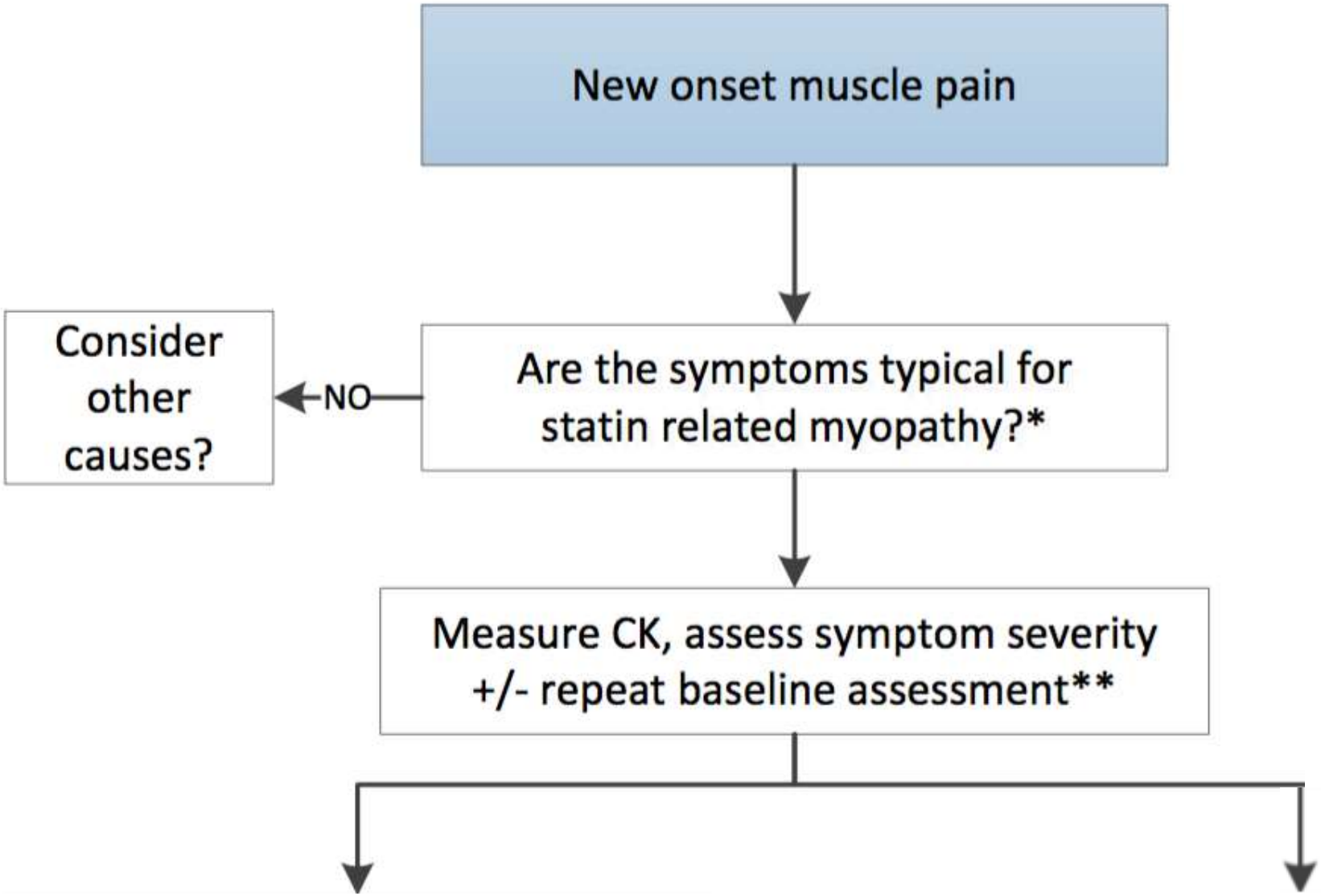
1. Before treatment check baseline thyroid, liver and renal function and consider baseline CK in at risk groups

2. Avoid high doses, highly lipophilic statins (eg simvastatin, atorvastatin) in at risk groups e.g. elderly, frail, renal or liver dysfunction, pre-existing musculoskeletal disease, alcohol abuse

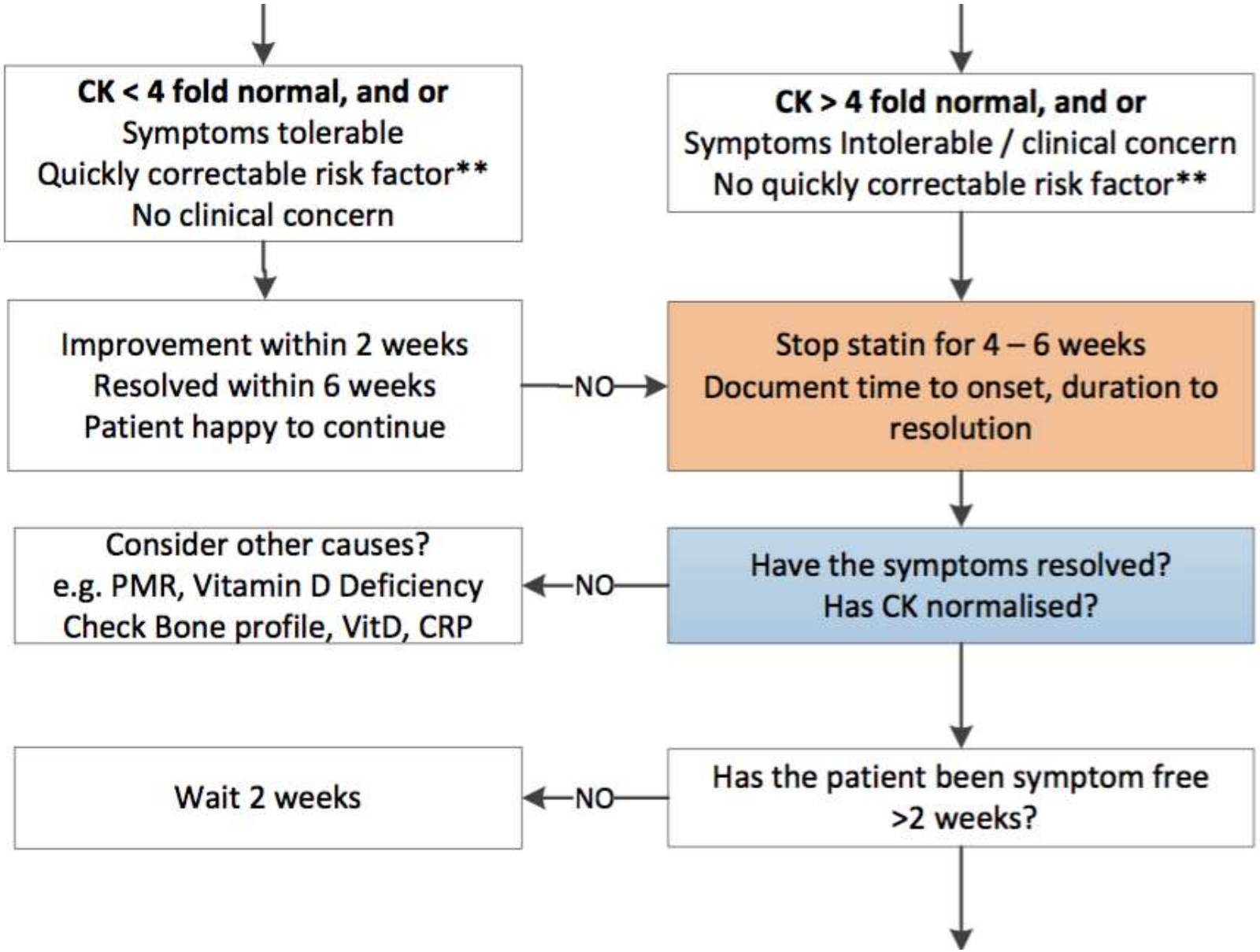
3. Consider any potential drug interactions, including grapefruit juice

4. Warn patients about side effects, specifically muscle symptoms

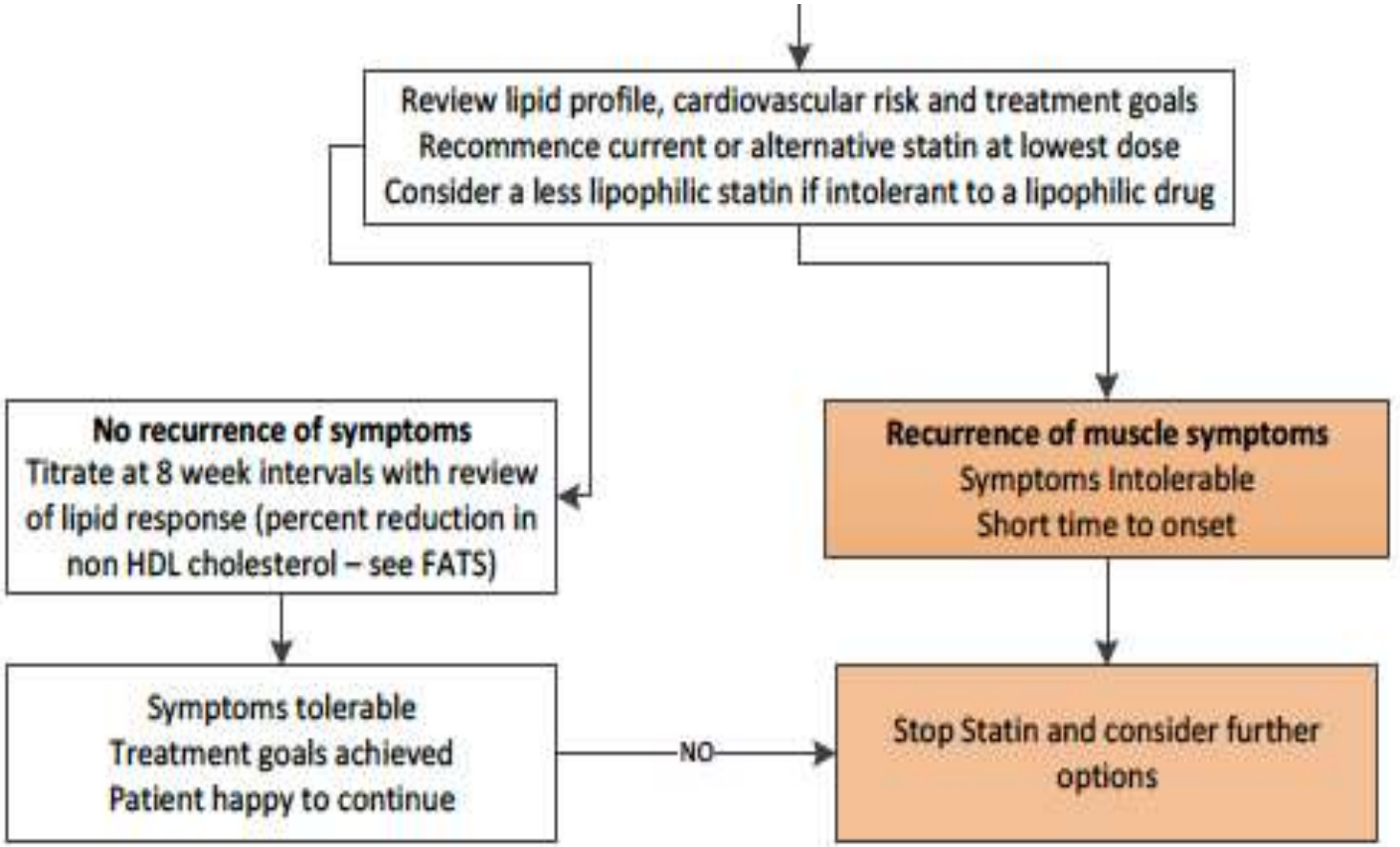
Suspected SRM - Initial assessment



Assess response to de-challenge



Reassess and re-challenge



Flowchart for Assessment of Suspected Statin Related Myopathy

Is it typical for SRM?

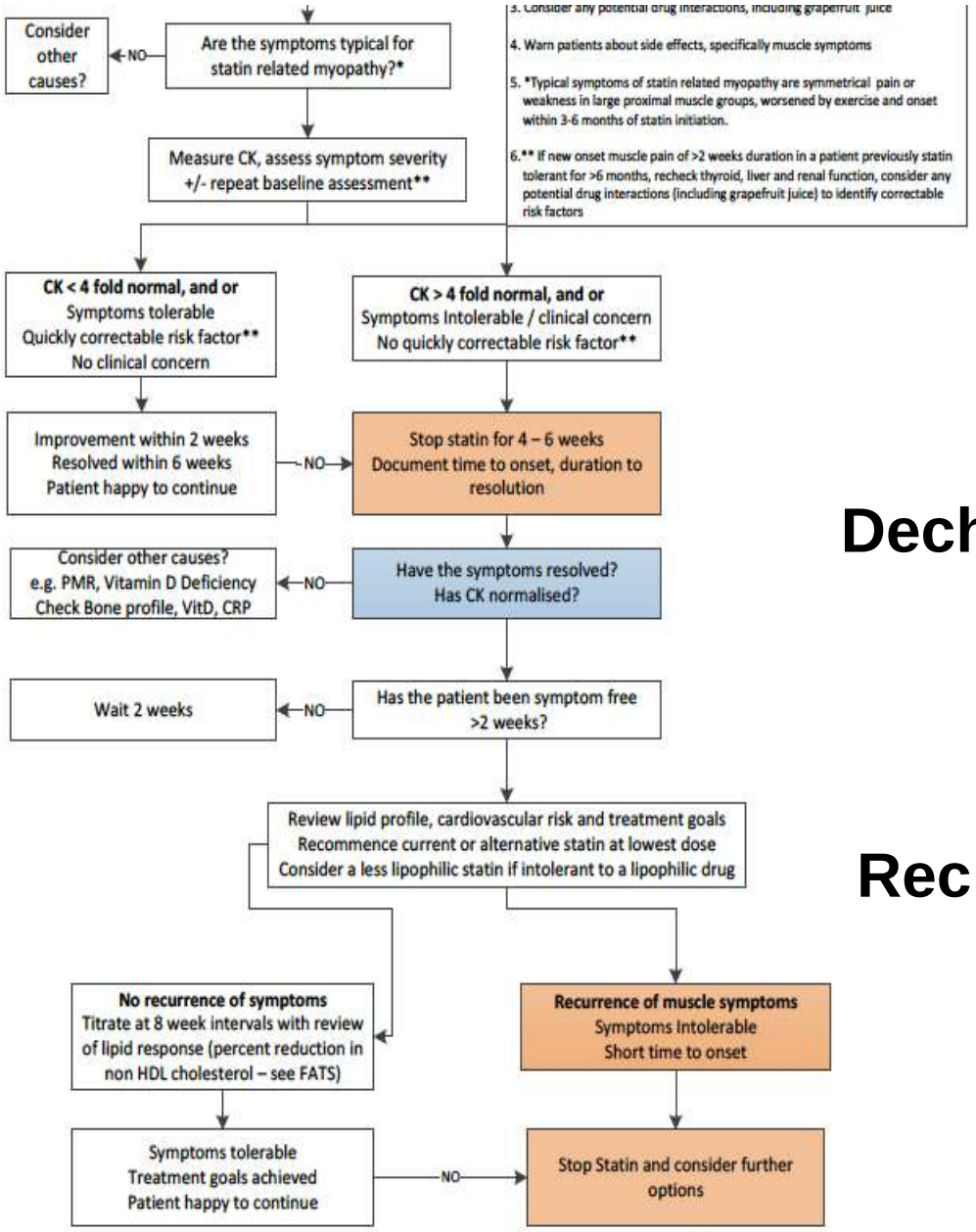
Is it tolerable?

Is CK increased?

Is the patient at risk?

Is it statin-related?

Is CVD Risk high?



Dechallenge

Rechallenge

Continue

Refer

Statin-based approaches to manage SAMS

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.**

AAC Statin Intolerance Pathway 2020

Options when intolerant to 2 or more statins

1. Low dose, non-daily long acting statin (atorvastatin 10 mg or rosuvastatin 5mg one to three days per week)
2. Ezetimibe, coadministered with maximum tolerated generic statin therapy, when dose titration is limited by intolerance to statin therapy (as defined above)
3. Ezetimibe monotherapy is an option for those who are intolerant to low dose, non-daily statin therapy (as defined above).
4. PCSK inhibitor therapy should be considered in eligible patients as defined in NICE TA393 and TA394.
5. Lipoprotein apheresis should be considered as a last resort in patients with Familial Hypercholesterolaemia and LDL-Cholesterol greater than 5 mmol/L despite maximum tolerated statin therapy or in in people with progressive vascular disease who are intolerant of statin therapy. These patients should be assessed in a specialist lipid clinic.

FATS Guidelines 2016

Statins are grouped into intensity categories

	Reduction in LDL cholesterol				
Dose (mg/day)	5	10	20	40	80
Fluvastatin	–	–	21%	27%	33%
Pravastatin	–	20%	24%	29%	–
Simvastatin	–	27%	32%	37%	42%*
Atorvastatin	–	37%	43%	49%	55%
Rosuvastatin	38%	43%	48%	53%	–
Atorvastatin +ezetimibe		52%	54%	57%	61%

20%–30%: low intensity

31%–40%: medium intensity

Above 40%: high intensity

Ezetimibe when combined with any statin is likely to give greater reduction in non-HDL-C/LDL-C than doubling the dose of the statin.

LDL=low-density lipoprotein.

*MHRA advice: there is an increased risk of myopathy with high-dose (80 mg) simvastatin. This dose should be considered only in people with severe hypercholesterolaemia and high risk of cardiovascular complications who have not achieved their treatment goals on lower doses, when benefits are expected to outweigh potential risks.

Summary

Statin related muscle toxicity (SRM) is pharmacological entity

Statin Associated Muscle Symptoms (SAMS) is not a diagnosis

Assessment of causality is established by dechallenge/rechallenge

CK should be measured to assess severity of muscle damage

Ezetimibe may be useful as an adjunct to statin or as monotherapy

Specialist advice should be sought about options for people at high risk of CVD who are intolerant to 3 different statins or if CK >10 ULN

PCSK9 inhibitor therapy should be considered in eligible patients as defined in NICE TA393 and TA394.

Case 1

- A 77 year old man, posterior circulation stroke age 73
- Referred to Lipid Clinic for advice of alternative lipid lowering treatment following myositis, statin related?
- Treated with simvastatin for secondary prevention after stoke, then atorvastatin 40mg for last 2 years
- Complained of fatigue and weight loss, ALT 229 on routine LFT, referred to hepatobiliary team.
- Endoscopy showed mild oesophagitis, but abdominal ultrasound and CT were normal excluding hepatobiliary and intra-abdominal pathology.
- After 6 months he complained of increasing muscle aches and weakness in addition to fatigue, and CK was measured

Case 1 – Blood results

	CK (U/L)	ALT (U/L)	
Apr 15	-	167	On atorvastatin 40 mg
Jun 15	-	229	Referred HBT
Dec 15	6818	268	On atorvastatin 40 mg
Jan 16	7507	292	Stopped statin
May 16	2975	111	Commenced Pred
Jun 16	936	54	Commenced MTX

Case 1 - Clinical and Laboratory Data

- **Height 1.67 m Weight 65.8 kg BMI 24.0**
- **No muscle tenderness or weakness**
- **Fasting Lipid Profile**
  T.Chol 6.2 mmol/L Triglyceride 1.1 mmol/L
  HDL-C 2.6 mmol/L LDL-C 3.4 mmol/L
- **CK 746 U/L (<320); ALT 46 u/L (<40)**
- **U&E, Thyroid Function normal.**

Case 1

- **How can the persistently high CK be explained?**

- **What investigation and/or treatment would you advise?**

Case 1 - Clinical and Laboratory Data

- **Height 1.67 m Weight 65.8 kg BMI 24.0**
- **No muscle tenderness or weakness**
- **Fasting Lipid Profile**
  T.Chol 6.2 mmol/L Triglyceride 1.1 mmol/L
  HDL-C 2.6 mmol/L LDL-C 3.4 mmol/L
- **CK 746 U/L (<320); ALT 46 u/L (<40)**
- **U&E, Thyroid Function normal.**
- **Standard autoimmune screen and muscle antibody panel were negative**
- **Anti-HMG CoA Reductase antibody awaited**

Case 1 – Management

- **Continued on immunosuppressive therapy and low fat lipid lowering diet only**
- **To consider addition of ezetimibe when CK stabilises and inflammation subsides**
- **Statins should be avoided if anti-HMG-CoAR antibodies are positive**
- **Assess eligibilty for PCSK9i when on ezetimibe monotherapy, if tolerated**

Case 2

- **A 67 year old man, known FH due to *APOB* R3527Q**
- **Referred to Lipid Clinic 5 years earlier with severe hypercholesterolaemia (Total Cholesterol 8.7 mmol/L) due to elevated LDL-C (6.6 mmol/L) and bilateral Achilles tendon xanthomata, family history of CVD**
- **Unable to tolerate simvastatin or atorvastatin due to myalgia and arthralgia mainly affecting lower limbs**
- **Treated sucessfully with gradual titration of rosuvastatin, on 20mg nocte for past 3 years**
- **Recently complains of increasing muscle and joint pains and difficulty with rising from seated position**

Case 2

- **How can these symptoms be explained?**

- **What investigation and/or treatment would you advise?**

Case 2 - Clinical and Laboratory Data

- **Height 1.69 m Weight 79.6 kg BMI 27.9**
- **No muscle tenderness but proximal weakness**
- **Fasting Lipid Profile**
  T.Chol 4.6 mmol/L Triglyceride 0.8 mmol/L
  HDL-C 1.6 mmol/L LDL-C 2.6 mmol/L
- **CK 73 U/L (40 - 320)**
- **U&E, Thyroid Function normal.**

Case 2 - Clinical and Laboratory Data

- **Height 1.69 m Weight 79.6 kg BMI 27.9**
- **No muscle tenderness but proximal weakness**
- **Fasting Lipid Profile**
  T.Chol 4.7 mmol/L Triglyceride 0.8 mmol/L
  HDL-C 1.6 mmol/L LDL-C 2.7 mmol/L
- **CK 259 U/L (<320)**
- **U&E, Thyroid Function normal.**
- **CRP <5 mg/L**
- **Vitamin D 12 nmol/L (<25 Vitamin D deficiency)**

Case 2 – Management

- **Prescribed loading dose of Vitamin D 20,000 units twice weekly reducing to maintenance dose of 800 u daily after 7 weeks.**
- **Continued on rosuvastatin 20 mg nocte**
- **Advised to reduce or stop if symptoms persist**

Case 2 – Outcome

- **Muscle pains resolved completely within 6 weeks**
- **Repeat non-fasting lipid profile 3 months later**
  - T.Chol 4.6 mmol/L
  - Trigs 0.8 mmol/L
  - HDL-C 1.8 mmol/L
  - LDL-C 2.4 mmol/L

Case 2 – Outcome

- **Muscle pains recurred within 4 weeks**
- **Repeat non-fasting lipid profile (external lab)**
  - T.Chol 6.4 mmol/L
  - Trigs 1.8 mmol/L
  - HDL-C 1.6 mmol/L
  - LDL-C 4.0 mmol/L
  - CK – not done