STATINS: MONITORING EFFICACY AND SIDE EFFECTS

KEY RECOMMENDATIONS

- **For Lipid measurements fasting is NOT required.** Non-fasting specimens are recommended which are also suitable for triglycerides when this is appropriate.
- **Before statin initiation** NICE recommends a baseline non-fasting **Total cholesterol, HDL-cholesterol and triglycerides.**
- **At 3 months and 12 months after starting treatment NICE recommends a repeat total cholesterol and HDL cholesterol.**
- **At annual reviews, we have a local policy of advising only total cholesterol measurement.**
- **NICE recommends a baseline ALT before statin initiation.** Locally we advise this does not need to be repeated again unless liver disease is present or suspected. Statins do not cause liver disease.
- If there is *pre-existing* generalised muscle pain before statin initiation, ***consider*** **a baseline creatine kinase (CK)**. Repeat CK measurements as appropriate (see below).
- **True statin related muscle symptoms** occur in fewer than 1% of patients.
  However, muscle symptoms are more commonly reported and their management is described below.

MONITORING STATIN EFFICACY

National and international guidelines recommend high intensity statins for patients with established cardiovascular disease including IHD, Stroke/TIA or peripheral arterial disease.[1,2] The NICE recommended dose is atorvastatin 80mg which may be reduced where clinically appropriate to atorvastatin 40mg in people who are frail or over 80 years.

The NICE guidelines states that following statin initiation, *"if a greater than 40% reduction in non-HDL cholesterol is not achieved:*

- *Discuss adherence and timing of dose*
- *Optimise adherence to diet and lifestyle measures*
- *Consider increasing dose if started on less than atorvastatin 80 mg*."[1].

NICE advises Total cholesterol, HDL cholesterol and triglycerides before starting a statin and total and HDL cholesterol at 3 months. Locally clinical leads have advised that total cholesterol is the only blood measurement routinely required at annual reviews of people who are on a statin.

For audit purposes a serum cholesterol of <5mmol/l has been used nationally in the UK and is a useful measure of organisational performance at practice or CCG level.

HOW COMMON ARE STATINS SIDE EFFECTS AND ARE THEY CAUSED BY STATINS?

Reported side effects are the most common reason for statin treatment discontinuation. Reported studies vary widely in their estimates of statin intolerance. Although, routine data variably reports 5-20% of patients as possibly statin intolerant, this is mainly the consequence of a 'nocebo' type effect largely resulting from of taking a medicine that had variably bad publicity.[3] A more certain diagnosis of statin intolerance is likely in around 2% of patients on statins and is dose related – around 5% on atorvastatin 80mg [4,5]

Finegold *et al.*'s large meta-analysis (over 83,000 patients) of statins use for primary and secondary prevention concluded that: "only a small minority of symptoms reported on statins are genuinely due to the statins: almost all would occur just as frequently on placebo" [6]. In other words, in randomised blinded trials of statins, there is no significant difference between groups in discontinuation rates or myopathy. The same study reported a small increase in Type 2 diabetes (in the order of 1 new case for every 100 patients treated for 5 years). However, statins remain associated with an overall reduction in cardiovascular events in these patients and benefits outweigh any possible harm in people with and without diabetes.

Patients can be confidently reassured that statins are among the most researched and safe medicines. They are well tolerated, serious side effects are extremely rare and they are one of the most effective medicines in widespread use.

WHAT SHOULD I DO ABOUT STATINS AND MUSCLE PAIN?

The heterogeneous cluster of muscular symptoms reported after statin initiation (or dose or statin changes) have been termed **statin-associated muscle symptoms (SAMS)**[7]. There are three muscle-related conditions: myalgias (i.e. muscle pain with no muscle damage and/or no sizable raise in serum CK); statin induced myopathy 1 in 10,000 per year (i.e. actual destruction of skeletal muscle with significant increase of CK in blood) and rhabdomyolysis 1-2 in 100,000 per year (associated with widespread systemic dysfunction). The NICE and European guidelines differ in their advice for monitoring and management of SAMS; their advice[1,8], and ours[9], is summarised in Table 1.

NICE recommends that a baseline CK prior to statin initiation is only necessary if there is pre-existing muscle pain and to recheck this only if the patient reports SAMS. If the CK is <3x ULN, advise statin continuation. If it is >5x ULN consider a statin holiday and titrated low dose statin re-introduction. If it is persistently >5x ULN, stop the statin and refer for further advice.

To assist GPs in the monitoring and management of SAMS, we have developed a composite flowchart combining advice into a practicable consensus (Figure 1).

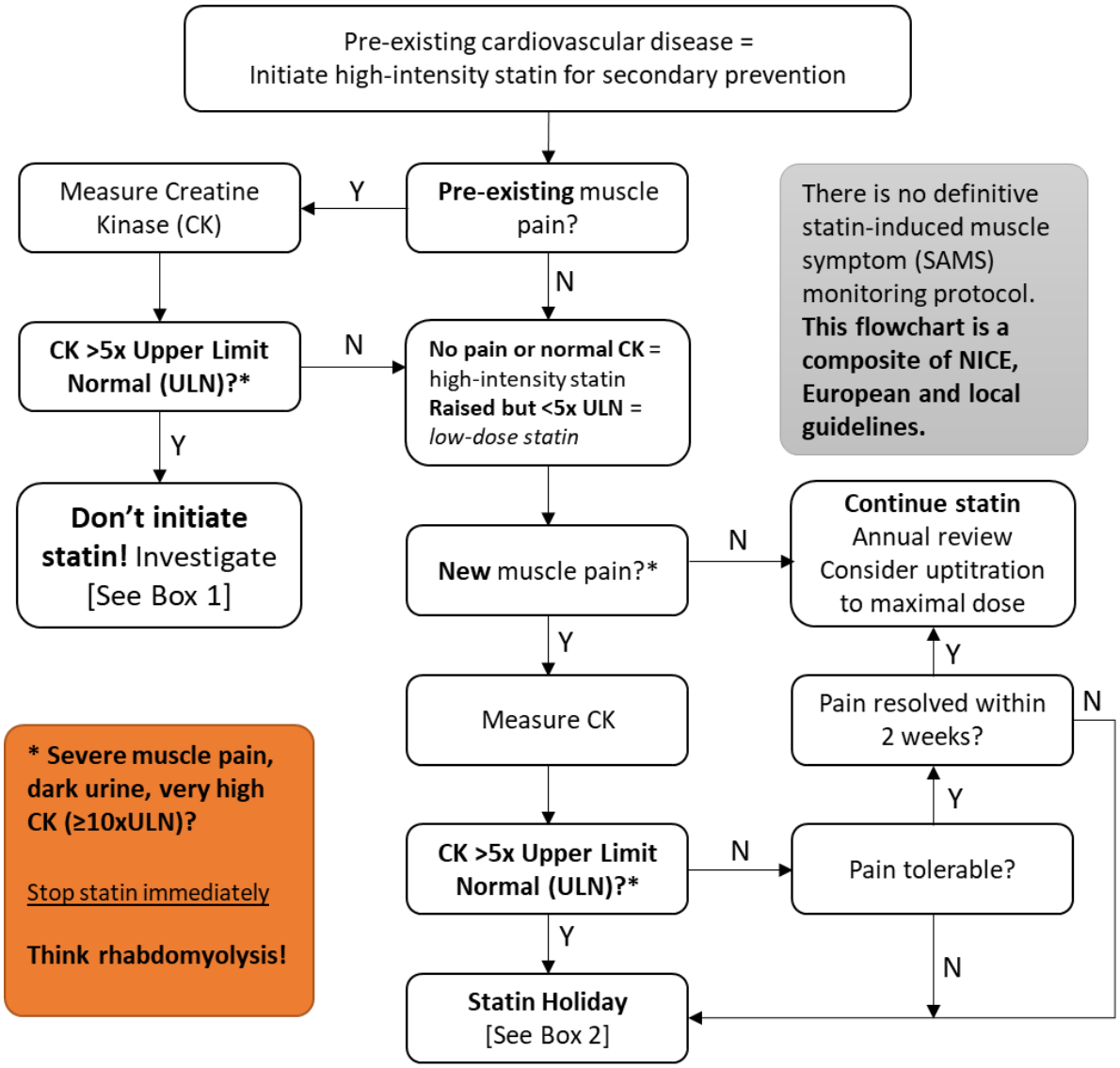
DO STATINS DAMAGE THE LIVER? SHOULD I CHECK LFTs REGULARLY?

Statins do not cause liver disease[10] but transitory low rises in liver function are common; **increases in ALT up to 3x ULN are normal and do not need further monitoring**. This mild elevation of ALT has not been shown to be associated with hepatotoxicity or impaired liver function. In patients with mild ALT-elevation due to steatosis there has been no indication that statins worsen liver disease[2]. In fact many clinicians would consider statins to be of overall benefit in patients with non-alcoholic fatty liver disease[11]. Since 2012, the U.S. Food and Drug Administration (FDA) safety labels for statins recommend that liver enzyme tests should be performed before starting statin therapy and only as clinically indicated thereafter. NICE recommends an ALT at initiation, and at 3-months and 12-months'.Our local guidance[9], agreed with hepatologists, is in line with the FDA guidance.

We recommend measuring ALT before starting a statin but not again unless indicated or in the presence or suspicion of pre-existing liver disease. In keeping with other guidelines, an ALT persistently overs 3x ULN warrants stopping statins and performing appropriate liver disease investigations (See Table 1).

REFERENCES

1. National Institute for Health and Care Excellence. Cardiovascular disease: risk assessment and reduction, including lipid modification (NICE clinical guideline CG181) [Revised 2016]. (2016). Available at: https://www.nice.org.uk/guidance/cg181. (Accessed: 9th September 2019)
2. Mach, F. *et al.* 2019 ESC/EAS Guidelines for the management of dyslipidaemias:: lipid modification to reduce cardiovascular risk: supplementary data. *Eur. Heart J.* (2019). doi:10.1093/eurheartj/ehz455
3. Tobert, J. A. & Newman, C. B. The nocebo effect in the context of statin intolerance. *J. Clin. Lipidol.* **10**, 739–747 (2016).
4. Mancini, G. B. J. *et al.* Diagnosis, prevention, and management of statin adverse effects and intolerance: proceedings of a Canadian Working Group Consensus Conference. *Can. J. Cardiol.* **27**, 635–62 (2011).
5. Toth, P. P. *et al.* Management of Statin Intolerance in 2018: Still More Questions Than Answers. *Am. J. Cardiovasc. Drugs* **18**, 157–173 (2018).
6. Finegold, J. A., Manisty, C. H., Goldacre, B., Barron, A. J. & Francis, D. P. What proportion of symptomatic side effects in patients taking statins are genuinely caused by the drug? Systematic review of randomized placebo-controlled trials to aid individual patient choice. *Eur. J. Prev. Cardiol.* **21**, 464–74 (2014).
7. Ryan, A., Heath, S. & Cook, P. Managing dyslipidaemia for the primary prevention of cardiovascular disease. *BMJ* **360**, k946 (2018).
8. Mach, F. *et al.* 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur. Heart J.* (2019). doi:10.1093/eurheartj/ehz455
9. Robson, J. & Anthoniou, S. *Summary Guidelines: CEG Statin guidance update*. (Blizard Institute. Centre for Primary Care and Public Health, 2015).
10. Bader, T. The myth of statin-induced hepatotoxicity. *Am. J. Gastroenterol.* **105**, 978–80 (2010).
11. Sigler, M. A., Congdon, L. & Edwards, K. L. An Evidence-Based Review of Statin Use in Patients With Nonalcoholic Fatty Liver Disease. *Clin. Med. Insights. Gastroenterol.* **11**, 1179552218787502 (2018).



BOX 1: Raised CK

Exclude exogenous cause (e.g. heavy exercise, surgery, IM injections)
Repeat after 7 days
If still elevated, consider:
→ TFT (hypothyroid, hyperthyroid (rare))
→ U&Es (metabolic disturbance)
→ other meds (e.g. fibrates, ARVs, β-blockers, ARBs, clozapine, hydroxycholorquine, isotretinoin, colchicine)
Rarer causes:
Connective tissue diseases, Cardiac/renal disease, Metabolic disease, Malignancy, Neuromuscular disease (inc. myopathies and muscular dystrophies)

BOX 2: Statin holiday

Statin holiday is 2-6 weeks off statin
Expect statin induced muscle pain to resolve within 2 weeks
Recheck CK at end of holiday
→ >5xULN: unlikely to be statin related. See Box 1
→ <5x ULN: try one of these options:
- Re-challenge with same statin
- Reduced dose in same intensity group (e.g. Ator 80mg → 40mg)
- Alternative statin in same intensity group (e.g. Ator 80mg → Rosuvastatin 40mg)
- Lower intensity statin (e.g. Ator 80mg → Pravastatin 20mg)

If none of these work, see Box 3.

BOX 3: Treatment alternatives

Atorvastatin and Rosuvastatin have longer half lives and can accommodate non-daily regimes.
Possible regimes:
- Atorvastatin 10 alternate days
- Rosuvastatin 5-10mg alternate days
- Rosuvastatin 10mg once a week

High risk patient and intolerant to 3 different statins?
→ Seek specialist advice (e.g. ezetimibe, PCSK9 inhibitor)

Figure 1: Monitoring of Statin-Associated Muscles Symptoms (SAMS) with high-intensity statins

Table 1: Monitoring of statin efficacy and side effect.

Guideline **Date publication** **Last update**	**NICE CG181 cardiovascular risk reduction** Jul-14 Sep-16	**2019 ESC/EAS lipid modification guidelines** Aug-19 n/a	**CEG Statin Guidance Update** Apr-15 n/a
↓Monitoring of↓			
Lipids			
How	Full lipid profile (total cholesterol, HDL cholesterol, triglycerides [non-fasting])	At least LDL-C, full lipid profile	Full lipid profile (total cholesterol, HDL cholesterol, triglycerides [non-fasting])
Pre-initiation	1x before initiation	2x before initiation	1x before initiation
Post-initiation	at 3 months treatment and 12 months [TC, HDL-c]	in 8±4 weeks	At 3 months and 12 months [TC, HDL-c]
Ongoing	Annual Review: TC, HDL-c	Annual review: Full lipid profile	Annual review (total cholesterol only)
Liver enzyme			
How	ALT or AST only	ALT only	ALT only
Pre-initiation	1x before initiation	1x before initiation	1x before initiation
Post-initiation	At 3 months and 12 months	After initiation: 1x after 8-12 weeks	see below
Ongoing	Nil further unless clinically indicated	Nil further unless signs liver disease	Nil further unless known or suspected liver disease; if so, repeat at 3 and 12 months
If abnormal:			
<3x ULN	Do not exclude from treatment	Continue and recheck liver enzymes in 4-6 weeks	remain on statin
>3x ULN	*Not specified*	Stop or reduce statin and recheck 4-6 weeks Cautious reintroduction at lower dose if ALT normalises. Investigate other causes if persists	review dose/investigate fully (liver screen, examination, travel, tattoo, transfusion and sexual history)

Table 1: CONTD.

Guideline	**NICE CG181 cardiovascular risk reduction**	**2019 ESC/EAS lipid modification guidelines**	**CEG Statin Guidance Update**
Date publication	Jul-14	Aug-19	Apr-15
Last update	Sep-16	n/a	n/a
↓Monitoring of↓			
CK (Muscle pain)			
How	Creatine Kinase	Creatine Kinase	If the patient develops adverse symptoms on the starting dose of atorvastatin, consider alternative statin (e.g. pravastatin or rosuvastatin)
Pre-initiation	Only if "they have had persistent generalised unexplained muscle pain"	1x before initiation	
Post-initiation	If muscle symptoms (pain, tenderness, weakness)	Only if myalgia	
Medication change	*Not discussed but presumably as above*	*Not discussed but presumably as above*	
Ongoing	Nil routine monitoring	Nil routine monitoring	
If abnormal:			
Pre-initiation	>5x ULN, do not start; recheck in 7/7; no statin if persists at >5x ULN	>4x ULN, Do not start treatment, recheck	
Post-initiation	Do not exclude from statin therapy if <3x ULN	<4x ULN: *no muscle pain = continue* *muscle pain = monitor symptoms and CK* *persisting symptoms = statin holiday then re-challenge with same statin (symptoms persist) or second statin (symptoms improve)* ≥4xULN and <10x ULN: *no symptoms = continue statin + CK every 2-6 weeks* *symptoms = stops statin, monitor for normalisation CK, rechallenge at lower dose* >10x ULN: *stop treatment, check renal, CK every 2 weeks*	