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. 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 80mg.”

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. 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.

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”. 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). 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, and ours, 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 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. In fact many clinicians would consider statins to be of overall benefit in patients with non-alcoholic fatty liver disease. 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, 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 over 3x ULN warrants stopping statins and performing appropriate liver disease investigations (See Table 1).

REFERENCES

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

- **Pre-existing cardiovascular disease =** Initiate high-intensity statin for secondary prevention

- **Measure Creatine Kinase (CK)**
  - **CK >5x Upper Limit Normal (ULN)?**
    - **Y**
      - Don’t initiate statin! Investigate [See Box 1]
    - **N**
      - **No pain or normal CK = high-intensity statin Raised but <5x ULN = low-dose statin**

- **Pre-existing muscle pain?**
  - **N**
    - **New muscle pain?**
      - **Y**
        - Measure CK
      - **N**
        - Continue statin
          - Annual review
          - Consider up titration to maximal dose

- **CK >5x Upper Limit Normal (ULN)?**
  - **Y**
    - Statin Holiday [See Box 2]
  - **N**
    - Pain resolved within 2 weeks?
      - **Y**
        - Stop statin immediately
        - Think rhabdomyolysis!
      - **N**
        - Pain tolerable?
          - **Y**
            - Continue statin
              - Annual review
              - Consider up titration to maximal dose
          - **N**
            - Measure CK

* Severe muscle pain, dark urine, very high CK (>10xULN)?
  - Stop statin immediately
  - Think rhabdomyolysis!

**BOX 1: Raised CK**
- Exclude exogenous cause (e.g., heavy exercise, surgery, IM injections)
- Repeat after 7 days
- If still elevated, consider:
  - TTF (hyperthyroid, hyperthyroid (rare))
  - U&Es (metabolic disturbance)
  - Other meds (e.g., fibrates, ARVs, β-blockers, ARBs, diuretics, hydroxychloroquine, isotretinoin, colchicine)
- Rarer causes:
  - Connective tissue diseases
  - Cardiac ventricular, Metabolic, Malignancy, Neuromuscular disease (i.e., 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.
  - <5xULN: 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)
# Monitoring of statin efficacy and side effect

<table>
<thead>
<tr>
<th>Guideline</th>
<th>NICE CG181 cardiovascular risk reduction</th>
<th>2019 ESC/EAS lipid modification guidelines</th>
<th>CEG Statin Guidance Update</th>
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<tbody>
<tr>
<td>Date publication</td>
<td>Jul-14</td>
<td>Aug-19</td>
<td>Apr-15</td>
</tr>
<tr>
<td>Last update</td>
<td>Sep-16</td>
<td>n/a</td>
<td>n/a</td>
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### Lipids

<table>
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<tr>
<th>How</th>
<th>NICE CG181</th>
<th>2019 ESC/EAS</th>
<th>CEG Statin</th>
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<tbody>
<tr>
<td>Full lipid profile (total cholesterol, HDL cholesterol, triglycerides [non-fasting])</td>
<td>At least LDL-C, full lipid profile</td>
<td>Full lipid profile (total cholesterol, HDL cholesterol, triglycerides [non-fasting])</td>
<td></td>
</tr>
<tr>
<td>Pre-initiation</td>
<td>1x before initiation</td>
<td>2x before initiation</td>
<td>1x before initiation</td>
</tr>
<tr>
<td>Post-initiation</td>
<td>at 3 months treatment and 12 months [TC, HDL-c]</td>
<td>in 8±4 weeks</td>
<td>At 3 months and 12 months [TC, HDL-c]</td>
</tr>
<tr>
<td>Ongoing</td>
<td>Annual Review: TC, HDL-c</td>
<td>Annual review: Full lipid profile</td>
<td>Annual review (total cholesterol only)</td>
</tr>
</tbody>
</table>

### Liver enzyme

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<tbody>
<tr>
<td>ALT or AST only</td>
<td>ALT only</td>
<td>ALT only</td>
<td></td>
</tr>
<tr>
<td>Pre-initiation</td>
<td>1x before initiation</td>
<td>1x before initiation</td>
<td>1x before initiation</td>
</tr>
<tr>
<td>Post-initiation</td>
<td>At 3 months and 12 months</td>
<td>After initiation: 1x after 8-12 weeks</td>
<td>see below</td>
</tr>
<tr>
<td>Ongoing</td>
<td>Nil further unless clinically indicated</td>
<td>Nil further unless signs liver disease</td>
<td>Nil further unless known or suspected liver disease; if so, repeat at 3 and 12 months</td>
</tr>
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### If abnormal:

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<tbody>
<tr>
<td>Do not exclude from treatment</td>
<td>Continue and recheck liver enzymes in 4-6 weeks</td>
<td>remain on statin</td>
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<tr>
<td>Not specified</td>
<td>Stop or reduce statin and recheck 4-6 weeks</td>
<td>review dose/investigate fully (liver screen, examination, travel, tattoo, transfusion and sexual history)</td>
<td></td>
</tr>
<tr>
<td>Cautious reintroduction at lower dose if ALT normalises. Investigate other causes if persists</td>
<td></td>
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**↓ Monitoring of ↓**

- **CK (Muscle pain)**

  | How | Pre-initiation | Post-initiation | Medication change | Ongoing | If abnormal: |
|-----|---------------|----------------|-----------------|------------------|----------|-------------|
|     | Creatine Kinase | Only if "they have had persistent generalised unexplained muscle pain" | If muscle symptoms (pain, tenderness, weakness) | Not discussed but presumably as above | Nil routine monitoring |

**If abnormal:**

- **Pre-initiation**
  - >5x ULN, do not start; recheck in 7/7; no statin if persists at >5x ULN

- **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

| Date publication | Jul-14 | Aug-19 | Apr-15 |
| Last update | Sep-16 | n/a | n/a |

If the patient develops adverse symptoms on the starting dose of atorvastatin, consider alternative statin (e.g. pravastatin or rosuvastatin).