STATINS: MONITORING EFFICACY AND SIDE EFFECTS

KEY RECOMMENDATIONS

- **Perform a baseline measurement of lipid status** before statin initiation; locally, we recommend limiting this test to total cholesterol (TC) measurement only.
- **Repeat the lipid status measurement at 3 months’ treatment.** Use this to monitor impact of treatment but do not cease treatment if target is not met. Targets are arbitrary, particularly in the context of statin use in secondary prevention.
- **Consider a baseline creatine kinase (CK) before initiation of statins if there is pre-existing generalised muscle pain.** Repeat CK measurements as appropriate (see below).
- **Limit your monitoring of liver function to a baseline ALT**, only perform further liver monitoring if clinically indicated.
- **Beware the nocebo effect.** Inform patients appropriately but remember true statin induced myopathy is rare.

WHY MONITOR STATIN EFFICACY?

National and transnational guidelines for CVD risk reduction and lipid modification recommend for relative statin effected cholesterol lowering\(^1,2\). The NICE guideline targets a \(>40\%\) reduction in non-HDL cholesterol\(^1\) and the European guideline a \(\geq 50\%\) reduction in LDL-C\(^2\). NICE does not give an absolute target but both QoF and the European guideline do (respectively total cholesterol \(\leq 5\) mmol/l and LDL-C \(\leq 3.0\) to \(\leq 1.4\) mmol/l (depending on risk stratification)). This is driven by the mounting evidence-based findings that the greater the fall in LDL-C, the lower the CVD risk reduction and that “no level of LDL-C below which benefits cease or harm occurs has been defined”\(^2\).

Therefore, fixing an actual reduction target seems moot –patients who are eligible for a statin should be on the statin even if the relative reduction target is not met; any fall in (LDL)-cholesterol is risk reducing and statins may well effect benefits beyond their impact on cholesterol levels (e.g. by reducing chronic inflammatory processes). **GPs wishing to abide by NICE and QoF parameters should perform a baseline and 3-months’ treatment non-HDL-C targeting a \(>40\%\) non-HDL-C reduction and <5.0 mmol/l total cholesterol.**

Locally however\(^3\), we recommend a baseline and 3 months’ post initiation total cholesterol only. Use the relative drop to assess the efficacy of the statin and to determine the need for dose titration, additional agent and further lifestyle interventions.

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

Reported side effects are the most common reason for statin treatment discontinuation. Epidemiological studies have shown that “about 70–80\% of statin-treated patients are tolerant to treatment, and 20–30\% are suspected to be statin intolerant” but that “a certain diagnosis of statin intolerance is found in about 5–6\% of patients”\(^4,5\). The reported incidence of statin side-effect is much lower in statin-taking patients participating in double-blinded RCT (who do not know if they are on a statin or not) than in statin-taking patients in observational studies (where patients know they are on a statin)\(^6\).

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” (including muscle pain and rhabdomyolysis)\(^7\). The same study did conclude that there is a small increase in Type 2 diabetes (in the order of 1 new case for every 100 patients treated for 5 years), but statins remain associated with a reduction in cardiovascular events and benefits outweigh any possible harm.
It is clear that the statin “nocebo effect” exists; “the goal of the nocebo-conscious clinician is to avoid creating negative expectations and to counter any that already exist” 9. Many strategies for this exist but the key is to remind patients that statins are typically well tolerated, serious side effects are rare and statins save lives and protect from life-changing events such as non-fatal MIs and strokes.

WHAT SHOULD I DO ABOUT STATINS AND MUSCLE PAIN?

The heterogeneous cluster of muscular symptoms reported following statin initiation (or dose or statin changes) have been termed statin-associated muscle symptoms (SAMS)8. It is important for GPs to try to distinguish between statin induced myopathy including rhabdomyolysis (i.e. actual destruction of skeletal muscle with concurrent significant detectable release of CK in blood) and myalgias (i.e. muscle pain with no muscle damage and/or no sizable raise in serum CK). Guidelines for monitoring and management of SAMS are almost as heterogeneous as the symptoms themselves! The NICE and European guidelines differ in their advice for monitoring and management of SAMS; their advice is summarised in Table 1.

As a rule of thumb: obtain a baseline CK prior to statin initiation only if there is pre-existing muscle pain and recheck this only if the patient reports SAMS. If the CK is <3x ULN, consider persevering with the statin. If it is >5x ULN consider a statin holiday and titrated statin reintroduction. If it is >10x ULN, stop the statin, assess for rhabdomyolysis and monitor renal function and CK regularly.

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

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

NO and probably not! 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 changes in liver function and in patients with mild ALT-elevation due to steatosis and there has been no indication that statins worsen liver disease5. Since 2012, the U.S. Food and Drug Administration (FDA) safety labels for statins have recommend that liver enzyme tests should be performed before starting statin therapy and (only) as clinically indicated thereafter. GPs wishing to meet abide by NICE should perform a baseline and 3-months and 12-months’ treatment ALT.

Our local guideline10 (based on expert panel opinion) deviates from NICE but echoes the FDA. 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 which case we advise a baseline, 3 months and 12 months’ ALT). In keeping with other guidelines, an ALT persistently overs 3x ULN warrants stopping statins and performing appropriate liver disease screens (See Table 1).

CURRENT GUIDELINES

Advice regarding the monitoring of statin efficacy and side effects from various agencies and from our expert panel is summarised in table 1.

REFERENCES

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

Measure Creatine Kinase (CK)

Y

Pre-existing muscle pain?

N

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

New muscle pain?*

N

Continue statin Annual review Consider up titration to maximal dose

Y

Measure CK

N

Pain resolved within 2 weeks?

Y

CK >5x Upper Limit Normal (ULN)?*

N

Pain tolerable?

N

Statin Holiday [See Box 2]

* Severe muscle pain, dark urine, very high CK (≥10xULN)?

Stop statin immediately

Think rhabdomyolysis!

There is no definitive statin-induced muscle symptom (SAMS) monitoring protocol. This flowchart is a composite of NICE, European and local guidelines.

BOX 1: Raised CK
Exclude exogenous cause (e.g., heavy exercise, surgery, IM injections)
Repeat after 7 days
If still elevated, consider:
- TTI (hypothyroid, hyperthyroid rare)
- UTIs (metabolic disturbance)
- Other med(s) (e.g., fibrates, ARBs, β-blockers, ARBs, xanthine, hydroxychloroquine, 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 10mg 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.

<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>
</tr>
</thead>
<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>
</tr>
<tr>
<td>↓Monitoring of↓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Lipids</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>How</td>
<td>Full lipid profile (total cholesterol, HDL cholesterol, triglycerides [non-fasting])</td>
<td>At least LDL-C, ideally full lipid profile</td>
<td>Total cholesterol</td>
</tr>
<tr>
<td>Pre-initiation</td>
<td>&gt;= 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 [TC, HDL-c and non-HDL-c only]</td>
<td>in 8±4 weeks</td>
<td></td>
</tr>
<tr>
<td>Medication change</td>
<td>No mention of test interval if target not reached and/or treatment changed</td>
<td>8±4 weeks until target reached</td>
<td></td>
</tr>
<tr>
<td>Ongoing</td>
<td>Consider an annual non-fasting lipid profile</td>
<td>Once target reached: annually</td>
<td>Consider regular review (total cholesterol only)</td>
</tr>
<tr>
<td><strong>Liver enzyme</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>How</td>
<td>ALT or AST only</td>
<td>ALT only</td>
<td>ALT only</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>Medication change</td>
<td>No mention of rpt interval if treatment changed</td>
<td>After treatment modification: 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>
<tr>
<td>If abnormal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3x ULN</td>
<td>Do not exclude from treatment</td>
<td>Continue and recheck liver enzymes in 4-6 weeks</td>
<td>remain on statin</td>
</tr>
<tr>
<td>&gt;3x ULN</td>
<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>
</tr>
</tbody>
</table>
Table 1: CONT'D.

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| ↓Monitoring of↓ | | | |
| CK (muscle pain) | Creatine Kinase | Creatine Kinase | If the patient develops adverse symptoms on the starting dose of atorvastatin, consider alternative statin (e.g. pravastatin or rosuvastatin) |

<table>
<thead>
<tr>
<th>How</th>
<th>Pre-initiation</th>
<th>Post-initiation</th>
<th>Medication change</th>
<th>Ongoing</th>
<th>If abnormal:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Only if &quot;they have had persistent generalised unexplained muscle pain&quot;</td>
<td>If muscle symptoms (pain, tenderness, weakness)</td>
<td>Not discussed but presumably as above</td>
<td>Nil routine monitoring</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1x before initiation</td>
<td>Only if myalgia</td>
<td>Not discussed but presumably as above</td>
<td>Nil routine monitoring</td>
<td></td>
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<th>Pre-initiation</th>
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<tr>
<td>&gt;5x ULN, do not start; recheck in 7/7; no statin if persists at &gt;5x ULN</td>
<td>Do not exclude from statin therapy if &lt;3x ULN</td>
</tr>
<tr>
<td>&gt;4x ULN, Do not start treatment, recheck</td>
<td>&lt;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) &gt;4xULN and &lt;10x ULN: no symptoms = continue statin + CK every 2-6 weeks symptoms = stops statin, monitor for normalisation CK, rechallenge at lower dose &gt;10x ULN: stop treatment, check renal, CK every 2 weeks</td>
</tr>
</tbody>
</table>