7. Can cholesterol be too low to warrant lipid-lowering therapy?

There has been no formal clinical trial data investigating the effect of statins in patients with initial total cholesterol levels below 3.5mmol/L. Epidemiological data suggests that there is a log linear relationship between cholesterol and CV risk down to levels of approximately 2mmol/L. Evidence for the safety of achieving these levels can be extrapolated from PROVE-IT, where there was no excess of adverse events associated with LDL as low as 1-1.5mmol/L.

A pragmatic approach would be to consider statin therapy in patients with established CV disease or diabetes with initial total cholesterol of > 2.5mmol/L; as cholesterol will be contributing to their CV risk, however minimally. (These patients are relatively rare in the UK population).

For primary prevention (patients without established CV disease, but with a calculated CV risk > 20% over 10 years); treatment should ~~only~~ be considered where baseline total cholesterol levels are in excess of 3.5mmol/L.

- *Wiviott SD, Cannon CP, Morrow DA, Ray KK, Pfeffer MA, Braunwald E; PROVE IT-TIMI 22 Investigators. Can low-density lipoprotein be too low? The safety and efficacy of achieving very low low-density lipoprotein with intensive statin therapy: a PROVE IT-TIMI 22 substudy. J Am Coll Cardiol. 2005 Oct 18;46(8):1411-6.*

8. What should I do with patients ~~with or at risk of CVD~~ whose primary lipid abnormality is raised triglycerides?

Most elevations of triglycerides are secondary to other causes, such as excess alcohol intake, diabetes, renal or liver disease. In patients with isolated raised triglycerides, care should be taken to ensure that secondary causes are identified and addressed.

There is little trial data to inform clinical practice regarding initiating lipid-lowering drug therapies in this instance. All statins have a significant TG lowering effect, as well as reducing total and LDL cholesterol levels. Statins are also supported by a broad evidence base demonstrating mortality and morbidity benefits in patients with or at risk of CV disease and initial total cholesterol levels as low as 3.5mmol/L. In most of these outcome studies, patients with raised triglycerides were excluded. In addition, there are few outcomes studies with other lipid-lowering drug classes. In view of this, in most patients with or at risk of CV disease, even if the primary lipid abnormality is raised TG, it is appropriate to initiate a statin in the first instance. In such patients, if triglycerides remain elevated despite statin therapy, seek specialist advice.

Where pre-treatment levels are significantly elevated (TG >10) then there is a risk of acute pancreatitis. Therefore TG >10 in the absence of obvious secondary causes should be referred directly to the lipid clinic for specialist management and treated with a fibrate in the intervening period.

9. What about statins in older people?

Though published guidelines do not consider it necessary to monitor lipid levels in patients over 74, elderly people with CVD may benefit from treatment with statins. There is evidence of a decrease in coronary events, but not mortality, in patients between 70 and 82 years of age. There is less evidence of stroke prevention, but there may be some benefit after 3 years of therapy. For primary prevention, NICE states that, if a person is 75 or over they should be considered at increased risk of CVD, and likely to benefit from statin treatment, particularly if they smoke or have high blood pressure. NICE found statins to be cost effective for all age groups (including people older than 75 years of age) at a 20% or greater 10-year risk of CVD.

It is advisable to prescribe statins in elderly patients by taking co-morbidities into account and assessing potential benefits to the individual patient. The decision to commence or withhold a statin should not be based on age alone.

- *~~http://www.prodigy.nhs.uk/guidance~~*
- *MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20, 536 high-risk individuals: a randomised placebo-controlled trial, Lancet, 2002, 360(9326): 7-22. • Shepherd J et al, Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial, Lancet. 2002 Nov 23; 360 (9346): 1623-30*
- *D Wood et al. Joint British recommendations on prevention of coronary heart disease in clinical practice. Heart 1998 80(suppl 2): 1-29.*

10. Which patients should be considered for cessation of statin therapy

Following discussion with the patient, consideration should be given to stopping statins in the following circumstances:

- A coexisting life-threatening condition (that shortened expected survival to less than two years) other than vascular disease (such as very severe chronic airways disease or any cancer other than non-melanoma skin cancer)
- Active liver disease (cirrhosis or hepatitis) or unexplained persistent elevations of serum transaminases (2 consecutive measurements with 3 or more times the upper limit of normal; exclude uncorrected hyperthyroidism)
- Inflammatory muscle diseases (such as polymyositis) or where creatine kinase > 5 times upper limit of normal (in the absence of strenuous exercise) or where myopathy is suspected. See SLCSN Guidance on Prescribing Statins for more information.
- If treatment with systemic itraconazole, ketoconazole, erythromycin, clarithromycin or telithromycin is unavoidable, therapy with simvastatin must be suspended during the course of treatment or, if long-term, initiation of an alternative statin should be considered
- Patients who are pregnant, or planning a pregnancy and in those who are breast-feeding
- Therapy with simvastatin should be temporarily stopped a few days prior to elective major surgery and when any major medical or surgical condition supervenes.

• Cannon et al. Intensive versus Moderate lipid lowering with statins after acute coronary syndromes. Nejm 2004, 350;15, 1495-1504
• MRC/BHF Heart Protection collaborative study group. Cholesterol-lowering therapy and of antioxidant vitamin supplementation in a wide range of patients at increased risk of coronary heart disease death: early safety and efficacy experience. Eur heart j 1999, 20, 725-41
• Zocor® data sheet, Merck, Sharp and Dohme Limited, last updated 30 Jan 2006. ~~www.medicines.org.uk~~

11. What is the role of diet in cholesterol-lowering?

Obesity is strongly associated with CVD and metabolic disorders. People with a BMI > 29 have a 4 fold increased risk of CVD (compared to those with BMI < 21) even when adjusted for other risk factors (age, smoking etc). Clinical trials of weight loss on cholesterol have shown variable effects. A relatively old meta-analysis demonstrated that for every 10kg of weight loss, total cholesterol fell by approximately 0.5mmol/l. This equates to an 8 – 10% reduction in total cholesterol. The greatest reduction occurred in the first 4 to 8 weeks of weight loss and the cholesterol levels increased if weight was regained. A 10% reduction in body weight is thought sufficient to maintain the lower cholesterol level.

- *Willett WC et al. JAMA 1995;273:461-465*
- *Dattilo AM, Kris-Etherton PM. Effects of weight reduction on blood lipids and lipoproteins: a meta-analysis. Am J Clin Nutr 1992;56:320-328.*

12. How safe are statins?

For most people, statins are safe and well-tolerated.

In the heart protection study (HPS) involving 20,536 patients treated with 40 mg/day of simvastatin (n = 10,269) or placebo (n = 10,267), the safety profiles were comparable between patients treated with simvastatin 40 mg and patients treated with placebo over the mean 5 years of the study. Discontinuation rates due to side effects were comparable (4.8% in patients treated with simvastatin 40 mg compared with 5.1% in patients treated with placebo).

Adverse reactions have also usually been mild and transient with atorvastatin. Less than 2% of patients were discontinued from clinical trials due to side effects attributed to atorvastatin. The most frequent (1% or more) adverse effects associated with atorvastatin, in patients participating in controlled clinical studies were: insomnia, headache, and gastrointestinal disorders (abdominal pain, dyspepsia, nausea, flatulence, constipation, diarrhoea).

The only well documented and consistent adverse effects (from large, controlled, randomised trials) associated with statins are muscle toxicity, including myopathy and rhabdomyolysis, and effects on liver enzymes.
A full discussion of the safety of statins can be found in appendix one.

- *Lipid modifying treatment; Merec bulletin; vol 19; no 3; Dec 2008*
- *MRC/BHF heart protection study of cholesterol lowering with Simvastatin in 20536 high-risk individuals; a randomised placebo-controlled trial; The Lancet; vol 360; issue 9326; pages 7-22; 6th July 2002*
- *SPC for Zocor® Simvastatin: last updated 09/12/2008 (www.medicines.org.uk*
- *SPC for Lipitor® Atorvastatin: last updated 24/12/2008 (www.medicines.org.uk)*
- *The safety of statins in clinical practice; The Lancet; Nov 24-30; 2007; 370; 1781-1790:*

13. Are statins suitable for use during pregnancy and breast-feeding or in women of child-bearing age?

Statin use is contraindicated in both pregnancy and breast-feeding. In women of child-bearing age it may be appropriate to delay the initiation of statin therapy or to address contraceptive needs depending on the wishes of the patient. For women already initiated on statin therapy and who are now considering pregnancy, the statin therapy should be withdrawn.

14. What should I do if my patients renal function deteriorates during treatment with simvastatin?

No modification of dosage should be necessary in patients with moderate renal insufficiency. In patients with severe renal insufficiency (creatinine clearance – EGFR < 30 ml/min), dosages above 10 mg/day should be carefully considered and, if deemed necessary, implemented cautiously

- *Merck, Sharpe and Dohme. Zocor – Summary of Product Characteristics. Accessed via http://emc.medicines.org.uk/), Mar 09.*

15. What drug interactions do I need to really worry about with simvastatin?

Simvastatin and atorvastatin are metabolised in the liver by the cytochrome P450 enzyme system, and drugs that affect this enzyme system significantly are likely to require modifications to dose or caution in the use of the combination. Interactions with the following drugs / drug classes are usually clinically significant this list is not exhaustive:

- **Anticoagulants** – The effects of warfarin can be increased by simvastatin and atorvastatin, although the effect is often small, this may require reductions in the warfarin dose. Pravastatin does not interact with warfarin
- **Amiodarone** – Amiodarone can inhibit simvastatin and to a lesser extent atorvastatin metabolism and can result in increased risk of myopathy. A maximum dose of simvastatin 20mg daily is recommended if used concomitantly with amiodarone.
- **Antifungals** – Azole antifungals (e.g. fluconazole and itraconazole) can markedly increase levels of simvastatin, leading to increased risk of toxicity. When short courses of systemic antifungal treatment are required, simvastatin should be temporarily stopped. Longer-term treatment may require a switch to a non-interacting statin, such as pravastatin. In cases where co-administration of itraconazole with atorvastatin is necessary, the maintenance dose of atorvastatin should not exceed 40 mg daily. Patients who normally require 80 mg of atorvastatin should either reduce their dosage during concomitant itraconazole treatment, or alternatively (for short courses of this antibiotic) where not practical, a temporary suspension of treatment with atorvastatin may be considered.
- **Calcium channel blockers** – Diltiazem and verapamil can significantly increase plasma levels of simvastatin and to a lesser extent atorvastatin, although the combinations need not be avoided. Patients on calcium channel blockers should be started on the lowest dose of statin and carefully titrated. The maximum dose of simvastatin for patients on concomitant verapamil is 20mg daily and for those on concomitant diltiazem is 40mg

daily. Patients on atorvastatin and diltiazem should be maintained on the lowest effective dose of atorvastatin to adequately control lipid levels.

- **Ciclosporin** – Ciclosporin and simvastatin / atorvastatin compete for the same metabolic pathway, leading to a significant increase in statin levels. Doses of simvastatin should not normally exceed 10mg daily in patients taking ciclosporin In cases where co-administration of atorvastatin with ciclosporin is necessary, the dose of atorvastatin should not exceed 10 mg.
- **Colchicine** – This interaction is rare but potentially important. Patients should be reminded to report muscle weakness or tenderness if taking simvastatin and given colchicine.
- **Danazol** – The combination of danazol and simvastatin increases the risk of muscle toxicity and the dose of simvastatin should not exceed 10mg daily if the combination is used.
- **Fibrates** – Both fibrates and statins can cause muscle toxicity, and the effects of taking both together may be additive or synergistic. Fibrate/statin combinations should normally be avoided (especially gemfibrozil), but if there are significant expected benefits then a low dose of simvastatin or atorvastatin should be used.
- **Imatinib** – Imatinib can increase serum levels of simvastatin, and the simvastatin dose should be decreased by half.
- **Macrolide antibiotics** – The makers of simvastatin recommend that treatment should be stopped if courses of erythromycin or clarithromycin are required, due to increased levels of simvastatin in plasma, although not all patients seem to be affected by this interaction. In cases where co-administration of clarithromycin with atorvastatin is necessary, the maintenance dose of atorvastatin should not exceed 20 mg daily. Patients who normally require 40mg or 80mg of atorvastatin should either reduce their dosage during concomitant clarithromycin treatment, or alternatively (for short courses of this antibiotic) where not practical, a temporary suspension of treatment with atorvastatin may be considered.
- **HIV Protease inhibitors** – The ability of protease inhibitors to increase plasma levels of simvastatin is well established, and this combination should normally be avoided. All HIV patients with or at risk of CVD requiring statin therapy should be managed by their local specialist HIV unit.
- **Rifampicin** – Rifampicin can reduce plasma levels of simvastatin, and the dose of simvastatin may need to be increased.

- *Joint Formulary Committee. British National Formulary, 52nd Ed. London: British Medical Association and Royal Pharmaceutical Society of Great Britain, 2006.*
- *Stockley, I H (Ed). Stockley's Drug Interactions (accessed via Medicines Complete, January 2007.)*
- *Merck, Sharpe and Dohme. Zocor – Summary of Product Characteristics. Accessed via ~~http://emc.medicines.org.uk/~~), Mar 09.*
- *Pfizer ltd. Lipitor Summary of Product Characteristics. Accessed via ~~http://emc.medicines.org.uk/~~), Apr 2009.*

16. What should I advise my patients about consumption of grapefruit and grapefruit juice?

Patients prescribed simvastatin should be advised to avoid eating grapefruit or drinking grapefruit juice. Grapefruit juice is a potent inhibitor of CYP450 3A4, which is responsible for the first-pass metabolism of simvastatin. This interaction leads to a substantial (9-fold) increase in peak serum drug levels and hence increases the risk of developing rhabdomyolysis. The interaction is well documented with grapefruit juice, but there are also case reports of increased simvastatin levels and adverse events associated with consumption of grapefruit itself.

If the patient is unwilling to stop grapefruit consumption, pravastatin and rosuvastatin are free of this interaction. Atorvastatin, metabolized via the same pathway as simvastatin, also interacts

with grapefruit juice but to a lesser extent. The CSM recommends that patients on atorvastatin should be advised to avoid consuming 'large quantities' of grapefruit juice.

- Committee on safety of medicines (2004): 'Current problems in Pharmacovigilance' Statins and Cytochrome P450 interactions. Vol. 30 Oct. 2004 1-2. ~~http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&useSecondary=true&ssDocName=CON007447&ssTargetNodeId=834~~

17. My patient is on warfarin – how do I start simvastatin?

Increases in International Normalised Ratio (INR) and associated risk of bleeding, have been reported in patients taking simvastatin with warfarin.

Simvastatin may be added to the therapeutic regimen of a patient on warfarin but the INR should be determined before starting the simvastatin and more frequently during early therapy (the first 4 – 6 weeks) to ensure no significant change in INR occurs. Once a stable INR has been achieved, monitoring intervals can be reduced to those usually recommended for patients on long-term warfarin. The same applies if the dose of simvastatin is changed or discontinued.

- *Zocor® data sheet, Merck, Sharp and Dohme Limited, last updated 30 Jan 2006.* ~~*www.medicines.org.uk*~~

18. My patient has developed muscle aches on a statin – what should I do?

Please refer to SLCSN Guidance on Prescribing Statins and Appendix One

19. My patient is complaining of aching joints since starting their statin - what should I do?

Statin-associated myositis is a significant adverse effect and needs to be identified and addressed with urgency. Joint ache can be due to referred muscle pain, a manifestation of myalgia, therefore the first step here is to exclude any muscular component and check creatine kinase (CK). In patients with very high initial cholesterol levels, isolated aching in the joints can occur early in treatment as deposited cholesterol is being mobilized out of the joints. The most commonly affected joints are the ankles and knuckles. In such cases, joint pain will generally dissipate over time and, provided muscle pain is not evident and CK not raised, these patients can be reassured and remain on statin therapy.

20. My patient wants to take her statin in the morning – will simvastatin work or should I use a longer acting agent first-line?

For simvastatin, the evidence suggests that a dose taken in the evening lowers cholesterol marginally more than the same dose taken in the morning. This effect may be clinically significant - one study showed a difference in total cholesterol of 0.38mmol/L and LDL cholesterol of 0.25mmol/L when comparing morning and evening efficacy.

However, morning doses of simvastatin do give substantial reductions in cholesterol from baseline and, on the basis of cost-effectiveness, should still be used first-line. If after an appropriate duration of therapy the cholesterol targets have not been met, then alternative agents should be considered. Morning dosing should be considered in patients with compliance problems - better to have a (large) partial effect, than no effect at all because the patient always forgets their evening dose; also adverse effects tend to be more obvious (especially GI upset) when statins are taken on an empty stomach just before bed, than with the evening meals or even earlier in the day if necessary. In fact, in 4S and HPS the dose was given at 6pm rather than the 'night-time' dose we have all become accustomed to recommending.

- *Wallace et al. 2003. Taking Simvastatin in the morning compared with in the evening. Randomised Controlled Trial 2003; 327: 788*
- *Bandolier Extra. Cholesterol and Statins. April 2004. Pages 26 - 27*

21. Carers only go in once a day to observe patients take medicines from their dosette, would changing to atorvastatin be better?

As discussed in the previous question, simvastatin is marginally less effective at lowering cholesterol when taken in morning compared to the evening. However, it still lowers cholesterol significantly from baseline and is therefore an appropriate first-line choice regardless of the time of day it is administered. In order to ensure compliance, the statin dose in this case should be given with the other prescribed medications, when the carer is available to assist and observe. As for any other patient, if target cholesterol levels are not achieved on simvastatin after an appropriate duration of treatment, atorvastatin may be a suitable second line alternative.

22. My patient feels sick after her night-time dose of simvastatin – what should I advise?

Gastrointestinal disturbances are common side effects of simvastatin, this is particularly evident if the dose is taken at night on an empty stomach. This adverse effect can be reduced by taking simvastatin with or after the evening meal. If GI disturbance persists, the patient should be advised to take the dose early in the day, for example, with lunch or breakfast.

- *Zocor® data sheet, Merck, Sharp and Dohme Limited, last updated 30 Jan 2006. ~~www.medicines.org.uk~~*

23. My patient complains she cannot get a good nights sleep since starting simvastatin – what should I do?

Insomnia is a common adverse effect of all statins and in the past we have advised that patients take their statin at night, which has probably contributed to this. The evidence suggests that the statin dose can be given with or after the evening meal. This may reduce the level of insomnia caused. If this does not improve with an evening dose, the patient should be advised to try taking their statin in the morning for a period of two weeks, and should consider taking the dose in the morning permanently if sleeplessness resolves. In persistent cases, switching to a water-soluble statin (such as pravastatin) taken in the morning may improve the situation. Lipid levels should be rechecked if the dose is permanently moved to the morning to ensure lipid targets are still being achieved.

In some cases, insomnia may be due to referred muscle pain, a manifestation of myalgia – a mild, sub-clinical form is often more noticeable at night. Muscle involvement should therefore be excluded in all patients.

24. What strategies are there to improve adherence?

It is thought that between a third and a half of all medicines prescribed for long-term conditions are not taken as recommended. It is estimated that 50% of people started on lipid-lowering drugs stop within one year, and 75% at 5 years.

Addressing non-adherence is not about getting patients to take more medicines per se. Rather, it starts with an exploration of patients' perspectives of medicines and the reasons why they may not want or are unable to use them. Healthcare professionals have a duty to help patients make informed decisions about treatment and use appropriately prescribed medicines to best effect.

Applying this approach in practice requires:

- a frank and open approach which recognises that non-adherence may be the norm (or is at least very common) and takes a no-blame approach, encouraging patients to discuss non-adherence and any doubts or concerns they have about treatment
- a patient-centred approach that encourages informed adherence, for example discussing the risk versus benefit of treatment.

- identification of specific perceptual and practical barriers to adherence for each individual, both at the time of prescribing and during regular review, because perceptions, practical problems and adherence may change over time.

There are many causes of non-adherence but they fall into two overlapping categories: **intentional and unintentional**. **Unintentional non-adherence** occurs when the patient wants to follow the agreed treatment but is prevented from doing so by barriers that are beyond their control E.g. problems with using the treatment. **Intentional non-adherence** occurs when the patient decides not to follow the treatment recommendations, this could be due to the patient's beliefs about medicines.

- *NICE CG76 (Jan 2009) Medicines adherence. Involving patients in decisions about prescribed medicines and supporting adherence*

25. When is it appropriate to use rosuvastatin?

Rosuvastatin is available within the sector and is recommended for use in specific groups of patients, usually under specialist supervision. Rosuvastatin is not currently licensed for the prevention of CV events.

The following groups of patients may be considered appropriate for rosuvastatin treatment once other strategies have been tried:

- Patients with familial hyperlipidaemia (FH), where other statins have failed to achieve a >50% fall in LDL cholesterol as endorsed by NICE FH guidance. These patients should be under the care of a lipid clinic.
- Patients with CVD requiring 'high intensity statin' therapy (ie post-ACS), with contraindications or drug interactions that prevent the use of high doses of atorvastatin or simvastatin in line with local guidance. Drug interactions that limit the dose of simvastatin and / or atorvastatin include amiodarone, verapamil, diltiazem, erythromycin (long-term), clarithromycin (long-erm), ciclosporin, itraconazole, ketoconazole, HIV protease inhibitors, nefazodone. Check the SPCs for the relevant drugs for an exhaustive list of interactions and see also Q15
- Patients with CVD requiring substantial falls in cholesterol to achieve the minimum audit standard (total cholesterol <5mmol/L and LDL<3mmol/L) with previous failure to tolerate simvastatin and atorvastatin, and where pravastatin is unlikely to deliver the lipid lowering potency required to reach these target levels.

Rosuvastatin, in line with other branded statins, should not be used for routine primary prevention, where simvastatin or pravastatin are the preferred agents on the basis of cost-effectiveness and affordability.

26. What is the role of ezetimibe in lipid modification?

Ezetimibe blocks the intestinal absorption of dietary and biliary cholesterol and related plant sterols, without affecting the uptake of triglycerides or fat-soluble vitamins. The efficacy of ezetimibe in protecting against CV events and its long-term safety are not yet established. Every effort should be made to optimise statin therapy before ezetimibe is introduced. Ezetimibe will give an additional reduction in total cholesterol of 10-14% regardless of the baseline statin used.

In NICE TA132, ezetimibe is recommended for adults with primary (heterozygous familial and non-familial) hypercholesterolaemia:

- whose condition is not appropriately controlled with a statin alone (defined as failure to achieve a target lipid level despite optimisation of statin therapy) or;
- in whom a statin is considered inappropriate or is not tolerated (defined as the presence of clinically significant adverse effects that are considered to represent an unacceptable risk to the patient or that may result in compliance with therapy being compromised e.g. muscle effects, gastro-intestinal disturbance or altered liver function tests)

The recommended dosage of ezetimibe is 10 mg/day, which may be administered at any time of the day, with or without food.

- *NICE TA 132: Hypercholesterolaemia – Ezetimibe. Nov 2007*

27. Is a fasting lipid profile essential for testing cholesterol levels?

A fasting lipid profile is preferable but not essential. Ideally we would recommend that patients have their lipid profile taken after an overnight fast. This can be particularly useful for measuring triglycerides (TGs), since a fasting state allows dietary TGs to be cleared. There is a correlation between fasting TG levels and CVD risk, but the relationship weakens when factors such as total cholesterol, HDL, glucose and obesity are taken into account. Other cholesterol sub-fractions are calculated from the measured triglyceride level, including LDL cholesterol. For that reason, if the patient is non-fasted, only the total cholesterol and HDL cholesterol levels can be considered accurate.

We appreciate that some diabetic patients may find it difficult to manage their control if being asked to fast for longer than usual, or are using insulin for the management of their diabetes. Therefore when undertaking lipid testing in diabetics we would recommend bloods are taken first thing in the morning (if necessary after a light breakfast).

It is recommended that when the results are available, you monitor them against previous lipid profile test results so as to see the overall trend and act accordingly.

28. Is there a role for co-enzyme Q10 in reducing statin-induced myopathy?

The evidence to date does not support the routine use of coenzyme Q10 supplementation with statin treatment at licensed doses. Previous studies have been inconclusive, primarily due to the low numbers of patients successfully recruited; although case reports do indicate a benefit. More information is needed about the cause of statin-induced myopathy, how exogenous coenzyme Q10 affects endogenous tissue levels and whether restoring these levels results in a clinical reduction in musculoskeletal toxicity. As the benefits of statins are well researched and they are in widespread use, it is important that measures are taken to reduce the risks associated with myopathy. Such measures include: using appropriate statin doses, measuring baseline creatine kinase levels before starting treatment in patients with predisposing factors, avoiding interacting medicines and educating patients to recognise and report the signs of myopathy early.

- *Bandolier Coenzyme Q10 and statin myopathy. 2007 161-165*
- *Leo Marcoff; Paul D. Thompson The role of Coenzyme Q10 in Statin Associated Myopathy. JACC 2007; 49 (23) Pages 2231-2237*
- *Should patients on statins take Coenzyme Q10 supplementation to reduce the risk of myotoxicity? www.nelm.nhs.uk. Accessed*
- *9.05.09*

Appendix One

Side Effects and Safety Issues with Statins

Myopathy and Rhabdomyolysis

Myopathy (muscle pain, tenderness or weakness), with a blood creatine kinase concentration greater than ten times the upper limit of the normal range, typically occurs in fewer than one in 10,000 patients on standard statin doses. This risk varies between statins and increases with the use of higher doses and interacting drugs. Rhabdomyolysis is a rarer (less than one case in 1,000,000 patients per year) and more severe form of myopathy (10% case fatality). This condition involves muscle breakdown with myoglobin release into the circulation, which can cause a brown discolouration of urine, and the risk of renal failure. Rhabdomyolysis is usually diagnosed when creatine kinase concentration is greater than 40 times the upper limit of normal, or if there is evidence of acute renal failure or worsened renal function. Stopping statin use reverses these side effects, usually leading to a full recovery.[1]

The risk of myopathy with statins seems to be affected by drugs which interfere with the metabolism of the statin via the cytochrome P450 liver enzyme system. Some patients are also more susceptible eg. renally impaired, hypothyroid, with a serious debility or those aged over 80 years.[1]

In controlled trials of standard dose statin treatment, only a very low extra risk of myopathy has been noted, typically less than 0.01%. In the three large trials (n=19500) of pravastatin 40mg daily compared to placebo, there were no reported cases.[4] In the two trials of atorvastatin 10mg daily versus placebo involving over 13,000 patients with diabetes or hypertension, there were three cases (2 in the atorvastatin arm and 1 in the placebo arm), and in the trials of simvastatin 20-40mg daily, the excess incidence of myopathy among those taking simvastatin was less than 0.01% per year.[1]

The product information for simvastatin gives the estimated incidence of myopathy with 80mg daily as 0.53% compared with 0.08% for 40mg daily. In a trial comparing simvastatin 80mg to placebo for 4 months and then 20mg dosing in 4497 patients with ACS, there were nine cases of myopathy among the 80mg group compared with one case in the placebo group.[3] Almost 25000 patients have been randomised into trials comparing atorvastatin 80mg with various standard regimens or placebo. No excess risk of myopathy was reported among those allocated this higher dose of atorvastatin; masked comparison with 10mg atorvastatin 4.8% risk compared to 4.7% with atorvastatin 10mg; or in the trial versus placebo 5.5% risk with 80mg compared to 6.0% risk with placebo.[1]

Although most likely to occur within a few months of starting statin treatment, or of increasing the dose, cases of myopathy have been reported even after some years of apparently stable statin treatment, usually as the result of starting an interacting drug.[1]

Routine measurement of creatine kinase (CK) is not of use in detecting the rare cases of myopathy at statin standard doses. Patients should be asked to report any new or unexplained muscle pain or weakness, and then creatine kinase should be measured in such patients.[1]

Liver Effects

Asymptomatic increases in the concentrations of liver transaminases (in particular alanine and aspartate transaminases) have been recorded with all statins, but are not clearly associated with an increased risk of liver disease. The increases in transaminases with statins are generally seen in the first six months of treatment and are asymptomatic, but reverse on stopping the statin treatment or with dose reduction. These changes could be a hepatic response to lipid-lowering rather than hepatotoxicity.[1]

In the HPS there was no significant excess of patients with elevated liver enzymes (alanine transaminase more than three times the upper limit of normal); 77 (0.75%) with simvastatin 40mg compared to 65 (0.63%) with placebo. However, there were more confirmed increases of alanine transaminase with the statin in the first four months of the study; 8 (0.08%) cases with simvastatin compared to 0 cases with placebo, compared with later in the trial.[1]

There is no convincing evidence from trials assessing standard statin doses that increases in either transaminase is associated with liver damage such as reported hepatitis or any other liver related serious events. The effect on transaminases seems to be dependent on the statin dose, and effects on other liver enzymes and bilirubin emerge with higher doses. However, unlike with myopathy, the effects may be because of a greater fall in LDL cholesterol.[1]

The only trial to have raised concern about statin hepatotoxicity compared atorvastatin 80mg daily with placebo in 3086 patients with ACS. Over the four months of the study, 38 (2.5%) of the atorvastatin patients compared with 9 (0.6%) of the placebo patients had transaminases over three times the upper limit of normal and three of the 38 patients taking atorvastatin 80mg were hospitalised with hepatitis.[1]

NICE advises that baseline liver enzymes should be measured before starting a statin. Transaminases should be measured within three months of starting treatment and at 12 months, but not again unless clinically indicated. Patients who have transaminases that are raised but are less than three times the ULN should not be routinely excluded from statin therapy.[4]

Statin product information contraindicates the prescribing of statins in active liver disease, so in patients with baseline liver abnormalities, active liver disease must first be excluded. At standard doses, effects on liver enzymes are rare (<1%), but at higher doses different statins vary in the degree to which they raise liver enzymes. This may just parallel their LDL cholesterol-lowering efficacy or could be a specific hepatotoxic effect of particular statins. [1]

Many other possible side effects are listed in the relevant statin product information (see www.medicines.org.uk).

Miscellaneous Effects

Less well known side-effects of statins as a class include depression, sleep disturbances, memory loss, and sexual dysfunction. Statins may also very rarely be associated with interstitial lung disease. Patients should be advised to seek help if they develop presenting features of interstitial lung disease such as dyspnoea, non-productive cough, and deterioration in general health. The incidence of peripheral neuropathy during statin therapy is similar to that of myopathy. NICE advises that if a person taking a statin develops an unexplained peripheral neuropathy, the statin should be discontinued and specialist advice should be sought. Any

suspected adverse drug reactions with statin treatment should be reported through the yellow card scheme.[5]

A meta-analysis from 2006 looked at the risk of adverse events with statins compared to placebo and reported that:
"statin therapy increased the risk of any adverse effect (AE) by 39% (OR = 1.4; 95% CI, 1.09-1.80; P = 0.008; NNH [number needed to harm] = 197) compared with placebo. Statins were associated with a 26% reduction in the risk of a clinical cardiovascular event (OR = 0.74; 95% CI, 0.69-0.80; P < 0.001; number needed to treat = 27). Therefore, treating 1000 patients with a statin would prevent 37 cardiovascular events, and 5 AEs would be observed.[6]

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