The safety of statins in clinical practice

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Statins are effective cholesterol-lowering drugs that reduce the risk of cardiovascular disease events (heart attacks, strokes, and the need for arterial revascularisation). Adverse effects from some statins on muscle, such as myopathy and rhabdomyolysis, are rare at standard doses, and on the liver, in increasing levels of transaminases, are unusual. Myopathy—muscle pain or weakness with blood creatine kinase levels more than ten times the upper limit of the normal range—typically occurs in fewer than one in 10 000 patients on standard statin doses. However, this risk varies between statins, and increases with use of higher doses and interacting drugs. Rhabdomyolysis is a rarer and more severe form of myopathy, with myoglobin release into the circulation and risk of renal failure. Stopping statin use reverses these side-effects, usually leading to a full recovery. Asymptomatic increases in concentrations of liver transaminases are recorded with all statins, but are not clearly associated with an increased risk of liver disease. For most people, statins are safe and well-tolerated, and their widespread use has the potential to have a major effect on the global burden of cardiovascular disease.

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Introduction

The statins are a widely used group of cholesterol-lowering agents that act by inhibiting the enzyme 3-hydroxy 3-methylglutaryl CoA (HMG CoA) reductase, which catalyses the rate-limiting step in cholesterol biosynthesis.[1,2] Since statins were first approved in 1987, their ability to reduce the risks of vascular death, non-fatal myocardial infarction, stroke, and the need for arterial revascularisation procedures has been shown by several large, high-quality randomised trials.[3]

In these trials, the extent of risk reduction was judged to be directly proportional to the degree to which LDL (low-density lipoprotein) cholesterol was lowered consistent with this being the main mechanism.[3,4] As a consequence, and because of the additional benefit shown with more intensive statin therapy,[5–7] there has been a trend toward using higher doses of statin. Furthermore, cholesterol-lowering is now recommended for a wide range of people at cardiovascular risk, including those with average and below-average lipid levels.[8,9] This change is leading to increased statin use and to the use of more intensive regimens. Hence, the safety of this group of drugs is of considerable importance.

Six statins are available in most parts of the world: lovastatin (first licensed in 1987 but not available in the UK), simvastatin (1988), pravastatin (1991), fluvastatin (1994), atorvastatin (1997), rosuvastatin (2003), and pitavastatin[10,11] (2003—available in Japan and India only) (table 1). Cerivastatin was approved in 1998 but then withdrawn in 2001 because of a high risk of rhabdomyolysis.[12]

This Review will examine two aspects of statin safety: the safety of achieving and maintaining low levels of total and LDL cholesterol; and the specific safety of the available statins at different doses. The adverse effects on muscle and on liver enzymes generally apply to all statins, but other aspects of safety (or the propensity for these adverse effects) should not automatically be extrapolated from one statin to another. This Review concentrates on safety information derived from randomised trials of specific statins, taking account of reports of spontaneous adverse effects and other sources of safety data.[13,14] Controlled randomised trials avoid the bias inherent in spontaneous reporting of adverse effects or retrospective study designs, and are therefore the most appropriate means of assessing common adverse effects. Although such trials might exclude some vulnerable individuals, a follow-up of 5–6 years allows time for participants to become at risk, and therefore provide valuable safety information. In contrast, observational studies without a control group are less informative about common symptoms[15] but, along with other sources of data, remain important for detection of rare side-effects.[14]

In this Review, "standard dose" refers to the commonly prescribed daily doses which typically reduce LDL cholesterol by 30–45% (ie, atorvastatin 10–20 mg, fluvastatin 40–80 mg, lovastatin 40 mg, pravastatin 40 mg, rosuvastatin 10 mg, and simvastatin 20–40 mg).

All statins competitively inhibit the rate-limiting enzyme HMG CoA reductase in the metabolic pathway of cholesterol biosynthesis.[16] They therefore reduce the concentration of downstream metabolic by-products including mevalonate,[17] which in turn leads to increased expression of LDL receptors on hepatocytes, and to increased uptake of LDL cholesterol from the circulation.[16] Statins also tend to reduce the production of

Search strategy and selection criteria

I searched PubMed for publications between 1985 and 2006, using search terms including "safety of statins", "myopathy", "rhabdomyolysis", "hepatotoxicity", "safety", and "randomized" in various combinations and with individual statin names. I concentrated on larger randomised studies but referenced smaller-scale studies, observational studies, and other reviews where appropriate. I also searched the reference lists of articles identified by this search strategy and selected those judged relevant. I used manufacturers' published information about individual statins and consulted experts in the field. My reference list was modified on the basis of comments from peer reviewers.

	Licensed dose range (% LDL cholesterol reduction)*	Metabolism	Most important drug interactions increasing myopathy risk†
Lovastatin	20–80 mg daily (30% with 40 mg)	Mainly CYP3A4	Potent inhibitors of CYP3A4‡,
Simvastatin	10–80 mg (41% with 40 mg)	Mainly CYP3A4	Potent inhibitors of CYP3A4
Pravastatin	20–80 mg daily (34% with 40 mg)	Sulphation, biliary, and urinary excretion	
Fluvastatin	40–80 mg daily (23% with 40 mg)	CYP2C9 (some CYP2C8 and CYP3A4)	Inhibitors of CYP2C9
Atorvastatin	10–80 mg daily (38% with 10 mg)	CYP3A4	Potent inhibitors of CYP3A4
Rosuvastatin	5–40 mg daily (45% with 10 mg)	Minimal metabolism (via CYP2CP and some CYP2C19) and biliary excretion	
Pitavastatin	2–4 mg daily (42% with 2 mg)	Minimal metabolism (via CYP2C8 and CYP2C9), lactonisation, and bilary excretion	Unclear

*Typically, doubling of a statin dose produces an additional 6% absolute decrease in LDL cholesterol—eg, simvastatin 20 mg daily reduces LDL by 35% and 40 mg daily by 41%. †With all statins, the risk of myopathy is also increased by ciclosporin and gemfibrozil, and possibly other fibrates; prescribing information will provide further details and other interactions. ‡Including itraconazole, ketoconazole, erythromycin, clarithromicin, telithromycin, nefazodone, HIV protease inhibitors, and regular ingestion of grapefruit juice. Information from relevant Data Sheets[19]

Table 1: **Efficacy and safety characteristics of statins**

apolipoprotein B, leading to reduced VLDL (very low density lipoprotein) secretion from the liver.[18] Statins have qualitatively similar effects on lipid levels, but their efficacy in lowering LDL cholesterol varies (table 1).

Statins are metabolised in the liver; detailed discussion of their metabolism and mechanisms of drug interactions can be found elsewhere.[19,20] Statins that are metabolised predominantly by the cytochrome P-450 system can interact with other drugs, some of which involve commonly prescribed drugs (table 1 and panel).[21] Statins also vary in their propensity to cause drug interactions through other mechanisms (eg, by blocking organic anion transporter peptides);[20,22] genetic polymorphisms within these systems also affect drug disposition and the likelihood of interactions. Prescribing information should therefore be routinely consulted when drug interactions are possible.

Maintaining very low cholesterol levels

Observational cohort studies have consistently shown that people with low total cholesterol levels (eg, <4·0 mmol/L) are at a higher risk of subsequent death from cancers, respiratory causes, haemorrhagic stroke, and non-medical causes of death than are people with higher baseline cholesterol levels.[23,24] Some of these associations can be explained by reverse causality (eg, cancer-reducing cholesterol levels while increasing risk of subsequent death), but concerns remain that low total cholesterol levels, as well as lowering cholesterol to very low levels, could be harmful.[25,26] However, populations eating diets which are low in saturated fats often have average total cholesterol about 4 mmol/L, very low rates of coronary heart disease, and no clear excess of deaths from other causes.[27,28] Also, neonates have LDL cholesterol of about 1 mmol/L, as do people with familial hypobetalipoproteinaemia, a rare and generally benign condition caused by heterozygous mutations in apolipoprotein B.[29]

Collective results from large randomised controlled trials of statin treatment have now provided confirmation that reducing cholesterol and maintaining low cholesterol levels for at least 5 years is not only safe but beneficial.[3] Neither overall, nor in individual trials that lowered LDL cholesterol to well below average levels,[30–32] was there any increased risk of the types of non-vascular death suggested by the observational data. A meta-analysis[3] of individual patient data from 14 controlled statin trials in a total of 90 056 participants shows that similar numbers died from non-vascular causes irrespective of whether they were given statin treatment (1730 [3·8%] statin *vs* 1801 [4·0%] control; p=0·1). This result was applicable both overall and for particular causes of non-vascular death such as cancer, hepatic, or respiratory disease. The numbers of people developing cancer over 5 years were also similar (2567 [6·4%] statin *vs* 2536 [6·4%] control). Haemorrhagic strokes were rare but similar in the two groups (105 [0·2%] statin *vs* 99 [0·2%] control; 99% CIs 0·78–1·41; p=0·7) but the wide confidence interval cannot exclude a small risk.

Three of the standard-dose statin trials have provided data from extended follow-up.[33–35] All demonstrated sustained benefits from cholesterol-lowering therapy on cardiovascular mortality or morbidity, and reassuring long-term safety information.

Trials of more intensive statin therapy published since 2004 achieved substantial and sustained LDL cholesterol reductions, typically to below 2·0 mmol/L in those allocated intensive treatment.[5–7,36–39] There is no clear evidence of any serious adverse effect associated with these low LDL levels in these trials, totalling more than 27 000 randomised participants followed-up for up to 5 years (table 2). Furthermore, evidence from these studies

***Panel:* Drugs that might interact with statins**

Ciclosporin

Fibrates

- Gemfibrozil, bezafibrate, fenofibrate, and ciprofibrate

Azol anti-fungals

- Itraconazole, ketoconazole, and miconazole

Macrolide antibiotics

- Erythromycin, telithromycin, and clarithromycin

Anti-arrhythmics

- Verapamil, amiodarone

Nefazodone

Protease inhibitors

- Amprenavir, atazanavir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, and tipranavir

	Statin comparison higher *vs* lower	Medical condition of participants	Alanine transaminase three times upper limit of normal higher *vs* lower	Creatine kinase ten times upper limit of normal, or myopathy higher *vs* lower	Rhabdomyolysis higher *vs* lower	Non-vascular death higher *vs* lower
PROVE–IT (4162)[7,37]	A 80 mg *vs* P 40 mg	Acute coronary syndromes	69 (3·3%) *vs* 23 (1·1%)	2 (0·1%) *vs* 3 (0·15%)	0 (0%) *vs* 0 (0%)	17 (0·8%) *vs* 27 (1·3%)
Phase Z of the A to Z trial* (4497)[36]	S 80 mg *vs* S 20 mg	Acute coronary syndromes	19 (0·9%) *vs* 8 (0·4%)	9 (0·4%) *vs* 1 (0·04%)	3 (0·1%) *vs* 0 (0%)	21 (0·9%) *vs* 21 (0·9%)
TNT* (10 001)[5,38]	A 80 mg *vs* A10 mg	Stable CHD	60 (1·2%) *vs* 9 (0·2%)	(0·0%) *vs* (0·0%)	2 (0·04%) *vs* 3 (0·06%)	158 (3·2%) *vs* 127 (2·5%)
IDEAL (8888)[6]	A 80 mg *vs* S 20–40 mg	Stable CHD	43 (0·97%) *vs* 5 (0·11%)	6 (0·14%) *vs* 11 (0·25%)	2 (0·05%) *vs* 3 (0·07%)	143 (3·2%) *vs* 156 (3·5%)
SPARCL* (4731)[39]	A 80 mg *vs* placebo	Post stroke or TIA (no CHD%)	51 (2·2%) *vs* 11 (0·5%)	7 (0·3%) *vs* 7 (0·3%)	2 (0·1%) *vs* 3 (0·1%)	117 (4·9%) *vs* 94 (3·9%)

CHD=coronary heart disease. TIA=transient ischaemic attack. A=atorvastatin. P=pravastatin. S=simvastatin. *Reported as persistent elevation in alanine or aspartate transaminase.

Table 2: **Safety results from large randomised trials of intensive statin therapy**

suggests it is beneficial to maintain these low cholesterol levels, and to initiate statin treatment even in patients with already low levels, if they are otherwise at high risk.

Specific adverse effects of statins

The only well-documented, consistent adverse effects associated with statins are muscle toxicity, including myopathy and rhabdomyolysis, and effects on liver enzymes.[1] Many other possible side-effects are listed in the product information, but given the lack of confirmatory evidence from large controlled randomised trials, these are likely to be either rare or not truly caused by statin treatment (at least at standard doses). However, there is only limited safety information available about rosuvastatin or pitavastatin from large-scale randomised comparisons.

Effects on muscle

Myopathy is defined as any muscle symptom—pain, tenderness, or weakness—accompanied by a creatine kinase concentration greater than ten times the upper limit of normal for the particular laboratory[40] (also called myositis).[41] Rhabdomyolysis is severe myopathy involving muscle breakdown and myoglobin release into the circulation, which can cause a brown discolouration of urine and risk of renal failure. Rhabdomyolysis is usually diagnosed when creatine kinase concentration is greater than 40 times the upper limit of normal, or there is evidence of end organ damage (eg, acute renal failure or worsened renal function), or both, but differences in definition make comparisons between studies difficult. Myalgia refers to muscle pain with no rise in creatine kinase concentration to greater than ten times the upper limit of normal.

All statins can cause myopathy and rhabdomyolysis.[13,21,42] The risk of these conditions varies between statins, but for all types, the risk of adverse effects are more likely with higher doses. This risk is not clearly related to the LDL-lowering efficacy; for example, cerivastatin was not particularly effective, but was much more likely than other statins to cause rhabdomyolysis.[12,13,43] Other cholesterol-lowering agents, in particular fibrates, also rarely cause myopathy, but combinations of statins with some fibrates seem to increase the risk. This is especially true of gemfibrozil, which, in addition, increases plasma concentrations of some statins by inhibiting their glucuronidation.[44,45] The risk of myopathy with all statins seems to be particularly affected by drug interactions that are sometimes related to the metabolism of particular statins via the cytochrome P450 system (table 1),[19] but other mechanisms might also be involved.[20] Some patients (eg, those with renal impairment, hypothyroidism, serious debility, or the those who are older than 80 years) are more susceptible than others to myopathy.

Despite causing myopathy, there is no clear evidence from randomised trials that statins cause myalgia, although this is widely believed. For example, in the large randomised controlled Heart Protection Study, participants were asked specifically about new or unexplained muscle pain or weakness at every 4–6 month follow-up and, if they had symptoms, their creatine kinase levels were measured. At each time-point after randomisation, 6–7% of participants reported such symptoms but at no time were there any significant differences between those allocated active simvastatin compared with those on placebo. By the end of the study, 32·9% of those on simvastatin and 33·2% on placebo had reported muscle pain at least once.[30] Pooled data from trials of pravastatin[46] and atorvastatin,[47,48] and large trials of lovastatin,[32,49] and fluvastatin,[50,51] also indicate no increased myalgia in those taking statins. Similarly, reports of muscle cramp do not seem to increase with statin treatment.[42,52] Asymptomatic elevation of creatine kinase can sometimes occur with statin therapy but the clinical relevance of this is unclear.

Standard doses

In controlled trials of standard dose statin treatment, only a very low extra risk of myopathy has been noted (typically well under 0·01%). In the three large trials (total n=19 500) of pravastatin 40 mg daily compared with placebo, there were no reported cases;[46] in the two trials of atorvastatin 10 mg daily versus placebo involving over 13 000 patients with diabetes or hypertension, there were three cases (2 atorvastatin *vs* 1 placebo);[53,54] and in the

trials of simvastatin 20 or 40 mg daily, the excess incidence of myopathy among those on simvastatin was <0·01% per year.[30,55]

Fluvastatin (40 or 80 mg) has been assessed in two large trials. No cases of myopathy were reported in the 1600 patients allocated fluvastatin 40 mg twice daily or placebo in one trial.[51] There were two cases of rhabdomyolysis (one on treatment, the other on placebo) in 2102 patients with a renal transplant randomised to fluvastatin (40 mg daily doubling to 80 mg after 2 years) or placebo, which were associated with severe trauma and both individuals restarted study treatment.[50] In the primary prevention trial of lovastatin (20–40 mg),[32] there were no cases of myopathy. But in an earlier trial of about 8000 people, there were six cases; two on 40 mg lovastatin and four on 80 mg daily.[56]

There are insufficient data from controlled trials of rosuvastatin to assess the risk accurately but, because it was licensed after the withdrawal of cerivastatin, more extensive safety data has been demanded by regulatory agencies.[57] Although spontaneous reporting rates may be higher than for other statins during comparable periods,[58] the US Food and Drug Administration evaluation and other's interpretation[59-61] suggests that rosuvastatin has a similar safety profile to the other statins. Data from large, controlled trials will be available for rosuvastatin within the next few years (including in vulnerable populations such as those with renal disease).[62] A systematic review of randomised statin trials and cohort studies provides an overall estimated risk of myopathy with statin use of 11 per 100 000 person-years of follow-up, with the risk of rhabdomyolysis about one-third of this (3–4 per 100 000 person-years).[63] But, these incidence rates for adverse effects need to be interpreted in the context of the dose of statin and the presence of interacting drugs, since over half the reports in that review, and in FDA data, occurred in people taking drugs that affect statin metabolism, especially fibrates.[42,63]

Higher doses

Almost 25 000 patients have been randomised into trials comparing atorvastatin 80 mg daily with various standard statin regimens or placebo.[5-7,39] No excess risk of myopathy was reported among those allocated this dose of atorvastatin in these trials (table 2), nor in pooled data from earlier trials.[64] A doubling of the risk of myalgia leading to discontinuation of treatment was seen in one of these trials with atorvastatin 80 mg daily compared with simvastatin. However, the trial's open design makes interpretation of this finding difficult,[6] and no similar excess of treatment-related myalgia was seen in the masked comparison with atorvastatin 10 mg daily (4·8% atorvastatin 80 mg *vs* 4·7% 10 mg daily; p=0·72)[5] or in the trial versus placebo (5·5% atorvastatin 80 mg *vs* 6·0% placebo).[39] One trial has reported using simvastatin 80 mg daily among 4497 participants with acute coronary syndromes.[36] Patients were allocated either simvastatin 40 mg daily for one month increasing to 80 mg daily or to placebo for 4 months followed by simvastatin 20 mg daily for 2·4 years. In that trial there was a somewhat higher myopathy risk with simvastatin 80 mg daily, with nine cases of myopathy among those allocated 80 mg compared with only one in the standard treatment group who was on placebo at the time. This finding is supported by the product information for simvastatin which gives the estimated incidence of myopathy with 80 mg daily as 0·53%, compared with 0·08% for 40 mg daily. The product information for rosuvastatin indicates a higher risk of myopathy with doses above 20 mg daily, but these doses have not been assessed in large randomised comparisons.

Thus, all statins occasionally cause myopathy which could progress to rhabdomyolysis. It is rare with the standard doses that have been on the market for some years, but the risk increases with higher statin doses (although with atorvastatin 80 mg the risk remains very low). Myopathy or rhabdomyolysis are usually reported in association with concomitant use of interacting drugs (especially fibrates). Although most likely to occur within a few months of starting statin treatment, or of increasing the dose, cases have been reported even after some years of apparently stable statin treatment, usually as the result of starting an interacting drug. Insufficient data are available to reliably assess the comparative risk with pitavastatin.

Detecting myopathy

Routine measurement of creatine kinase is not helpful for detecting the rare cases of myopathy at statin standard doses. Product information recommends that patients should be asked to report new or unexplained muscle pain or weakness, and that creatine kinase should be measured in such patients. However, as indicated by the controlled trial data, muscle aches and pain are common in untreated patients and very unlikely to be due to myopathy. Other common causes such as unusual physical activity, trauma, thyroid disease, and infections, any of which can raise creatine kinase levels should be considered.[40] Muscle weakness, or bilateral proximal muscle pain with no obvious cause are more specific symptoms, and such patients should have their creatine kinase measured. Myopathy is present if creatine kinase is more than ten times the upper limit of normal. Typically, alanine transaminase and aspartate transaminase (derived from muscle) will also be elevated and will fall as the myopathy improves. A greater increase in aspartate transaminase compared with alanine transaminase is seen early after injury but, since aspartate transaminase falls faster than alanine transaminase, it cannot be relied upon as a diagnostic feature.[65] Elevations of creatine kinase to five to ten times the upper limit of normal might be associated with muscle symptoms and require discontinuation of treatment but are more often due to other causes. In patients with myopathy, brown discolouration of urine indicates the presence of gross myoglobinuria.

The best means of detecting myopathy clinically is

awareness of the main risk factors, in particular: understanding the potential for drug interactions, which are product-specific (table 1) so prescribing information should be consulted; having a high index of suspicion if high-dose statin therapy is being used; and paying particular attention to vulnerable patients.

Managing myopathy

If myopathy or rhabdomyolysis is detected, statin treatment should immediately be stopped. If creatine kinase is substantially raised (eg, >10 000 IU/L), a high fluid intake should be recommended to minimise the risk of renal impairment, and supportive management might be necessary. After this, creatine kinase levels should fall and muscle pain and function improve over the course of a few days; full recovery usually occurs within a few weeks. If a particular drug interaction has been implicated, it may be appropriate to restart the statin without the interacting drug. Otherwise a lower dose or alternative statin could be tried with careful monitoring.

Elevations of creatine kinase lower than ten times the upper limit of normal, with accompanying symptoms, should lead to further monitoring to see if the creatine kinase is rising or falling. It might be useful to measure thyroid function since both hypothyroidism and hyperthyroidism can adversely affect muscle.

Effects of statins on the liver

Since the first introduction of statins it has been clear that a small percentage of patients experience an increase in liver enzymes (in particular, alanine and aspartate transaminases).[1] Typically, with standard doses, little or no effect is seen on gamma glutamyl transferase, alkaline phosphatase, or bilirubin.[52] Abnormalities in concentrations of these indicators of liver function should prompt further investigation of liver dysfunction.[40] The increases in transaminases with statins are generally seen in the first 6 months of treatment, are asymptomatic, and reverse on stopping the statin treatment or with dose reduction. They may also return to normal with continuation of the statin.[41,66]

The question is whether the effect on transaminases indicates hepatotoxicity or rather some sort of hepatic reaction to reduction of lipid levels. Other cholesterol-lowering agents, including fibrates, resins (which are not systemically absorbed), niacin,[67] and ezetimibe,[68] all increase liver enzymes, which suggests these changes could be a hepatic response to lipid-lowering rather than hepatotoxicity.[66]

Standard doses

Data from the randomised trials do not indicate that statins are hepatotoxic. Although hepatitis and liver failure have been reported spontaneously and from trials of statins, it is not clear whether they are causally related or that the risk is over and above the background risk of sporadic liver failure.[69,70] Given the proven benefits of statins, labelling people as statin-intolerant because of effects on liver enzymes has potentially important consequences for their cardiovascular risk management, so needs to be done carefully.

Only minor and non-significant numbers of patients on statins with raised alanine or aspartate transaminase levels have been recorded in large randomised trials. Typically, the raised levels have been in the first few months after randomisation.[32,46] For example, in the Heart Protection Study[30] there was no significant excess of patients overall with elevated liver enzymes (alanine transaminase more than three times the upper limit of normal: 77 [0·75%] simvastatin *vs* 65 [0·63%] placebo; p=0·36). However, in keeping with other data there were more confirmed increases of alanine transaminase in the first 4 months of the study (8 [0·08%] simvastatin *vs* 0 [0·00%] placebo) compared with later in the trial.

There is no convincing evidence from the statin trials that increases in either transaminase are associated with liver damage. In none of the large randomised studies which assessed standard statin doses (atorvastatin 10 mg, fluvastatin 40–80 mg, pravastatin 40 mg, or simvastatin 20–40 mg) is there any clear excess risk of reported hepatitis, or any other liver related serious adverse events.[30,46,48,50,51,53,54,71]

Higher doses

The effect on transaminases seems to be dependent on statin dose, and effects on other liver enzymes and bilirubin emerge with higher doses.[72,73] But, unlike with myopathy, the effects might be because of a greater fall in LDL cholesterol.[61] In one large atorvastatin database less than 0·2% of patients on placebo or atorvastatin 10 mg daily had persistent raised alanine or aspartate transaminase compared with 0·6% of those on atorvastatin 80 mg daily.[64] The only trial to have raised a concern about statin hepatotoxicity compared atorvastatin 80 mg daily with placebo in 3086 patients with acute coronary syndromes. Over the 4 months of the study,[75] 38 (2·5%) atorvastatin compared with nine (0·6%) placebo patients had transaminases more than three times the upper limit of normal, and three of the 38 on atorvastatin were hospitalised with hepatitis. The long-term large randomised trials of atorvastatin 80 mg daily compared with lower statin doses or placebo confirm the excess of persistent elevations of transaminases with this dose of atorvastatin (table 2) (and similarly some excess with simvastatin 80 mg[36]) but have not reported any hepatitis or liver failure.[5,6,39]

Management of raised transaminases

The lack of effect of statins on adverse hepatic outcomes (with the possible exception of atorvastatin 80 mg) raises several clinical questions about the increased transaminases. Are all statins the same in this respect? If a patient develops raised enzymes with one statin should

another be tried or should statin treatment be continued? Is it safe to start a statin in individuals with raised enzymes? Is there any risk of clinical hepatitis? Is it safe to start statin treatment in people with raised γ-glutamyl transferase due to excessive alcohol intake?

Statin product information recommends baseline measurement of liver function and contraindicates the drugs in active liver disease, so in patients with baseline liver abnormalities, active 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.[73] This may just parallel their LDL cholesterol-lowering efficacy, or could be some specific hepatotoxic effect of particular statins. A logical approach is to increase the statin dose slowly in those at risk of transaminase rises. Routine monitoring of liver function after starting statin treatment is no longer recommended for simvastatin, pravastatin, or lovastatin up to 40 mg daily (since the extensive controlled trial data are reassuring), but remains recommended in product information for the other statins and higher doses, despite the lack of evidence of adverse outcomes. If alanine or aspartate transaminsases are more than three times the upper limit of normal in an asymptomatic patient with no other liver abnormalities, the enzymes should be checked within a week and statin treatment stopped temporarily if alanine transaminase is still at this level. Increases to between two to three times the upper limit of normal in an asymptomatic patient necessitate monitoring, but will often resolve while on treatment.

Most of the randomised trials excluded patients with transaminase levels more than 1·2, 1·5 or 2 times the upper limit of normal, and so the safety of statins in these people has not been systematically assessed. If statin therapy is indicated in patients whose alanine or aspartate transminase are abnormal but stable over a few months, and who have no other evidence of active disease, it may be reasonable to start statin treatment with monitoring at intervals (eg, 3 and 6 months) but with continued treatment if transaminases remain stable.[40,75] Furthermore, non-alcoholic steatohepatitis (fatty liver) may possibly improve with lipid-lowering therapy[76] and no evidence has been found suggesting worsened outcome among people with raised enzymes from hepatitis B or C.[75,77] If, however, other liver function tests such as bilirubin are abnormal or the enzymes are suggestive of an obstructive picture, statin therapy should generally be avoided until further investigation is undertaken.[70,78]

Other adverse effects at high statin doses

Other treatment-related, non-serious adverse events have been reported with atorvastatin 80 mg daily in trials where it has been compared with lower statin doses[5,6] or simvastatin 80 mg.[73] In particular, gastrointestinal effects such as diarrhoea, abdominal pain, or nausea. These effects were not reported in the trial comparing simvastatin 80 mg with 20 mg daily;[36] no comparable large-scale randomised or long-term data exist for rosuvastatin at similarly potent doses.

Safety of statins in vulnerable groups

Alcohol

Most large randomised trials excluded people with excessive alcohol intake from participation, making assessment of the safety of statins in these people difficult. Nevertheless, there is no clear evidence that statin myopathy is more common among those consuming large amounts of alcohol, although excess alcohol intake is a risk factor for rhabdomyolysis induced by pressure necrosis.[79,80] In the Heart Protection Study,[81] no upper limit for alcohol intake was imposed provided that liver function tests were within acceptable ranges, and patients were thought likely to be compliant. Over 2000 (11%) participants reported baseline alcohol intake >21 units per week and there was no evidence that these people were at any greater risk of myopathy or of statin-associated excess of raised alanine transaminase.

Pregnancy

All statins are contraindicated in pregnancy and breastfeeding. Premenopausal women treated with statins should be warned to avoid becoming pregnant, and to stop treatment if they plan to conceive. Although there are reports of congenital abnormalities in the babies of women who took statins during early pregnancy,[82] prospective collection of data does not clearly support the view that statins are teratogenic in people or animals.[83–85]

Warfarin

Some statins (simvastatin, fluvastatin, and rosuvastatin) potentiate the effect of coumarin anticoagulants such as warfarin. The usual recommendation is to check the anticoagulation control (eg, International Normalised Ratio) when statin treatment is started, stopped, or modified. The change in the required dose of warfarin is usually small, but occasional patients will experience clinically important changes to their anticoagulant control.

Renal function

There is now a considerable body of evidence that most statins are safe to prescribe in the presence of moderate renal impairment, and might even preserve glomerular filtration.[86] The large controlled trials of simvastatin, pravastatin, and atorvastatin[54,81,87] have excluded patients with overt renal failure, but included participants with blood creatinine levels up to 1·5–2·0 times the upper limit of normal, or 150 or 200 μmol/L (depending on the trial). Hence, some patients had estimated glomerular filtration rates in the range 30–60 mL/min. People with this degree of renal impairment are at substantially increased risk of cardiovascular disease and the limited trial data suggest benefit with statins in these subgroups,

although they may be at increased risk of myopathy. Only one trial (with low statistical power) has assessed the value of statin therapy in people with overt renal failure.[88] That trial of atorvastatin 20 mg daily versus placebo in 1255 people with diabetes on maintenance haemodialysis did not show a significant cardiovascular benefit, and the role of statins for the prevention of cardiovascular disease in patients with chronic renal failure remains unclear.[89]

Rosuvastatin has been associated with an increase in the risk of proteinuria (mostly tubular in origin) particularly at higher doses.[90] It is usually transient and has not been associated with worsened renal function. Rosuvastatin 10 mg daily is being assessed in a randomised trial of 2750 patients with chronic renal failure receiving haemodialysis, with results expected this year.[62] Other than isolated case reports, proteinuria has not been associated with other statins, and recent meta-analyses show a trend toward statins lessening proteinuria (rather than causing it), as well as indicating that statins are associated with small improvements in renal function in long-term randomised trials.[86,91]

Elderly patients

No dose adjustment is recommended for elderly patients on statins, although the very elderly may be at increased risk of myopathy. People up to the age of 80 years have been included in randomised trials, and the safety profile and relative benefits of treatment are generally similar to those in younger adults.[3,30]

Heart faliure

Concerns exist that statins could be harmful in patients with heart faliure,[92,93] partly because low cholesterol levels are associated with poor outcomes in such patients.[94,95] However, in one large study,[96] patients with high levels of brain type (N-terminal pro-B type) natiuretic peptide (N-BNP) consistent with heart failure derived as much cardiovascular benefit from simvastatin as other patients with no evidence of any hazard. Other studies have shown similar benefits in patients with heart failure.[97,98]

Children

Statin therapy is only very rarely indicated for children with severe familial hyperlipidaemias and should only be prescribed under specialist care. Long-term effects of treating children with statins are unknown but short-term and small-scale studies in children and adolescents have not raised safety concerns and no adverse effects have been seen on growth or sexual maturation.[99–101]

Other possible effects of statins

Despite concerns about a variety of possible adverse effects of statins (including causing lens opacities,[102] sleep disturbance,[103,104] mood disorders,[105,106] dementias,[107] and peripheral neuropathy[108,109]), data from controlled randomised comparisons have not confirmed any of these adverse effects.[110–114] For example, in the largest of the studies suggesting that statins may cause peripheral neuropathy, a relative risk of 3·7 (95% CI 1·8–7·6) was reported in association with 2–3 years' low-dose statin use.[109] But in one large controlled study, the absolute risk of reported peripheral neuropathy was very low (11 [0·1%] simvastatin *vs* 8 [0·1%] placebo) with no significant excess in those allocated simvastatin 40 mg over 5 years.[114] Similarly, hopes that statins might protect against fractures because of positive effects on bone mineral density,[115,116] against dementia[117] by effects on cognitive function, and against macular degeneration are not supported by evidence from randomised trials.[30,118]

Conclusion

Statins are a well-tolerated and extensively studied group of drugs. Their proven impact on cardiovascular disease risk has been driving their widespread use. With a few caveats, and while awaiting good-quality randomised data for the newer drugs, statins seem to be a remarkably safe group of drugs when used at their usual doses. The recognised adverse effects, most importantly myopathy and rhabdomyolysis, are rare and, as with most drugs, increase with higher doses. Muscle pain is common in middle-aged patients (and often believed to be due to the drug because of product warnings), but is, nevertheless, unlikely to be due to statin treatment. Measurement of creatine kinase in such patients can exclude myopathy and allow safe continuation of treatment. Importantly, any risks of myopathy and rhabdomyolysis can be kept to a minimum by knowledge of potential drug interactions and the vulnerability of particular groups of patients.

Conflict of interest statement

I do not receive honoraria or speaker's fees from the pharmaceutical industry, but have been reimbursed for travel and accommodation for speaking at national and international meetings. I am an investigator in studies of simvastatin (funded by Merck) and provide advice to researchers on studies of atorvastatin and cerivastatin. I have undertaken unpaid consultancy work for Merck, Shering Plough, Astra Zeneca, and Pfizer.

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