Coenzyme Q10 and Adverse Effects of Statins

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Abstract

Background: Current evidence has established that statins are potent and effective agents with several pleiotropic effects in the treatment of coronary artery disease (CAD). Statins may have toxic effects, if given in higher doses and in combination.

Design: Literature review.

Methods: An Internet search and discussions with colleagues.

Results: The 1990s have been called the ‘statin decennial’ and the Nobel laureates suggested ‘CAD: eliminated with statins’. Statins were also proclaimed as wonder drugs, influencing a wide range of physiological, biochemical and biological functions. The list appears to be long and includes hypolipidaemic, vasodilative, antithrombotic, antioxidant, anti-inflammatory, antiproliferative, anticoagulant, angiogenic and bone formation inducing functions. In January 2002, the television network CNN announced in a dispatch from London that deaths resulting from the treatment of hypercholesterolaemia with cerivastatin (Baycol) have now exceeded 100. Concerned Americans discussed this issue in May 2002, and published advice with the intention of summarizing for professionals current knowledge about statin use, focusing on myopathy. The criteria for the diagnosis of myopathy are not concerned with the symptoms of patients in the absence of raised muscle enzymes. Coenzyme Q10 is not considered in prophylaxis because one study showed no decrease in coenzyme Q10 in muscles in the presence of toxicity, although some studies indicated a reduction in serum levels.

Conclusion: Several studies have reported a significant reduction in serum coenzyme Q10 in patients taking statins. Such concern was also expressed by the International College of Cardiology at their meeting in April 2002; it was proposed that coenzyme Q10 should be considered in the prevention as well as the treatment of statin intoxication.

Keywords: statin toxicity, ubiquinone, cerivastatin, cholesterol.

INTRODUCTION

Current evidence has established that statins [3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors] are potent and effective agents with several pleiotropic effects in the treatment of coronary artery disease (CAD) [1, 2] (Table 1). Interestingly, the 1990s have been called the ‘statin decennial’ and statins were proclaimed as wonder drugs, influencing a wide range of physiological, biochemical and biological functions. The list appears to be long and includes hypolipidaemic, vasodilative, antithrombotic, antioxidant, anti-inflammatory, antiproliferative, anticoagulant, angiogenic and bone formation inducing functions. Unfortunately, several of these beneficial effects have not been
### TABLE 1. Key statin trials with major outcome and adverse events

<table>
<thead>
<tr>
<th>Trial/statin/ primary or secondary prevention</th>
<th>Duration and numbers</th>
<th>Placebo vs. statin events</th>
<th>Absolute risk reduction</th>
<th>Incidence of malignancy</th>
<th>CK &gt; 10× upper limit</th>
<th>ALT &gt; 3× upper limit</th>
<th>AST &gt; 3× upper limit</th>
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<tbody>
<tr>
<td><strong>4S</strong></td>
<td>5.4 years, median (placebo: 2223; statin: 2221)</td>
<td>Primary: 256 (11.5%) vs. 182 (8.2%)</td>
<td>74 (3.3%)</td>
<td>Placebo: 61 Statin: 57</td>
<td>Placebo: 1 Statin: 6 (1 rhabdomyolysis)</td>
<td>Placebo: 23 Statin: 20</td>
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<tr>
<td>Simvastatin Prior AMI or angina secondary prevention</td>
<td></td>
<td>Secondary: 502 (22.6%) vs. 353 (15.9%)</td>
<td>149 (30%)</td>
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<tr>
<td><strong>LIPID</strong></td>
<td>6.1 years (mean) (placebo: 4502; statin: 4512)</td>
<td>Death: 633 (14.1%) vs. 498 (11%)</td>
<td>135 (3.1%)</td>
<td></td>
<td>Placebo: 10 Statin: 8</td>
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<tr>
<td>Pravastatin Prior AMI or unstable angina secondary prevention</td>
<td></td>
<td>AMI: 463 (10.3%) vs. 336 (29%)</td>
<td>127 (29%)</td>
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<tr>
<td></td>
<td></td>
<td>Primary: 373 (8.3%) vs. 287 (6.4%)</td>
<td>86 (1.9%)</td>
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<td></td>
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<td>Secondary: 2360 (52.4%) vs. 2029 (44.9%)</td>
<td>331 (7.3%)</td>
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TABLE 1. (Continued)

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<th>AST $&gt;3 \times$ upper limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>CARE Pravastatin Prior MI, secondary prevention</td>
<td>5 years (event rates) (placebo: 2078; statin: 2081)</td>
<td>CAD death: 119 (5.7%) vs. 96 (4.6%) AMI: 173 (8.3%) vs. 135 (6.4%) Primary: 549 (22.2%) vs. 430 (20.7%)</td>
<td>23 (1.1%)</td>
<td>119 (5.7%) Placebo: 161 Statin: 172</td>
<td>Placebo: 7 (4 myocitis) Statin: 12</td>
<td>Placebo: 73 Statin: 66</td>
<td></td>
</tr>
<tr>
<td>WOSCOPS Pravastatin Primary prevention 44% stroke</td>
<td>4.9 years (mean) (placebo: 3293; statin: 3302)</td>
<td>Deaths: 135 (4.1%) vs. 106 (3.2%) AMI: 204 (6.2%) vs. 143 (4.3%) Primary: 248 (7.5%) vs. 174 (5.3%)</td>
<td>29 (0.9%)</td>
<td>74 (2.2%) Placebo: 106 Statin: 116</td>
<td>Placebo: 1 Statin: 4 (myalgia: placebo 19; statin 20)</td>
<td>Placebo: 12 Statin: 16</td>
<td>Placebo: 20 Statin: 26</td>
</tr>
<tr>
<td>Trial/statin/primary or secondary prevention</td>
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<td>PROSPER Pravastatin Primary and secondary prevention</td>
<td>3.2 years (mean) (placebo: 2913; statin: 2891)</td>
<td>Primary: 473 (16%) vs. 408 (14.1%) Secondary: 356 (12.2%) vs. 292 (10.1%) Stroke: 131 (4.5%) vs. 135 (4.7%)</td>
<td>65 (1.9%)</td>
<td>64 (1.1%)</td>
<td>4 (0.2%) Placebo: 199 Statin: 245</td>
<td>Placebo: Myalgia: (placebo 32; statin 36)</td>
<td>Placebo: 1 Statin: 1</td>
</tr>
<tr>
<td>AFCAPS/TexCAPS Lovastatin Primary prevention</td>
<td>5.2 years (mean) (placebo: 3301; statin: 3304)</td>
<td>CAD deaths: 15 (0.5%) vs. 11 (0.3%) AMI: 81 (2.5%) vs. 45 (1.4%) Primary: 183 (5.5%) vs. 116 (3.5%)</td>
<td>4 (0.12%)</td>
<td>39 (1.3%)</td>
<td>67 (2%) Placebo: 259 Statin: 252</td>
<td>Placebo: 0.6% Statin: 0.6%</td>
<td>Placebo: 11 (0.3%) Statin: 18 (0.6%)</td>
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<th>ALT &gt; 3 × upper limit</th>
<th>AST &gt; 3 × upper limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPS Simvastatin, vitamin E</td>
<td>5 years (mean)</td>
<td>Vascular death: 937 (9.1%) vs. 781 (7.6%)</td>
<td>150 (1.5%)</td>
<td>552 (5.4%)</td>
<td>Placebo: 6 (0.06%) Statin: 11 (0.11%)</td>
<td>ALT &gt; 4 × upper limit: Placebo: 32 (0.31%) Statin: 43 (0.42%)</td>
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<tr>
<td>Primary and secondary prevention</td>
<td>(placebo: 10 267; statin: 10 269)</td>
<td>Secondary endpoint: 2585 (25.2%) vs.2033 (19.8%)</td>
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Cerivastatin: 52 deaths due to rhabdomyolysis and 10 times risk of rhabdomyolysis than other statins, especially those receiving full dose (0.8 mg day$^{-1}$) and gemfibrozil concomitantly.

CK, creatine kinase; ALT, alaninaminotransferase; AST, aspartaminotransferase; AMI, acute myocardial infarction; MI, myocardial infarction; CAD, coronary artery disease.
substantiated by randomized, controlled trials and only a few investigators consider some of these beneficial effects to be controversial [3].

On 18 January 2002, the global television network CNN announced in a dispatch from London that deaths resulting from the treatment of hypercholesterolaemia with cerivastatin (Baycol) have now exceeded 100. Subsequently, the Wall Street Journal (21 January 2002) reported that Bayer AG had given similar indications about deaths linked to Baycol. The American College of Cardiology/American Heart Association/National Heart Lung and Blood Institute discussed the matter in May 2002 and have since published advice [1] with the intention of summarizing for professionals current knowledge about statin use, focusing on myopathy. Their purpose was to provide updated recommendations for the appropriate use of statins, including cautions, contraindications and safety monitoring for therapy with this group of agents. The International College of Cardiology discussed the issue of cerivastatin intoxication at their meeting in April 2002, in particular the causes of this adverse manifestation and how to terminate the toxicity of this great terminator of atheroma.

STATIN INTOXICATION

The Food and Drug Administration (FDA) of the USA introduced seven statins for general use between 1987 and 2003. They were: lovastatin (Mevacor), pravastatin (Pravachol), simvastatin (Zocor), fluvastatin (Lescol), atorvastatin (Lipitor), cerivastatin (Baycol) and rosuvastatin (Crestor) [1–3] (Table 2). The long-term side-effects of these statins, especially in general use, are not known. Several small-scale reports indicate that statins can cause myopathies and rhabdomyolysis with renal failure, and an increase in transaminases [3–10]. Many authors have reported various adverse manifestations of statins during randomized, controlled trials. Lovastatin and simvastatin are about to become available as generic products. All these drugs reduce cholesterol through inhibition of HMG-CoA reductase. However, there are differences in other characteristics such as potency, lipophilicity, pharmacokinetics and in some of the non-lipid-lowering properties. These controversial issues remain unresolved [2, 3]. A warning letter was issued by the FDA on 1 May 2000 concerning liver failure as an adverse reaction to treatment with statins, based on a report on half of the 62 patients who died from liver failure [3, 6]. It has been suggested that muscle injury can occur in 1% of users of statins, which in the USA alone equals 130,000 patients with muscle toxicity manifestations [3]. Higher levels of transaminase elevation with statin therapy are dose dependent and occur in 0.5–2.0% of cases. Reversal of increased liver enzymes is frequently observed after a decrease in dose, and elevations are often not seen with either rechallenge or on administration of another statin [10]. It has also been observed that statins do not have adverse effects on outcome in patients with chronic transaminase elevations due to viral hepatitis [6]. Statin therapy of hyperlipidaemia may sometimes improve the increase in transaminase in patients with fatty liver [6]. Treatment with statins is also implicated in the greater incidence of cataracts, neoplasia, peripheral neuropathies and some psychiatric disturbances without such evidence in the large blinded controlled trials [3–21].

MYOSITIS AND MYOPATHY

Myopathy is a general term referring to any disease of the muscles, and myalgia means muscle pain or weakness without an increase in creatine kinase. Myositis refers to muscle symptoms with an increase in creatine kinase, whereas in rhabdomyolysis, there are severe muscle symptoms with joint pain, marked weakness and a 10-fold rise in creatine kinase levels, usually with brown urine and urinary myoglobin [1]. In randomized, controlled
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Atorvastatin</th>
<th>Lovastatin</th>
<th>Pravastatin</th>
<th>Simvastatin</th>
<th>Fluvastatin</th>
<th>Cerivastatin</th>
</tr>
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<tbody>
<tr>
<td>Maximal dose (mg dl⁻¹)</td>
<td>80</td>
<td>80</td>
<td>40</td>
<td>80</td>
<td>40</td>
<td>0.3</td>
</tr>
<tr>
<td>Maximal LDL-C reduction (%)</td>
<td>60</td>
<td>40</td>
<td>34</td>
<td>47</td>
<td>24</td>
<td>28</td>
</tr>
<tr>
<td>Serum LDL-C reduction (%)</td>
<td>50</td>
<td>34</td>
<td>34</td>
<td>41</td>
<td>24</td>
<td>28</td>
</tr>
<tr>
<td>Serum triglyceride reduction (%)</td>
<td>29</td>
<td>16</td>
<td>24</td>
<td>18</td>
<td>10</td>
<td>13</td>
</tr>
<tr>
<td>Serum HDL-C increased (%)</td>
<td>6</td>
<td>8.6</td>
<td>12</td>
<td>12</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Penetration of CNS</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Renal excretion (%)</td>
<td>2</td>
<td>10</td>
<td>20</td>
<td>13</td>
<td>&lt;6</td>
<td>33</td>
</tr>
<tr>
<td>Mechanism of hepatic metabolism</td>
<td>Cytochrome P450 3A4</td>
<td>Cytochrome P450 3A4</td>
<td>Sulphation</td>
<td>Cytochrome P450 3A4</td>
<td>Cytochrome P450 2C9</td>
<td>Cytochrome P450 3A4, 2C8</td>
</tr>
</tbody>
</table>

LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; CNS, central nervous system.
trials, the incidence of non-specific muscle pain or joint pain is similar (5% each) in intervention and control groups [14–21]. However, some patients may have mild to moderate elevations of creatine kinase without muscle complaint. The temporal association of such adverse effects with statin therapy is enough to imply that statin therapy may be the cause of these effects. Failure to discontinue statin therapy in these asymptomatic patients may cause further damage, leading to rhabdomyolysis and acute renal necrosis.

RISK FACTORS

Myositis can occur in patients with complex medical problems who are taking multiple medications. High-dose statin monotherapy, combined with other medications such as cyclosporine, fibrates, macrolide antibiotics, certain antifungal drugs and niacin, is an important predisposing factor of statin toxicity [3–11]. One of the most important factors for predicting the risk of myopathy is the route of metabolism of statins. Most of them are metabolized by the cytochrome P450 family, with the exception of pravastatin [22, 23]. Lovastatin, simvastatin and atorvastatin are metabolized by cytochrome P450 P3A, like nifedipine, felodipine, amiodarone, macrolide antibiotics, cisapride, omeprazole, etc. Fluvastatin is metabolized by cytochrome P450 P2C9, like diclofenac, warfarin or tolbutamide, etc. That is why, during treatment with pravastatin, there were fewer observed muscle complications. Another point in favour of pravastatin is that it is a hydrophilic statin, in contrast to all the other above-named statins, which does not cause ‘increased fluidity of muscle cell membranes’ responsible for the increased risk of myopathy development [24]. Coenzyme Q10 is an omnipresent substance also serving like a coenzyme in mitochondrial phosphorylation. It should be synthesized endogenously from mevalonate-isoprene as a result of HMG-CoA reductase activity [25]. Thus, it is not surprising that coenzyme Q10 concentrations are decreased during statin therapy due to both a decrease in low-density lipoprotein (LDL) cholesterol and the inhibition of its synthesis (Fig. 1). It has been shown that during statin therapy, a significant decrease in coenzyme

![Diagram of cholesterol and coenzyme Q10 synthesis pathway]

*PP - pyrophosphate

FIG. 1. The cholesterol and coenzyme Q10 synthesis pathway.
Q10 was observed (up to 40%) and a subsequent disorder of mitochondrial energetic metabolism may lead to myopathy [24].

IMPACT OF LIPID GUIDELINES AND MYOPATHY

About one billion people in the world may have serum cholesterol levels where statins may be indicated. Therefore, any intoxication of statins, despite its low occurrence, may become a public concern. According to one news report (Chem Market Reporter, 11 June 2001), worldwide sales of hypocholesterolaemic and hypotriglyceridaemic agents have reached $15.9 million, which may increase to $36 million in the USA alone with the publication of new guidelines for the USA [12]. Approximately five of the 14 expert panel members declared a financial relationship with up to 11 pharmaceutical companies, which may indicate individual influence on the guidelines [3]. However, almost all of these investigators are the best in the field and are known for their integrity and academic honesty. Moreover, this report [12] has been revised [1], and includes recent information on myopathy compiled by the FDA, as well as information from clinical trials. There is uniform agreement that a reduction in total and LDL cholesterol reduces cardiovascular risk, which is reflected in the aggressive approach advocated in the current guidelines [12]. It is possible that the current emphasis on lipid management will continue in the USA and it is likely to be followed in other developed and developing countries [1].

The guidelines are endorsed by the American Heart Association, as well as the American College of Cardiology. This report is based on rigorous clinical trial evidence to identify additional high-risk subjects for treatment, causing a marked increase in the number of patients who may be candidates for statin administration. Apart from CAD, other forms of atherosclerotic disease, diabetes mellitus, the presence of multiple risk factors and severe hypercholesterolaemia are important indications for statin therapy, according to the new guidelines. In several of these situations, one noteworthy advantage of the guidelines is that many patients with a borderline increase in cholesterol will be treated with the smallest dose of a statin, whereas in some patients, relatively high doses of statins or a combination therapy will be required to achieve treatment goals. The International College of Cardiology emphasizes the necessity of catching patients at the early stage of LDL increase (>90 mg dl$^{-1}$), administering the lowest dose of a statin rather than waiting to treat severe hypercholesterolaemia with higher doses and combinations [13]. There are some parallels with the treatment of arterial hypertension. In contrast with JNC I, different classes of drugs are now recommended by JNC VI, such as drugs of first choice even administered in combination, preferentially in low dosage [26–28]. In recent years, there has been a strong tendency in clinical trials towards the use of higher doses of statins, with the aim of achieving target levels of lipid profile. These target levels could also be achieved in many patients with lower doses of statins, used in monotherapy or in combination but with different groups of drugs, including ezetimibe [28] or antithrombotic substances like sulodexide which also has beneficial effects on the lipid profile [29]. There is still a need to emphasize the role of diet, which can lead not only to a decrease in atherogenic lipids, but also to a decrease in cardiovascular morbidity and mortality [30, 31].

A lipid-lowering diet and exercise offer a significant opportunity to decrease the statin dose used in monotherapy or in combination. To prevent the side-effects of statins, including myopathy, it is useful to combine statins with coenzyme Q10, but more clinical studies are needed. The secondary targets of therapy, such as hypertriglyceridaemia, low high-density lipoprotein (HDL) cholesterol and high LDL plus very low LDL, are also identified for treatment by the NCEP panel, which will cause a further increase in the use of lipid-lowering agents. Therefore, it is necessary to pay greater attention to efficacy, safety and the cost-effectiveness of a lipid-lowering regimen including statins and the role of coenzyme Q10.
DIFFERENCES IN THE EFFECTS AND OUTCOMES

All statins are powerful LDL-lowering agents widely used in all countries to improve cardiovascular risk profiles. Randomized, controlled, clinical trials have demonstrated a decline in CAD and total mortality, a reduction in myocardial infarctions, revascularization procedures, stroke and peripheral vascular disease during a mean duration of treatment of approximately 5.4 years [14–21]. The safety of statin therapy outside clinical trials has not been fully studied. It is likely that the incidence of statin intoxication may be higher in clinical situations where patients are less carefully monitored as compared with clinical trials.

The rate of fatal rhabdomyolysis is 16–80-fold greater for cerivastatin compared with other statins [5]. Since Bayer AG indicated that 100 deaths appeared to be linked to Baycol, it has withdrawn cerivastatin (Baycol) from the market. At the time of withdrawal, the FDA in the USA had received reports of 31 deaths in the US alone due to rhabdomyolysis associated with the use of cerivastatin, 12 of which involved a concomitant administration of gemfibrozil. Despite all the positive effects of statins demonstrated in large clinical trials, there is still a gap between the use of statins in clinical practice and statin evidence-based medicine. There are some possible explanations: First, there is always a delay after publishing the results of trials. Second, in clinical trials, selected subgroups of patients are evaluated; safety precautions are more strict, which is why many doctors are afraid of the possible side-effects of lipid-lowering therapy in common clinical practice. Third, following evidence-based medicine, cardiovascular diseases and mainly CAD impose a massive economic burden not only on developing countries but also on highly developed countries, e.g. in the USA in 1998 about 28% of adults were eligible for lipid-regulating therapy according to earlier NCEP II guidelines [32]. Lipid-lowering therapy is considered to be lifelong therapy and from this point of view we still lack reliable information, especially long-term safety data. The International College of Cardiology strongly supports the recommendations of NCEP ATP III to treat elevated atherogenic lipids to their target levels and to guarantee the safety of such therapy. The possible risks of widely prescribed statin therapy should be decreased by the administration of lower doses, combined with coenzyme Q10, and the avoidance of risky combinations of drugs which interfere with metabolism via cytochrome P450.

The role of a lipid-lowering diet and exercise is indisputable and may support lower doses of lipid-lowering drugs or even the lower use of these drugs. The use of coenzyme Q10 even in smaller doses of 30 mg day\(^{-1}\) may be rewarding in the prevention of statin intoxication. In a randomized, controlled (initially double-blind) trial, the effects of oral treatment with coenzyme Q10 (120 mg day\(^{-1}\)) plus lovastatin (10–20 mg day\(^{-1}\)) or lovastatin alone were compared for 1 year for adverse effects of statins in patients with acute myocardial infarction [33]. Of 144 patients, 36 (49.3%) of 73 in the coenzyme Q10 group and 31 (43.6%) of 71 in the control group received lovastatin (10–20 mg day\(^{-1}\)). The adverse effects of treatment showed that fatigue (40.8 vs. 6.8%, \(p < 0.01\)) was significantly more common in the control group compared with the coenzyme Q10 group, indicating that coenzyme Q10 appears to be useful in preventing lovastatin intoxication. Three patients in each group were also receiving Bezalip. It is possible that the addition of coenzyme Q10 to statins may be useful, especially when higher doses are involved, for the prevention of deaths due to myopathy which occurs possibly due to statin-induced coenzyme Q10 deficiency.

CAN STATINS DESTROY A DRUG COMPANY?

The presumption of the Lancet [34] is quite interesting and logical and so is the suggestion of Bayer that physicians using cerivastatin are equally responsible for statin intoxication.
Physicians should have studied the literature from Bayer carefully before prescribing, and should have instructed patients to come for advice on coenzyme Q10 more frequently, especially when higher doses or combinations were being prescribed. Patients claiming compensation are more numerous in the USA (7800 vs. 500) than in Germany. It is not clear how far patients can be responsible for the toxicity when they do not follow the doctor’s advice on scheduled visits. Is it logical to suggest that coenzyme Q10 administration in conjunction with statins can also prevent deaths due to myopathy as well as the death of a company?

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REFERENCES


