

# The clinical use of HMG CoA-reductase inhibitors and the associated depletion of coenzyme Q<sub>10</sub>. A review of animal and human publications

Peter H. Langsjoen\* and Alena M. Langsjoen

*East Texas Medical Center and Trinity Mother Francis Health System, Tyler, TX 75701, USA*

**Abstract.** The depletion of the essential nutrient CoQ<sub>10</sub> by the increasingly popular cholesterol lowering drugs, HMG CoA reductase inhibitors (statins), has grown from a level of concern to one of alarm. With ever higher statin potencies and dosages, and with a steadily shrinking target LDL cholesterol, the prevalence and severity of CoQ<sub>10</sub> deficiency is increasing noticeably. An estimated 36 million Americans are now candidates for statin drug therapy. Statin-induced CoQ<sub>10</sub> depletion is well documented in animal and human studies with detrimental cardiac consequences in both animal models and human trials. This drug-induced nutrient deficiency is dose related and more notable in settings of pre-existing CoQ<sub>10</sub> deficiency such as in the elderly and in heart failure. Statin-induced CoQ<sub>10</sub> deficiency is completely preventable with supplemental CoQ<sub>10</sub> with no adverse impact on the cholesterol lowering or anti-inflammatory properties of the statin drugs. We are currently in the midst of a congestive heart failure epidemic in the United States, the cause or causes of which are unclear. As physicians, it is our duty to be absolutely certain that we are not inadvertently doing harm to our patients by creating a wide-spread deficiency of a nutrient critically important for normal heart function.

**Keywords:** Coenzyme Q<sub>10</sub> deficiency, ubiquinone, CoQ<sub>10</sub>, HMG CoA reductase inhibitors, statins, congestive heart failure, CHF

## 1. Introduction

All large statin trials excluded patients with New York Heart Association class III and IV heart failure such that long term safety of statins in patients with heart failure has not been established.

HMG CoA-reductase inhibitors or statins are an effective class of drugs for lowering LDL cholesterol. These drugs have been associated with some beneficial impact on cardiovascular morbidity and mortality. As such, statins have become some of the most widely prescribed drugs in the United States with many millions of patients taking them on a regular basis. According to the most recent NCEP (National Cholesterol Education Program) guidelines, the indications for the use of statins have been broadened such that patients with even low normal LDL cholesterol levels are now being treated in hopes of favorably altering the incidence of stroke and myocardial infarction. Statins are frequently used in the

---

\* Address for correspondence: Peter H. Langsjoen, M.D., P.A., 1107 Doctors Drive, Tyler, TX 75701, USA. Tel.: +1 903 595 3778; Fax: +1 903 595 4962; E-mail: langsjoen@compuserve.com.

elderly and have gained very broad acceptance in the medical community. Statins have been noted to have significant anti-inflammatory and plaque-stabilizing effects which has added to their broader usage.

It is well established that the mevalonate pathway is involved not only in the biosynthesis of cholesterol but also in the biosynthesis of the essential co-factor required for energy production, coenzyme Q<sub>10</sub> (CoQ<sub>10</sub>, ubiquinone). As such, HMG CoA reductase inhibitors block the cellular production of both cholesterol and of coenzyme Q<sub>10</sub> [23,59]. This drug-nutrient interaction has been reviewed [7,8].

## 2. Background

Coenzyme Q<sub>10</sub> is the coenzyme for mitochondrial enzyme complexes involved in oxidative phosphorylation in the production of ATP [38,46,47]. This bioenergetic effect of CoQ<sub>10</sub> is believed to be of fundamental importance in its clinical application, particularly as relates to cells with exceedingly high metabolic demands such as cardiac myocytes. The second fundamental property of CoQ<sub>10</sub> involves its antioxidant (free radical scavenging) functions [5,67]. CoQ<sub>10</sub> is the only known naturally occurring lipid soluble antioxidant for which the body has enzyme systems capable of regenerating the active reduced ubiquinol form [16]. CoQ<sub>10</sub> is carried in the blood with low density lipoprotein and serves to diminish the oxidation of LDL cholesterol in settings of oxidative stress [1]. CoQ<sub>10</sub> is known to be closely linked to vitamin E and serves to regenerate the reduced (active) alpha-tocopherol form of vitamin E [10] as well as the reduced form of ascorbate [24]. Other more recently discovered aspects of CoQ<sub>10</sub> function include its involvement in extramitochondrial electron transfer, e.g. plasma membrane oxidoreductase activity [67], involvement in cytosolic glycolysis [36], and potential activity in both Golgi apparatus and lysosomes [22,53]. CoQ<sub>10</sub> also plays a role in improvement in membrane fluidity [37]. The multiple biochemical functions of CoQ<sub>10</sub> have been reviewed by Crane [11].

Coenzyme Q<sub>10</sub> is clearly necessary for cellular ATP production and is of particular importance in heart muscle function given this tissue's extreme energy requirements. A deficiency of CoQ<sub>10</sub> in the blood and the heart muscle has been documented in congestive heart failure [19,28]. An Australian group of cardiovascular surgeons has recently documented impairment in myocardial function secondary to age-related CoQ<sub>10</sub> deficiency in patients undergoing coronary artery bypass surgery (CABG). That impairment was completely eliminated with incubation of the atrial myocardium with CoQ<sub>10</sub> [57]. Later these researchers performed a trial of preoperative supplemental CoQ<sub>10</sub> therapy and found improved outcomes in coronary artery bypass surgery [58]. The clinical experience with supplemental CoQ<sub>10</sub> in cardiovascular disease, including congestive heart failure, ischemic heart disease, hypertensive heart disease and heart surgery has been reviewed [33,34].

In the US we are presently in the midst of a congestive heart failure (CHF) epidemic, with a significant increase in the incidence of CHF over the past decade. The annual number of deaths directly from CHF increased from 10,000 in 1968 to 42,000 in 1993. The rate of hospitalizations for heart failure increased more than three times between 1970 and 1994. In the largest health system study of its kind, researchers at the Henry Ford Heart and Vascular Institute in Detroit found that the annual number of heart failure cases more than doubled from 1989 to 1997. Over that nine-year period, 26,442 cases were identified in the Henry Ford Health System in Detroit. Strikingly, the annual prevalence rose from 9 to 20 cases per 1000 health system patients. These results were compiled in the Resource Utilization Among Congestive Heart Failure (REACH) study [44].

Statins were first released in 1987 and are considered the most effective medications for managing elevated concentrations of low-density lipoprotein cholesterol. Although it is believed that they are generally well tolerated by most patients they can produce a variety of muscle-related complaints or

myopathies, of which rhabdomyolysis is the most serious one. The issue was recently discussed in an article by Thompson et al. [66] where the following are indicated as the possible mechanisms of statin-induced muscle injury:

- reduction of the cholesterol content of skeletal muscle membranes
- reduction of the levels of ubiquinone
- reduction in farnesyl pyrophosphate, an intermediary for the production of ubiquinone, which is required for the activation of small GTP-binding regulatory proteins.

In the present article we will examine the existing literature on animal studies and human trials evaluating the effect of statins on coenzyme Q blood and/or tissue levels. Statin-induced depletion of CoQ<sub>10</sub> must be considered in the above mentioned epidemic of heart failure. The coenzyme Q<sub>10</sub>-lowering effect of statin medications has clinical relevance and must be considered by all physicians when prescribing this class of medication.

### 3. Animal studies

From 1990 through 2001 there have been 15 published animal studies involving six different animal species – six rat studies, three hamster studies, three dog studies, one rabbit study, one guinea pig study and one study looking at squirrel monkeys, mini pigs and hamsters – evaluating the effect of statins on coenzyme Q blood and/or tissue levels. Nine of these 15 studies looked specifically at the adverse consequences of this statin-induced CoQ depletion: decreased ATP production, increased injury after ischemia/reperfusion, increased mortality in cardiomyopathy, and skeletal muscle injury and dysfunction. Some of the animals use coenzyme Q<sub>9</sub> as their native ubiquinone which is a shorter chain homologue of coenzyme Q<sub>10</sub> and in those cases the term coenzyme Q or CoQ is used.

The first animal data was published in 1990 by Willis et al. and documented statistically significant decreases in CoQ concentration in blood, heart and liver in 45 adult male Holtzman rats when treated with lovastatin. This statin-induced blood and tissue CoQ deficiency could be completely prevented by supplementing the lovastatin treated animals with coenzyme Q<sub>10</sub> [70]. In 1992, Low et al. found similar decreases in ubiquinone in liver and heart in rats treated with lovastatin (mevinolin), confirming observations by Willis et al. [42].

In 1993, Fukami et al. studied simvastatin treated rabbits and specifically looked at those animals with elevations in creatinine kinase, lactate dehydrogenase, and skeletal muscle necrosis [20]. The simvastatin treated rabbits were noted to have significantly reduced liver and cardiac muscle CoQ content as compared to the control group. Interestingly, skeletal muscle ubiquinone content in this study was not affected. Also in 1993, Belichard et al. studied lovastatin in cardiomyopathic hamsters and found a 33% decrease in ubiquinone content in heart muscle as compared to control [4]. Cholesterol lowering in cardiomyopathic hamsters with fenofibrate did not lower coenzyme Q<sub>10</sub> levels. Statins are the only class of lipid-lowering drugs that are known to block the synthesis of mevalonate.

In 1994, Diebold et al. documented a depletion in CoQ<sub>10</sub> content in heart muscle in guinea pigs when treated with lovastatin in older age (2 years of age) animals, and further observed no significant depletion in CoQ<sub>10</sub> content in heart muscle in the guinea pigs in the younger age group (2 to 4 months of age) [14]. The authors evaluated mitochondrial function as measured by the potential to phosphorylate ADP to ATP, and again documented a decrease by up to 45% in cardiac mitochondria in the 2-year-old animals treated with lovastatin, and no significant decrease in phosphorylation in the younger age group animals. This sensitivity for older animals to show clinically relevant heart muscle CoQ<sub>10</sub> depletion is of concern

in humans as older patients are treated with statin medications and are observed to be more fragile and more susceptible to side effects. Also in 1994, Loop et al. documented again that lovastatin decreased CoQ content in rat liver that could be completely prevented with supplemental coenzyme Q [41].

In 1995, Satoh et al. evaluated ischemic reperfusion in dog hearts and documented that simvastatin significantly decreased myocardial CoQ<sub>10</sub> levels and worsened ischemia reperfusion injury [61]. Water soluble pravastatin was also studied in this dog model and did not appear to cause worsening of mitochondrial respiration in the dog heart muscle, nor did the pravastatin reduce myocardial CoQ<sub>10</sub> levels. It is believed that the lipid soluble simvastatin may be more detrimental in this model due to better membrane penetration of this fat soluble drug.

In 1997, Morand et al. studied hamsters, squirrel monkeys, and mini pigs, and documented CoQ<sub>10</sub> depletion in heart and liver with simvastatin treatment [48]. The investigators saw no decrease in CoQ<sub>10</sub> in heart and liver using the experimental cholesterol lowering drug 2,3-oxidosqualene:lanosterol cyclase, which blocks the synthesis of cholesterol below the mevalonate level and thus does not impair the biosynthesis of coenzyme Q<sub>10</sub>.

In 1998, Nakahara et al. evaluated simvastatin (a lipophilic inhibitor of HMG CoA-reductase) or pravastatin (a hydrophilic inhibitor) [52]. In group I, rabbits were treated with simvastatin at 50 mg/kg per day for four weeks. There was a 22% to 36% reduction in ubiquinone content in skeletal muscle and the observation of skeletal muscle necrosis and elevated CK levels. Group II rabbits were treated with pravastatin at 100 mg/kg per day for four weeks, which did not cause skeletal muscle injury and reduced CoQ<sub>10</sub> in skeletal muscle by 18% to 52%. In group III, treated with high dose pravastatin at 200 mg/kg per day for three weeks followed by 300 mg/kg per day for another three weeks, there was a greater reduction in CoQ<sub>10</sub> skeletal muscle content from 49% to 72% depletion and evidence of skeletal muscle necrosis and CK elevation. In 1998, Sugiyama observed that pravastatin caused a significant decrease in the activity of mitochondrial complex I in diaphragm skeletal muscle in rats age 35–55 weeks [65]. The authors concluded that careful clinical examination of respiratory muscle function is necessary in patients treated with pravastatin, particularly in the elderly.

In 1999, Ichihara et al. studied the effect of statins on ischemia reperfusion in dogs and observed that pretreatment of the dogs with the lipophilic HMG CoA-reductase inhibitors simvastatin, atorvastatin, fluvastatin, and cerivastatin all worsened recovery of myocardial contraction after ischemia reperfusion, but the water soluble pravastatin had no detrimental effect on myocardial contraction in this model [25]. In 2000, Satoh et al. further observed a detrimental effect from atorvastatin, fluvastatin, and cerivastatin in dog ischemia reperfusion, confirming that lipophilic HMG CoA-reductase inhibitors enhance myocardial stunning in association with ATP reduction after ischemia and reperfusion [60].

In 2000, Caliskan et al. studied rats treated with simvastatin and found significant reductions in plasma cholesterol and ATP concentrations, indicating an impairment in bioenergetics related to CoQ depletion [9]. In 2000, Marz et al. studied hamsters with inherited cardiomyopathy and concluded that lovastatin but not pravastatin at a dose of 10 mg/kg body weight significantly increased the mortality of cardiomyopathic hamsters, as a result of inhibition of myocardial ubiquinone [43]. Finally, in 2001 study by Pisarenko et al. in rats treated with simvastatin at 24 mg/kg for 30 days showed a significant decrease in ATP and creatinine phosphate in myocardium, again indicating that statin-induced CoQ<sub>10</sub> depletion has a detrimental impact on energy production in the heart muscle [56].

### *3.1. Summary of animal studies*

Animal studies to date uniformly document varying degrees of coenzyme Q depletion in blood and in tissue with statin therapy, and that the coenzyme Q deficiency is associated with adverse effects in

cardiomyopathic hamster models, in the ischemia reperfusion injury in dog models, as well as in liver and cardiac coenzyme Q content in rabbits causing skeletal muscle damage. A decrease in cardiac CoQ content and in ATP production has been documented in two years old (elderly) guinea pigs. Significant CoQ depletion was documented in the heart and liver in hamsters, squirrel monkeys, and mini pigs. It is also noteworthy that the lipid soluble statins appear to show more animal toxicity, particularly in the ischemia reperfusion dog models. One can surmise from these animal studies that statins have the potential to produce clinically meaningful coenzyme Q depletion in several animal species and that the depletion is dose related. In all animal studies where supplemental coenzyme Q was given to the animals prior to the institution of statins, the coenzyme Q blood and tissue depletion was completely prevented.

#### 4. Human trials

From 1990 to date there have been 15 published studies in humans evaluating the effects of statins on CoQ<sub>10</sub>. Nine of those were controlled trials and eight of those nine studies demonstrated significant CoQ<sub>10</sub> depletions secondary to statin therapy.

Human observations on the interaction between statins and coenzyme Q<sub>10</sub> were first published in 1990 by Folkers et al., that observed five patients with pre-existing cardiomyopathy that exhibited a significant decline in blood CoQ<sub>10</sub> level and clinical deterioration after having been started on lovastatin [17]. That decrease in CoQ<sub>10</sub> blood level and decline in clinical status was reversed through an increase in supplemental CoQ<sub>10</sub>.

In 1993, Watts et al. studied 20 hyperlipidemic patients treated with a low cholesterol diet and simvastatin and compared them to 20 hyperlipidemic patients treated with diet alone and 20 normal controls [68]. Patients treated with simvastatin had significantly lower plasma coenzyme Q<sub>10</sub> levels and a lower coenzyme Q<sub>10</sub> to cholesterol ratio than either patients on diet alone or normal controls. The depletion of plasma CoQ<sub>10</sub> was significantly associated with the dose of simvastatin. It was concluded that simvastatin may lower plasma CoQ<sub>10</sub> concentration and that that reduction may be proportionally greater than the reduction in cholesterol. The authors felt that that adverse effect of simvastatin on the biosynthesis of coenzyme Q<sub>10</sub> may be clinically important and requires further study. Also in 1993, Ghirlanda et al. studied 30 hypercholesterolemic patients and 10 healthy volunteers in a double-blind controlled trial, comparing placebo with either pravastatin or simvastatin for a three-month treatment period [21]. These HMG CoA-reductase inhibitors showed significant reduction in both total cholesterol and plasma CoQ<sub>10</sub> levels, not only in hypercholesterolemic patients but also in the normal healthy volunteers.

In 1994, Bargossi et al. performed a randomized controlled trial evaluating 34 hypercholesterolemic patients treated with either 20 mg of simvastatin for six months or 20 mg of simvastatin plus 100 mg of supplemental CoQ<sub>10</sub> [3]. The study demonstrated that simvastatin lowered both LDL cholesterol and plasma and platelet CoQ<sub>10</sub> levels. The depletion of CoQ<sub>10</sub> in both plasma and platelets was prevented in the supplemental CoQ<sub>10</sub> group without affecting the cholesterol lowering effect of simvastatin.

In 1995, Laaksonen et al. documented a significant decrease in serum CoQ<sub>10</sub> levels in hypercholesterolemic patients treated for four weeks with simvastatin, with no reduction in skeletal muscle CoQ<sub>10</sub> [29]. In 1996, Laaksonen et al. evaluated skeletal muscle biopsy specimens in 19 hypercholesterolemic patients treated with simvastatin at 20 mg per day and found no depletion of skeletal muscle CoQ<sub>10</sub> concentration as compared to control subjects [30].

In 1996, De Pinieux et al. evaluated 80 hypercholesterolemic patients – 40 patients treated with statins, 20 patients treated with fibrates, and 20 untreated controls [13]. Further, they evaluated 20

non-hyperlipidemic health controlled patients. Serum CoQ<sub>10</sub> levels were significantly lower in statin treated patients and were not depleted in fibrate treated patients or in untreated controls. Lactate to pyruvate ratios were significantly higher in statin treated patients, indicating mitochondrial dysfunction in patients treated with statins, which was not observed in untreated hypercholesterolemic patients or in healthy controls.

In 1997, Palomaki et al. studied 27 hypercholesterolemic men in a double-blind placebo controlled crossover trial with six weeks of lovastatin at 60 mg per day [54]. Lovastatin therapy was associated with a significant decline in serum ubiquinol content as measured per LDL phosphorus, and there was an increased oxidizability of LDL in the lovastatin treated patients.

In 1997, Mortensen et al. studied 45 hypercholesterolemic patients in a randomized double-blind trial with either lovastatin or pravastatin for 18 weeks [50]. A dose-related significant decline in total serum CoQ<sub>10</sub> was found in the pravastatin group from  $1.27 \pm 0.34$  to  $1.02 \pm 0.31$  mmol/L,  $p < 0.01$ . In the lovastatin group, there was a more pronounced decrease in serum CoQ<sub>10</sub> level from  $1.18 \pm 0.36$  to  $0.84 \pm 0.17$  mmol/L  $p < 0.001$ . The authors concluded that although HMG CoA-reductase inhibitors are safe and effective within a limited time horizon, continued vigilance of a possible adverse consequence from coenzyme Q<sub>10</sub> lowering seems important during long-term therapy.

In 1998, Palomaki et al. evaluated 19 men with hypercholesterolemia and coronary artery disease treated with lovastatin with or without CoQ<sub>10</sub> supplementation [55]. In statin treated patients supplemented with ubiquinone the lag time in copper mediated oxidation of LDL increased by 5% ( $p = 0.02$ ). Upon AMVN (2,2-azobis (2,4-dimethylvaleronitrile)) oxidation the faster depletion of LDL ubiquinol and shortened lag time in conjugated diene formation during lovastatin therapy was significantly ameliorated with CoQ<sub>10</sub> supplementation.

In 1999, Miyake et al. studied 97 non-insulin-dependent diabetic patients treated with simvastatin and observed a significant decrease in serum CoQ<sub>10</sub> concentrations along with the decrease in serum cholesterol [45]. Oral CoQ<sub>10</sub> supplementation in diabetic patients receiving simvastatin significantly increased serum coenzyme Q<sub>10</sub> level without affecting the cholesterol levels. Furthermore, the supplemental coenzyme Q<sub>10</sub> significantly decreased cardiothoracic ratios from  $51.4 \pm 5.1$  to  $49.2 \pm 4.7\%$  ( $p < 0.03$ ). The authors concluded that serum coenzyme Q<sub>10</sub> levels in diabetic patients are decreased by statin therapy and may be associated with subclinical diabetic cardiomyopathy, reversible by coenzyme Q<sub>10</sub> supplementation.

In 1999, De Lorgeril et al. studied in a double-blind fashion 32 patients treated with 20 mg of simvastatin compared to 32 patients treated with 200 mg of fenofibrate [12]. Serum CoQ<sub>10</sub> levels were significantly reduced after treatment with simvastatin but not with fenofibrate. No significant change in left ventricular ejection fraction could be determined after 12 weeks of therapy. They observed a loss of myocardial reserve with a flattening of the ejection fraction response to exercise, which could be explained by the statin-induced diastolic dysfunction in those patients. Unfortunately, only systolic measurements of ejection fraction were obtained in this study.

In 2001, Bleske et al. failed to show a depletion in whole blood CoQ<sub>10</sub> in 12 young, healthy volunteers with normal cholesterol levels treated with either pravastatin or atorvastatin for four weeks [6]. Also in 2001, Wong et al. documented that the beneficial anti-inflammatory effect of simvastatin on human monocytes was completely reversible with supplemental mevalonate but not with CoQ<sub>10</sub>, indicating that supplemental CoQ<sub>10</sub> would not interfere with this important statin-mediated anti-inflammatory effect [71]. The most recent statin/CoQ study was a randomized controlled trial by Jula et al., published in JAMA [26]. Simvastatin at 20 mg per day caused a reduction in serum CoQ<sub>10</sub> of 22% ( $p < 0.001$ ). The clinical consequences of this significant CoQ<sub>10</sub> deficiency were not evaluated in this short term trial.

#### 4.1. Summary of human trials

In human trials evaluating coenzyme Q<sub>10</sub> in statin therapy there appears to be frequent and significant depletion in blood CoQ<sub>10</sub> levels, particularly when statins are taken at higher doses and most notably in the elderly. In one study involving patients with preexisting CHF, the depletion in blood coenzyme Q<sub>10</sub> levels was associated with a drop in ejection fraction and clinical deterioration. Supplemental CoQ<sub>10</sub> has been found to prevent the depletion of CoQ<sub>10</sub> in blood and in one study also to prevent the depletion measured in platelet CoQ<sub>10</sub> levels. The serum depletion of CoQ<sub>10</sub> was associated with an elevation in lactate to pyruvate ratio, suggesting an impairment in mitochondrial bioenergetics, secondary to statin-induced CoQ<sub>10</sub> depletion. Furthermore, two trials demonstrated enhanced oxidizability of LDL cholesterol related to the lowering of serum CoQ<sub>10</sub> by statins. Supplemental CoQ<sub>10</sub> has been shown to increase the CoQ<sub>10</sub> content in low density lipoproteins and to decrease significantly LDL cholesterol oxidizability. One trial demonstrated no significant CoQ<sub>10</sub> depletion in 12 young normolipidemic volunteers treated with statins and one trial found no skeletal muscle depletion of CoQ<sub>10</sub> in statin treated hypercholesterolemic patients. In diabetic patients, the CoQ<sub>10</sub> depletion with statin therapy appears to be associated with subclinical cardiomyopathy, with significant improvement in cardiothoracic ratios upon CoQ<sub>10</sub> supplementation.

From these studies, one can conclude that supplemental CoQ<sub>10</sub> prevents the statin induced CoQ<sub>10</sub> deficiency state without altering the cholesterol-lowering ability of these drugs and appears to have benefit both in terms of decreasing the oxidizability of low density lipoprotein cholesterol, as well as preventing or reversing observed detrimental clinical changes.

#### 4.2. Safety and drug interactions

Coenzyme Q<sub>10</sub> is sold in the United States and abroad as an over-the-counter nutrient and is widely recognized as completely safe with no reported toxicity in over a thousand published human and animal trials. The most recent animal safety study was published in 1999 by Williams et al. [69]. Potential CoQ<sub>10</sub> toxicity was assessed in rats administered CoQ<sub>10</sub> by oral gavage for 1 year at 100, 300, 600, and 1200 mg per kg body weight per day. No adverse changes in mortality, clinical signs, body weight, food consumption, or clinical pathology results occurred.

In human clinical trials the highest doses used were 1200 mg/day in 23 patients with Parkinson disease [62] and up to 3,000 mg/day in case study in patients with familial cerebellar ataxia with primary muscle CoQ<sub>10</sub> deficiency [51] with no adverse effects noted. To date, there have been at least 34 placebo controlled trials using CoQ<sub>10</sub> in cardiovascular disease involving a total of 2152 patients with no toxicity or drug interactions reported in the CoQ<sub>10</sub> group as compared to the placebo group. Most of these controlled trials have been reviewed [33,34]. In addition to these controlled trials there have been many open-label long term trials in cardiovascular disease using CoQ<sub>10</sub> in doses up to 600 mg per day with up to eight year follow up, again with a complete lack of toxicity. In heart failure alone there have been at least 39 open trials with supplemental CoQ<sub>10</sub> published involving a total of 4498 patients again with remarkable safety with the only reported side-effects being rare cases of mild nausea.

Long term safety and tolerability of CoQ<sub>10</sub> was documented by Langsjoen in 1990 in a six year study of 126 heart failure patients [35]. Later, in 1993, Morisco published a double blind controlled trial on 641 heart failure patients treated with either placebo or CoQ<sub>10</sub> for one year [49]. The investigators found a significant reduction of hospitalizations for worsening of heart failure in the CoQ<sub>10</sub> group and no evidence of side effects. In 1994 Baggio published an open-label multi-center trial on 2664 patients with heart failure, treated with 150 mg CoQ<sub>10</sub> per day for three months and reported good tolerability [2].

Also in 1994 Langsjoen published long term observations on 424 cardiac patients, treated with 75 to 600 mg of CoQ<sub>10</sub> per day for up to eight years with no adverse effects or drug interactions [32]. One out of the 424 patients experienced transient nausea.

There have been two case reports published claiming potential interaction between CoQ<sub>10</sub> and coumadin (warfarin), suggesting that CoQ<sub>10</sub> has a vitamin K-like effect [31,64]. This has not been corroborated by other investigators and was the subject of a prospective trial [15]. Physicians wisely and routinely follow prothrombin times very closely in patients on coumadin, particularly after any change in diet, medication or over-the-counter supplements. In this author's 18 year experience with the use of CoQ<sub>10</sub> in many thousands of cardiac patients we have yet to see a single case of CoQ<sub>10</sub>-coumadin interaction at doses up to 600 mg of CoQ<sub>10</sub> per day (unpublished observations).

## 5. Conclusions

The widely prescribed HMG CoA-reductase inhibitors block the endogenous biosynthesis both of cholesterol and of coenzyme Q<sub>10</sub>, and the decrease in both substances is related to the dose as well as the potency of these drugs. The depletion of coenzyme Q<sub>10</sub> appears to be well tolerated in younger and healthier patients, particularly in the short term, but the data reveal detrimental cardiac effects in several animal models, particularly in older animals, and there is good evidence to support a detrimental effect in humans with pre-existing cardiac dysfunction when subjected to this statin-induced coenzyme Q<sub>10</sub> depletion. CoQ<sub>10</sub> is known to be deficient in congestive heart failure, with the degree of deficiency in blood and cardiac tissue correlating with the severity of the CHF [19,28]. Normal whole blood levels of CoQ<sub>10</sub> are about  $1.0 \pm 0.2 \mu\text{g/ml}$  with deficiency in the range of  $0.6 \pm 0.2 \mu\text{g/ml}$ . It is also known that CoQ<sub>10</sub> levels steadily fall after the age of 40 [27,63]. Statin drugs produce a depletion in coenzyme Q<sub>10</sub>, which in settings of pre-existing CoQ<sub>10</sub> deficiency, such as in CHF [18,19,28,39,40] and ageing [27], has the ability to worsen myocardial function. As the potency of statin drugs increases and as the target LDL cholesterol level decreases, the severity of CoQ<sub>10</sub> depletion will increase with an increasing likelihood of impairment in heart muscle function. This tragic scenario may very well be prevented by using supplemental CoQ<sub>10</sub> with all HMG CoA reductase inhibitors.

## References

- [1] R. Alleva, M. Tomasetti, S. Bompadre and G.P. Littarru, Oxidation of LDL and their subfractions: kinetic aspects and CoQ<sub>10</sub> content, *Molecular Aspects of Medicine* **18** (1997), s105–s112.
- [2] E. Baggio, R. Gandini, A.C. Plancher, M. Passeri and G. Carmosino, Italian multicenter study on the safety and efficacy of coenzyme Q<sub>10</sub> as adjunctive therapy in heart failure. CoQ<sub>10</sub> Drug Surveillance Investigators, *Molecular Aspects of Medicine* **15** (1994), s287–s294.
- [3] A.M. Bargossi, M. Battino, A. Gaddi, P.L. Fiorella, G. Grossi, G. Barozzi, R. Di Giulio, G. Descovich, S. Sassi and M.L. Genova et al., Exogenous CoQ<sub>10</sub> preserves plasma ubiquinone levels in patients treated with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, *Int. J. Clin. Lab. Res.* **24**(3) (1994), 171–176.
- [4] P. Belichard, D. Pruneau and A. Zhiri, Effect of a long-term treatment with lovastatin or fenofibrate on hepatic and cardiac ubiquinone levels in cardiomyopathic hamster, *Biochim. Biophys. Acta* **1169**(1) (1993), 98–102.
- [5] R.F. Beyer and L. Ernster, The antioxidant role of coenzyme Q, in: *Highlights in Ubiquinone research*, G. Lenaz, O. Barnabei, A. Rabbi and M. Battino, eds, Taylor and Francis, London, 1990, pp. 191–213.
- [6] B.E. Bleske, R.A. Willis, M. Anthony, N. Casselberry, M. Datwani, V.E. Uhley, S.G. Secontine and M.J. Shea, The effect of pravastatin and atorvastatin on coenzyme Q<sub>10</sub>, *Am. Heart. J.* **142**(2) (2001), E2.
- [7] E.G. Bliznakov and D.J. Wilkins, Biochemical and clinical consequences of inhibiting coenzyme Q<sub>10</sub> biosynthesis by lipid-lowering HMG-CoA reductase inhibitors (statins): A critical Overview, *Advances in Therapy* **15**(4) (1998), 218–228.

- [8] E.G. Bliznakov, Lipid-lowering drugs (statins), cholesterol, and coenzyme Q<sub>10</sub>. The Baycol case – a modern Pandora's box, *Biomed Pharmacother* **56** (2002), 56–59.
- [9] S. Caliskan, M. Caliskan, F. Kuralay and B. Onvural, Effect of simvastatin therapy on blood and tissue ATP levels and erythrocyte membrane lipid composition, *Res. Exp. Med. (Berl.)* **199**(4) (2000), 189–194.
- [10] A. Constantinescu, J.J. Maguire and L. Packer, Interactions between ubiquinones and vitamins in membranes and cells, *Molecular Aspects of Medicine* **15** (1994), s57–s65.
- [11] F.L. Crane, Biochemical functions of coenzyme Q<sub>10</sub>, *J. Am. Coll. Nutr.* **20**(6) (2001), 591–598.
- [12] M. de Lorgeril, P. Salen, L. Bontemps, P. Belichard, A. Geysant and R. Itti, Effects of lipid-lowering drugs on left ventricular function and exercise tolerance in dyslipidemic coronary patients, *J. Cardiovasc. Pharmacol.* **33**(3) (1999), 473–478.
- [13] G. De Pinieux, P. Chariot, M. Ammi-Said, F. Louarn, J.L. Lejonc, A. Astier, B. Jacotot and R. Gherardi, Lipid-lowering drugs and mitochondrial function: effects of HMG-CoA reductase inhibitors on serum ubiquinone and blood lactate/pyruvate ratio, *Br. J. Clin. Pharmacol.* **42**(3), 333–337.
- [14] B.A. Diebold, N.V. Bhagavan and R.J. Guillory, Influences of lovastatin administration on the respiratory burst of leukocytes and the phosphorylation potential of mitochondria in guinea pigs, *Biochim. Biophys. Acta* **1200**(2) (1994), 100–108.
- [15] J. Engelsen, J.D. Nielsen and K. Winther, Effect of coenzyme Q<sub>10</sub> and Ginkgo biloba on warfarin dosage in stable, long-term warfarin treated outpatients. A randomised, double blind, placebo-crossover trial, *Thromb. Haemost.* **87**(6) (2002), 1075–1076.
- [16] L. Ernster and P. Forsmark-Andree, Ubiquinol: an endogenous antioxidant in aerobic organisms, *Clinical Investigator* **71**(8) (1993), S60–S65.
- [17] K. Folkers, P. Langsjoen, R. Willis, P. Richardson, L.J. Xia, C.Q. Ye and H. Tamagawa, Lovastatin decreases coenzyme Q levels in humans, *Proc. Natl. Acad. Sci. USA* **87**(22) (1990), 8931–8934.
- [18] K. Folkers, G.P. Littarru, L. Ho, T.M. Runge, S. Havanonda and D. Cooley, Evidence for a deficiency of coenzyme Q<sub>10</sub> in human heart disease, *Int. Z. Vitaminforsch* **40**(3) (1970), 380–390.
- [19] K. Folkers, S. Vadhanavikit and S.A. Mortensen, Biochemical rationale and myocardial tissue data on the effective therapy of cardiomyopathy with coenzyme Q<sub>10</sub>, *Proc. Natl. Acad. Sci. USA* **82**(3) (1985), 901–904.
- [20] M. Fukami, N. Maeda, J. Fukushige, Y. Kogure, Y. Shimada, T. Ogawa and Y. Tsujita, Effects of HMG-CoA reductase inhibitors on skeletal muscles of rabbits, *Res. Exp. Med. (Berl.)* **193**(5) (1993), 263–273.
- [21] G. Ghirlanda, A. Oradei, A. Manto, S. Lippa, L. Uccioli, S. Caputo, A.V. Greco and G.P. Littarru, Evidence of plasma CoQ<sub>10</sub>-lowering effect by HMG-CoA reductase inhibitors: a double-blind, placebo-controlled study, *J. Clin. Pharmacol.* **33**(3) (1993), 226–229.
- [22] L. Gille and H. Nohl, The existence of a lysosomal redox chain and the role of ubiquinone, *Arch Biochem Biophys* **375**(2) (2000), 347–354.
- [23] J.L. Goldstein and M.S. Brown, Regulation of the mevalonate pathway, *Nature* **343**(6257) (1990), 425–430.
- [24] C. Gomez-Diaz, J.C. Rodriguez-Aguilera, M.P. Barroso, J.M. Villalba, F. Navarro, F.L. Crane and P. Navas, Antioxidant ascorbate is stabilized by NADH-coenzyme Q<sub>10</sub> reductase in the plasma membrane, *J. Bioenerg Biomembr* **29**(3) (1997), 251–257.
- [25] K. Ichihara, K. Satoh, A. Yamamoto and K. Hoshi, Are all HMG-CoA reductase inhibitors protective against ischemic heart disease? (Article in Japanese), *Nippon Yakurigaku Zasshi* **114**(1) (1999), 142–149.
- [26] A. Jula, J. Marniemi, H. Risto, A. Virtanen and T. Ronnema, Effects of diet and simvastatin on serum lipids, insulin, and antioxidants in hypercholesterolemic men. A randomized controlled trial, *JAMA* **287**(5) (2002), 598–605.
- [27] A. Kalen, E.L. Appelkvist and G. Dallner, Age-related changes in the lipid compositions of rat and human tissues, *Lipids* **24**(7) (1989), 579–584.
- [28] N. Kitamura, A. Yamaguchi, O. Masami, O. Sawatani, T. Minoji, H. Tamura and M. Atobe, Myocardial tissue level of coenzyme Q<sub>10</sub> in patients with cardiac failure, in: *Biomedical and Clinical Aspects of Coenzyme Q*, (Vol. 4), K. Folkers and Y. Yamamura, eds, Elsevier, Amsterdam, 1984, pp. 243–252.
- [29] R. Laaksonen, K. Jokelainen, T. Sahi, M.J. Tikkanen and J.J. Himberg, Decreases in serum ubiquinone concentrations do not result in reduced levels in muscle tissue during short-term simvastatin treatment in humans, *Clin. Pharmacol. Ther.* **57**(1) (1995), 62–66.
- [30] R. Laaksonen, K. Jokelainen, J. Laakso, T. Sahi, M. Harkonen, M.J. Tikkanen and J.J. Himberg, The effect of simvastatin treatment on natural antioxidants in low-density lipoproteins and high-energy phosphates and ubiquinone in skeletal muscle, *Am. J. Cardiol.* **77**(10) (1996), 851–854.
- [31] C. Landbo and T.P. Almdal, Interaction between warfarin and coenzyme Q<sub>10</sub>, (Article in Danish), *Ugeskr. Laeger.* **160**(22) (1998), 3226–3227.
- [32] H. Langsjoen, P. Langsjoen, P. Langsjoen, R. Willis and K. Folkers, Usefulness of coenzyme Q<sub>10</sub> in clinical cardiology: a long-term study, *Molecular Aspects of Medicine* **15** (1994), s165–s175.

- [33] P.H. Langsjoen and A.M. Langsjoen, Review of coenzyme Q<sub>10</sub> in cardiovascular disease with emphasis on heart failure and ischemia reperfusion, *Asia Pacific Heart J.* **7**(3) (1998), 160–168.
- [34] P.H. Langsjoen and A.M. Langsjoen, Overview of the use of CoQ<sub>10</sub> in cardiovascular disease, *BioFactors* **9** (1999), 273–284.
- [35] P.H. Langsjoen, P.H. Langsjoen and K. Folkers, Long-term efficacy and safety of coenzyme Q<sub>10</sub> therapy for idiopathic dilated cardiomyopathy, *Am. J. Cardiol.* **65**(7) (1990), 521–523.
- [36] A. Lawen, R.D. Martinius, G. McMullen, P. Nagley, F. Vaillant, E.J. Wolvetang and A.W. Linnane, The universality of bioenergetic disease: The role of mitochondrial mutation and the putative inter-relationship between mitochondria and plasma membrane NADH oxidoreductase, *Molecular Aspects of Medicine* **15** (1994), s13–s27.
- [37] G. Lenaz and D. Esposti, Physical properties of ubiquinones in model systems and membranes, in: *Coenzyme Q. Biochemistry, Bioenergetics and Clinical Applications of Ubiquinone*, (Chapter IV), G. Lenaz, ed., John Wiley & Sons, 1985, pp. 83–105.
- [38] G. Lenaz, R. Fato, C. Castelluccio, M. Battino, M. Cavazzoni, H. Rauchova and G.P. Castelli, Coenzyme Q saturation kinetics of mitochondrial enzymes: Theory, experimental aspects and biomedical implications, in: *Biomedical and Clinical Aspects of Coenzyme Q*, (Vol. 6), K. Folkers, T. Yamagami and G.P. Littarru, eds, Elsevier, Amsterdam, 1991, pp. 11–18.
- [39] G.P. Littarru, L. Ho and K. Folkers, Deficiency of coenzyme Q<sub>10</sub> in human heart disease. Part I, *Internat. J. Vit. Nutr. Res.* **42**(2) (1972), 291–305.
- [40] G.P. Littarru, L. Ho and K. Folkers, Deficiency of coenzyme Q<sub>10</sub> in human heart disease. Part II, *Internat. J. Vit. Nutr. Res.* **42**(3) (1972), 413–434.
- [41] R.A. Loop, M. Anthony, R.A. Willis and K. Folkers, Effects of ethanol, lovastatin and coenzyme Q<sub>10</sub> treatment on antioxidants and TBA reactive material in liver of rats, *Molecular Aspects of Medicine* **15** (1994), s195–s206.
- [42] P. Low, M. Andersson, C. Edlund and G. Dallner, Effects of mevinolin treatment on tissue dolichol and ubiquinone levels in the rat, *Biochim. Biophys. Acta* **1165**(1) (1992), 102–109.
- [43] W. Marz, R. Siekmeier, H.M. Muller, H. Wieland, W. Gross and H.G. Olbrich, Effects of lovastatin and pravastatin on the survival of hamsters with inherited cardiomyopathy, *J. Cardiovasc. Pharmacol. Ther.* **5**(4) (2000), 275–279.
- [44] P.A. McCullough, E.F. Philbin, J.A. Spertus, S. Kaatz, K.R. Sandberg and W.D. Weaver, Confirmation of a heart failure epidemic: findings from the Resource Utilization Among Congestive Heart Failure (REACH) study, *J. Am. Coll. Cardiol.* **39**(1) (2002), 60–69.
- [45] Y. Miyake, A. Shouzu, M. Nishikawa, T. Yonemoto, H. Shimizu, S. Omoto, T. Hayakawa and M. Inada, Effect of treatment with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors on serum coenzyme Q<sub>10</sub> in diabetic patients, *Arzneimittelforschung* **49**(4) (1999), 324–329.
- [46] P. Mitchell, Possible molecular mechanism of the protonmotive function of cytochrome systems, *J. Theor. Biol.* **62** (1976), 327–367.
- [47] P. Mitchell, The classical mobile carrier function of lipophilic quinones in the osmochemistry of electron-driven proton translocation, in: *Highlights in Ubiquinone Research*, G. Lenaz, O. Barnabei, A. Rabbi and M. Battino, eds, Taylor and Francis, London, 1990, pp. 77–82.
- [48] O.H. Morand, J.D. Aebi, H. Dehmlow, Y.H. Ji, N. Gains, H. Lengsfeld and J.F. Himber, Ro 48-8.071, a new 2,3-oxidosqualene:lanosterol cyclase inhibitor lowering plasma cholesterol in hamsters, squirrel monkeys, and minipigs: comparison to simvastatin, *J. Lipid Res.* **38**(2) (1997), 373–390.
- [49] C. Morisco, B. Trimarco and M. Condorelli, Effect of coenzyme Q<sub>10</sub> therapy in patients with congestive heart failure: a long-term multicenter randomized study, *Clinical Investigator* **71**(8) (1993), S134–S136.
- [50] S.A. Mortensen, A. Leth, E. Agner and M. Rohde, Dose-related decrease of serum coenzyme Q<sub>10</sub> during treatment with HMG-CoA reductase inhibitors, *Molecular Aspects of Medicine* **18** (1997), s137–s144.
- [51] O. Musumeci, A. Naini, A.E. Slonim, N. Skavin, G.L. Hadjigeorgiou, N. Krawiecki, B.M. Weissman, C.Y. Tsao, J.R. Mendell, S. Shanske, D.C. De Vivo, M. Hirano and S. DiMauro, Familial cerebellar ataxia with muscle coenzyme Q<sub>10</sub> deficiency, *Neurology* **56**(7) (2001), 849–855.
- [52] K. Nakahara, M. Kuriyama, Y. Sonoda, H. Yoshidome, H. Nakagawa, J. Fujiyama, I. Higuchi and M. Osame, Myopathy induced by HMG-CoA reductase inhibitors in rabbits: a pathological, electrophysiological, and biochemical study, *Toxicol. Appl. Pharmacol.* **152**(1) (1998), 99–106.
- [53] H. Nohl and L. Gille, The existence and significance of redox-cycling ubiquinone in lysosomes, *Protoplasma* **217**(1–3) (2001), 9–14.
- [54] A. Palomaki, K. Malminiemi and T. Metsa-Ketela, Enhanced oxidizability of ubiquinol and alpha-tocopherol during lovastatin treatment, *FEBS Lett* **410**(2–3) (1997), 254–258.
- [55] A. Palomaki, K. Malminiemi, T. Solakivi and O. Malminiemi, Ubiquinone supplementation during lovastatin treatment: effect on LDL oxidation *ex vivo*, *J. Lipid Res.* **39**(7) (1998), 1430–1437.

- [56] O.I. Pisarenko, I.M. Studneva, V.Z. Lankin, G.G. Konovalova, A.K. Tikhaze, V.I. Kaminnaya and Y.N. Belenkov, Inhibitor of beta-hydroxy-beta-methylglutaryl coenzyme A reductase decreases energy supply to the myocardium in rats, *Bull. Exp. Biol. Med.* **132**(4) (2001), 956–958.
- [57] F.L. Rosenfeldt, S. Pepe, R. Ou, J.A. Mariani, M.A. Rowland, P. Nagley and A.W. Linnane, Coenzyme Q<sub>10</sub> improves the tolerance of the senescent myocardium to aerobic and ischemic stress: studies in rats and in human atrial tissue, *Biofactors* **9**(2–4) (1999), 291–299.
- [58] F.L. Rosenfeldt, S. Pepe, A. Linnane, P. Nagley, M. Rowland, R. Ou, S. Marasco and W. Lyon, The effects of ageing on the response to cardiac surgery: protective strategies for the ageing myocardium, *Biogerontology* **3**(1–3) (2002), 37–40.
- [59] H. Rudney, A.M.D. Nambudiri and S. Ranganathan, The regulation of the synthesis of coenzyme Q in fibroblasts and in heart muscle, in: *Biomedical and Clinical Aspects of Coenzyme Q*, (Vol. 3), K. Folkers and Y. Yamamura, eds, Elsevier/North-Holland Press, 1981, pp. 279–290.
- [60] K. Satoh and K. Ichihara, Lipophilic HMG-CoA reductase inhibitors increase myocardial stunning in dogs, *J. Cardiovasc. Pharmacol.* **35**(2) (2000), 256–262.
- [61] K. Satoh, A. Yamato, T. Nakai, K. Hoshi and K. Ichihara, Effects of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors on mitochondrial respiration in ischaemic dog hearts, *Br. J. Pharmacol.* **116**(2) (1995), 1894–1898.
- [62] C.W. Shults, D. Oakes, K. Kieburz, M.F. Beal, R. Haas, S. Plumb, J.L. Juncos, J. Nutt, I. Shoulson, J. Carter, K. Kompoliti, J.S. Perlmutter, S. Reich, M. Stern, R.L. Watts, R. Kurlan, E. Molho, M. Harrison, M. Lew and Parkinson Study Group, Effects of coenzyme Q<sub>10</sub> in early Parkinson disease: evidence of slowing of the functional decline, *Arch. Neurol.* **50**(10) (2002), 1541–1550.
- [63] M. Soderberg, C. Edlund, K. Kristensson and G. Dallner, Lipid composition of different regions of the human brain during aging, *J. Neurochem.* **54**(2) (1990), 415–423.
- [64] O. Spigset, Reduced effect of warfarin caused by ubidecarenone, *Lancet* **344**(8933) (1994), 1372–1373.
- [65] S. Sugiyama, HMG CoA reductase inhibitor accelerates aging effect on diaphragm mitochondrial respiratory function in rats, *Biochem. Mol. Biol. Int.* **46**(5) (1998), 923–931.
- [66] P.D. Thompson, P. Clarkson and R.H. Karas, Statin-associated myopathy, *JAMA* **289**(13) (2003), 1681–1690.
- [67] J.M. Villalba, F. Navarro, C. Gomez-Diaz, A. Arroyo, R.I. Bello and P. Navas, Role of cytochrome b5 reductase on the antioxidant function of coenzyme Q in the plasma membrane, in: *Molecular Aspects of Medicine*, (Vol. 18), G.P. Littarru, M. Alleva, M. Battino and K. Folkers, eds, 1997, pp. s7–s13.
- [68] G.F. Watts, C. Castelluccio, C. Rice-Evans, N.A. Taub, H. Baum and P.J. Quinn, Plasma coenzyme Q (ubiquinone) concentrations in patients treated with simvastatin, *J. Clin. Pathol.* **46**(11) (1993), 1055–1057.
- [69] K.D. Williams, J.D. Maneke, M. AbdelHameed, R.L. Hall, T.E. Palmer, M. Kitano and T. Hidaka, 52-Week oral gavage chronic toxicity study with ubiquinone in rats with a 4-week recovery, *J. Agric. Food. Chem.* **47**(9) (1999), 3756–3763.
- [70] R.A. Willis, K. Folkers, J.L. Tucker, C.Q. Ye, L.J. Xia and H. Tamagawa, Lovastatin decreases coenzyme Q levels in rats, *Proc. Natl. Acad. Sci. USA* **87**(22) (1990), 8928–8930.
- [71] B. Wong, W.C. Lumma, A.M. Smith, J.T. Sisko, S.D. Wright and T.Q. Cai, Statins suppress THP-1 cell migration and secretion of matrix metalloproteinase 9 by inhibiting geranylgeranylation, *J. Leukoc. Biol.* **69**(6) (2001), 959–962.