

## The Statin Drug-Cholesterol-CoQ<sub>10</sub>-Low Energy Controversy

W. V. Judy, PhD  
SIBR Research, Ind.  
4112 20<sup>th</sup> Street West  
Bradenton, FL 34205

### INTRODUCTION

A major controversy has developed in the USA and around the world over the possible excess use and adverse effects of statin drugs. Statins are used to lower the production of cholesterol and in doing such reduce the build up of fatty deposits in blood vessels. These cholesterol deposits have been clearly shown to be the major contributor to heart attack and stroke. The adverse effects of the statin is an induced low energy syndrome caused by the statin inhibitor of the enzyme HMG-CoA reductase essential for the production of both cholesterol and coenzyme Q<sub>10</sub> (CoQ<sub>10</sub>) (1). CoQ<sub>10</sub> is essential for energy synthesis in all the cells in the human body (2). Thus, the induced low energy resulting from the reduction of the HMG-CoA reductase and therefore the reduced production of CoQ<sub>10</sub> is the adverse side effect of the statin drugs that will greatly influence the quality of life and resistance to age related conditions in the aging American population.

Today some 10 to 12 million Americans are taking statin drugs for the control of LDL cholesterol. The prevalence of coronary artery disease (CAD) is escalating (3). An estimated 12.6 million Americans have CAD. More than 102.3 million Americans have total cholesterol greater than 200mg/dL, and of those 41.3 million have levels greater than 240mg/dL, despite advances in medical management. With the new guidelines for LDL control defined by the NCEP (National Cholesterol Education Program), the indications for the use of statin drugs have been broadened considerably. With these new guidelines patients with low normal LDL cholesterol levels are now being treated with the statins in a hope of reducing the incidence of heart attack and stroke. The general approach is to use statins in perhaps 36 million Americans, not only to reduce cholesterol build up in blood vessels but also as an anti-inflammatory agent in the blood vessels, thereby stabilizing plaque and thus reducing morbidity and mortality due to stroke and heart attack in older individuals. The negative implications of wide spread use of statin drugs is perhaps far more detrimental in an aging society. This is via the statin reduction of CoQ<sub>10</sub> and thus the available energy required by all cells for life processes. This critical impact will expose more elderly to a reduced quality of life, increased morbidity associated with age related degenerative diseases, and mortality.

In this review the emphasis is being placed on the statin drugs inhibition of CoQ<sub>10</sub> as shown via clinical studies, and the relationship between low CoQ<sub>10</sub> and heart conditions leading to death. An immense amount of clinical data has been collected on the essential role of CoQ<sub>10</sub> in other clinical conditions involving all age levels of the American people. Only a few of these will be reviewed to show a probable wider scope of excess statin drug use in the USA.

### THE STATIN DRUGS

Statin drugs or HMG-CoA reductase inhibitors are by far the most effective class of drugs for lowering LDL cholesterol. Since it is the LDL cholesterol that when oxidized in blood causes vascular fatty plaque build up leading to cardiovascular morbidity and mortality, it should be clear why millions of patients are given these drugs daily. The clinical data most definitely shows that the statins are associated with a beneficial effect on the morbidity and mortality of patients with obstructive vascular disease. Large scale and long-term clinical studies (5, 6) in middle aged men (N=6595) with moderate hypercholesterolemia and taking 40mg/day Pravastatin reduced the risk of heart attack and death by 31% compared to placebo, and also substantial reduction in the risks of heart attacks (31%), all cardiac death (32%) and all causes of

death (22%) (6). Another study found a 27% reduction in both fatal and non-fatal heart attack, unstable angina, and sudden death compared with 3301 placebo controls, as well as 33% reduction in revascularization procedures (by-pass surgery), a 32% reduction in stable angina and a 40% reduction in the incidence of fatal and non-fatal heart attack (6). The Scandinavian Simvastatin survival study (7) demonstrated a significant long-term treatment effect of 20 to 40mg/day Simvastatin in 2271 coronary patients compared to placebo in 2273 coronary patients. There was a 30% decline in all causes of death, a 42% reduction in the risk factors of coronary death and a 34% decrease in recurrent coronary events. These patients had angina or previous heart attack and total cholesterol between 213 and 309mg/dL. It is no doubt that the statin drugs reduce morbidity and mortality. The number of patients taking statins will increase from 12 million to perhaps more than 36 million in the next decade due to the recent change in the guidelines for cholesterol control established by the National Cholesterol Education Program (4). These new guidelines state that individuals who have previously had an acceptable LDL of 124mg/dL should be given statins to reduce the LDL to 100mg/dL or lower, thereby, hopefully, reducing the incidence of stroke and heart attack even further. The use of statins in the elderly has gained acceptance in the medical community due to its significant anti-inflammatory and plaque stabilizing effects. All in all more elderly who have no symptomatology of excess cholesterol or vascular obstruction will be given statin drugs. It is this population, who also has reduced CoQ<sub>10</sub> levels due to age, that will be put at risk by statin drug therapy.

Coenzyme Q<sub>10</sub> is essential for energy synthesis in all living cells (2). It is responsible for 95% of the energy produced in our bodies. As little as a 25% reduction in blood or cellular CoQ<sub>10</sub> content will cause a significant reduction in energy synthesis. This will have some rather severe adverse effects in the elderly population. These are: low energy syndromes, fatigue, muscle cramps, muscle wasting and heart failure. In fact congestive heart failure has more than doubled in the past ten years and is expected to double again in this decade. So why is there a controversy between the statin drugs, CoQ<sub>10</sub>, and low energy syndromes? The battle line is clinically (drug) induced low energy syndrome with multiple adverse effects on body functions and quality of life. Again, this controversy stems from the fact that cholesterol is made in the body in the same metabolic pathway (mevalonate) as CoQ<sub>10</sub>. Since statin drugs lower cholesterol synthesis by inhibiting a common essential co-factor (HMG-CoA reductase) it will also inhibit the synthesis of CoQ<sub>10</sub>. Statin drugs have been shown to inhibit CoQ<sub>10</sub> synthesis by 22 to 44% (5-7).

It is well established that the mevalonate pathway is involved in the biosynthesis of cholesterol and CoQ<sub>10</sub> and the rate-limiting co-factor is HMG-CoA reductase. The inhibition of HMG-CoA reductase reduces both cholesterol and COQ<sub>10</sub> synthesis (8, 1). This nutrient interaction has been reviewed (9).

Scientific peer-reviewed evidence provides the following facts:

1. Both cholesterol and CoQ<sub>10</sub> are synthesized in the same biochemical pathway (mevalonate) in the body.
2. The rate-limiting co-factor of both cholesterol and CoQ<sub>10</sub> synthesis in the mevalonate pathway is HMG-CoA reductase.
3. CoQ<sub>10</sub> is essential for ATP synthesis in the mitochondria of all body cells and also functions as an antioxidant in the blood to prevent the oxidation of cholesterol, thus preventing the formation of vascular plaque. In the cell membrane it prevents lipid peroxidation and cell death (apoptosis).
4. Statin drugs reduce the LDL cholesterol synthesis by inhibiting the rate-limiting enzyme HMG-CoA reductase in the mevalonate pathway.
5. The inhibition of the HMG-CoA reductase by statins also reduces endogenous CoQ<sub>10</sub> in all cells.
6. The detrimental cardiac consequences from statin induced CoQ deficiency in man and animals have been scientifically confirmed.
7. The statin induced CoQ deficiency in man and animals is both dose and clinical condition dependent, thus the most rapid and severely affected are the elderly with

- already reduced CoQ<sub>10</sub> levels and pre-existing congestive heart failure and other low energy clinical conditions.
8. CoQ<sub>10</sub> supplementation reverses the statin induced CoQ<sub>10</sub> deficiencies and adverse effects.
  9. CoQ<sub>10</sub> supplementation is safe and has no adverse effects on statin drugs ability to lower cholesterol or on its anti-inflammatory or plaque stabilizing effects.

Every year there is an estimated 400,000 new cases of congestive heart failure (CHF) in the USA. Currently there are 4.8 million Americans diagnosed with CHF. Those with low to mild CHF (Class I and II) and treated by conventionally acceptable medical management should live 7 to 14 years. Those with more severe CHF (Class III and IV) could die within 2 to 5 years, even with the best medical management. It appears that the USA is in the midst of a CHF epidemic. All the causative factors for this epidemic are not known. The question is whether statin induced CoQ<sub>10</sub> deficiencies in the past 5 to 10 years and in the next 5 to 10 years could be a major contributing factor?

It is interesting that the clinical trials proving the benefits of statin drugs on hyperlipidemia excluded patients with New York Heart Association (NYHA) Class III and IV congestive heart failure. Thus, the long-term safety of statins in patients with CHF has not been established nor has the probable effect on statin inhibition of CoQ<sub>10</sub> and thus energy on the development or progress of CHF been clearly defined.

## COENZYME Q<sub>10</sub>

The multiple biochemical functions of CoQ<sub>10</sub> have been reviewed by Crane (2001), who discovered CoQ<sub>10</sub> in 1957 (10). Energy synthesis through oxidative phosphorylation in the enzyme complexes in the mitochondrial inner membrane is CoQ<sub>10</sub> dependent in that it takes an estimated 50 times more CoQ<sub>10</sub> than NADH and 7 times more CoQ<sub>10</sub> than cytochrome C to make this system function maximally (10). A small change in CoQ<sub>10</sub> could easily induce a large change in energy synthesis. This may be of major importance in organ systems with a high metabolic demand such as the heart cells. CoQ<sub>10</sub> is carried in the blood with the low-density lipoproteins (LDL) and reduces the oxidation of LDL cholesterol in settings of oxidative stress (11). This additional fundamental property of CoQ<sub>10</sub> as an antioxidant scavenger for free radicals (12) in the blood and in the cell membrane positions CoQ<sub>10</sub> as a prime protector of all phospholipid membranes. Thus, CoQ<sub>10</sub> may well be the primary protector antioxidant preventing cell distress, reducing the aging process and insuring longevity free of age related degenerative disease (13). Interaction of CoQ<sub>10</sub> with the antioxidant vitamin E (alpha tocopherol) involves the regeneration of the reduced (active) form to the oxidized form (14) as well as reduced forms of ascorbate. CoQ<sub>10</sub> is also involved in extramitochondrial electron transfer in plasma membrane oxidoreductase activity (15), cytosolic glycolysis (16) and an excellent potential activity cellular lysosome and Golgi apparatus (17). Since CoQ<sub>10</sub> is bound in cellular and organ membranes and not found in the cell cytosol (fluid media) it has been shown that CoQ<sub>10</sub> improves membrane fluidity (18).

The hearts extreme energy requirement, ATP production and CoQ<sub>10</sub> synthesis are proportionally linked. Diminished CoQ<sub>10</sub> means reduced ATP synthesis and reduced cardiac function. Blood and cardiac muscle CoQ<sub>10</sub> deficiencies have been well documented in heart failure (19, 20). The role of CoQ<sub>10</sub> as a protector of the cardiac cell has also been well demonstrated in high-risk patients in heart surgery (21,22). Patients with age related low plasma CoQ<sub>10</sub> levels are at risk when sent to coronary artery bypass surgery (CABG). This impairment is eliminated by pretreatment with exogenous CoQ<sub>10</sub> (23).

The number of deaths related to and the incidence of congestive heart failure in the USA over the past decade suggests that we are in the midst of a CHF epidemic (National Center of Health Statistics, NIH, and NHIB Institute). The number of annual deaths directly from CHF has increased four-fold (10,000 to 42,000) between 1968 and 1993 and this has increased even more in

the past ten years. More and more hospitalization and recurrent hospitalizations are reported due to the inability to either prevent or successfully treat CHF. Comparative statistics show that the major increase in CHF occurs in those age groups, 65 to 75 years old, and at a time when age related CoQ<sub>10</sub> synthesis is reduced by 45 to 55%. Since the statin drugs inhibit LDL cholesterol and CoQ<sub>10</sub> synthesis, we should expect to experience an even greater CHF epidemic in the next decade due to a projected tripling of the number of patients being treated with statin drugs.

Statins were first given in the USA in 1987. Currently, in 2003, some 16 years later, statins are taken by as estimated 12 to 13 million people in the USA for hyperlipidemia. During this interval there has been a steady accumulation of scientific data showing the adverse effects and CoQ<sub>10</sub> lowering effects of statin drugs. The statin drug producers, the clinical societies, and the FDA should acknowledge these findings. Physicians should also consider them when prescribing statin drugs for hyperlipidemia, especially in the elderly populations with age related CoQ<sub>10</sub> deficiencies.

## HUMAN CLINICAL TRIAL

In the past decade more than 15 studies in humans evaluating the effects of statin drugs on CoQ<sub>10</sub> have appeared in the literature. Of these studies nine were controlled trials and eight of these clearly showed a significant CoQ<sub>10</sub> depletion secondary to statin therapy.

Folkers et al (1990) first observed the statin (Lovastatin) lowering effects in five patients with pre-existing CHF (24). The observed decline in plasma CoQ<sub>20</sub> was also associated with a worsening of the heart failure. With CoQ<sub>10</sub> supplementation in combination with statin therapy, plasma CoQ<sub>10</sub> increased, the clinical CHF condition improved and the plasma LDL remained reduced.

Ghirlanda et al (1993) evaluated the cholesterol lowering effects in 30 hyperlipidemic and 10 healthy volunteers in double blind placebo controlled trial over a three-month interval (25). Again the statins, Pravastatin or Simvastatin, significantly reduced total cholesterol and plasma CoQ<sub>10</sub> in both the hypercholesterolemic and the normal volunteers.

Watts et al (1993) studied 20 hyperlipidemic patients treated with a low cholesterol diet and Simvastatin and compared their result with 20 hyperlipidemic patients treated with the diet alone, and 20 normal controls (26). In the patient group treated with diet and the statin Simvastatin, significantly lower plasma CoQ<sub>10</sub> level and a lower CoQ<sub>10</sub> to cholesterol ratio than found for either the group treated with diet alone or for the normal controls. The depletion of CoQ<sub>10</sub> worsened as the dosage of Simvastatin was increased. It was also shown that the reduction of CoQ<sub>10</sub> exceeded that of cholesterol in the statin treated group.

Bargossi et al (1994) conducted a randomized control trial in which 34 hypercholesterolemic patients were treated with 20mg/day Simvastatin for 60 months or 20mg/day of Simvastatin plus 100mg/day of CoQ<sub>10</sub> (27). The Simvastatin group had a significant reduction in LDL cholesterol accompanied by a reduction in plasma and platelet CoQ<sub>10</sub>. Simvastatin prevented CoQ<sub>10</sub> depletion in plasma and platelets in the Simvastatin plus CoQ<sub>10</sub> study group without affecting the lowering of plasma cholesterol.

Laaksonen et al (1995) observed a significant reduction in serum CoQ<sub>10</sub> levels in hypercholesterolemic patients treated with Simvastatin for four weeks (28). They observed no significant reduction in skeletal muscle CoQ<sub>10</sub>.

Laaksonen et al (1996) found that skeletal muscle biopsy for hypercholesterolemic patients treated with 20mg/day of Simvastatin had no significant reduction in skeletal muscle CoQ<sub>10</sub> concentration as compared to that found in control subjects (29). However, these patients did not belong to the elder population with age related diminished endogenous CoQ<sub>10</sub> synthesis.

DePinieux et al (1996) evaluated serum CoQ<sub>10</sub> and lactate to pyruvate ratios in 40 hypercholesterolemic patients receiving statins, 20 patients receiving fibrates, and 20 untreated controls and compared these results with those obtained from 20 non-hypercholesterolemic healthy control volunteers (30). Serum CoQ<sub>10</sub> levels were not changed in the fibrate treated or

control volunteers, but a significant lowering was found in the statin treated group. The statin treated group also had significantly higher lactate to pyruvate ratios, indicating mitochondrial dysfunction in patients treated with statins. This observation was not found in the untreated hypercholesterolemic or healthy control patients.

Mortensen et al (1997) in a randomized double blind trial evaluating either Lovastatin or Pravastatin in 45 hypercholesterolemic patients for 15 weeks found a dose related reduction in serum CoQ<sub>10</sub> (31). The reduction for Pravastatin was 24%, while that for Lovastatin was 40%.

Palomaki et al (1997) in a double blind placebo controlled crossover trial studied 17 hypercholesterolemic men receiving 60mg/day Lovastatin or placebo (32). Lovastatin therapy induced a significant decline in serum CoQ<sub>10</sub> (Ubiquinol) content as measured per LDL phosphorus. Also an increased oxidation of LDL cholesterol in the Lovastatin treated patients was observed.

Palomaki et al (1998) studied 19 men with hypercholesterolemia and coronary artery disease treated with Lovastatin with or without CoQ<sub>10</sub> supplementation (33). The copper mediated LDL oxidation lag time was increased significantly. CoQ<sub>10</sub> supplementation partially restored the faster LDL depletion and shortened lag time in conjugated diene formation.

Miyake et al (1999) observed a significant reduction in serum CoQ<sub>10</sub> along with a decrease in serum cholesterol in 97 type II diabetic patients treated with Simvastatin (34). Oral CoQ<sub>10</sub> supplementation in the patients receiving Simvastatin significantly increased serum CoQ<sub>10</sub> levels without affecting cholesterol levels. CoQ<sub>10</sub> supplementation significantly reduced the size of the heart. The lowering of plasma CoQ<sub>10</sub> was accompanied by an elevation of blood sugar that was reversed by oral CoQ<sub>10</sub> supplementation.

DeLorgeril et al (1999) in a double blind study design in 32 patients treated with 20mg of Simvastatin compared to 32 patients treated with 200mg of Fenofibrate found no significant change in resting left ventricular ejection fraction after 12 weeks of therapy (35). However, a loss of myocardial reserve during exercise was demonstrated by the flattening of the ejection fraction response.

Bleske et al (2001) failed to show a whole blood CoQ<sub>10</sub> depletion in 12 young, healthy volunteers with normal cholesterol treated with either Pravastatin or Atrovastatin for one month (36). It was concluded that the statins had no effect on CoQ<sub>10</sub> synthesis in normal young volunteers without hypercholesterolemia.

Wong et al (2001) showed that the anti-inflammatory action of Simvastatin on the human monocyte was not reversed with CoQ<sub>10</sub> supplementation (37). This indicates that CoQ<sub>10</sub> given with statin drugs will not interfere with the statin mediated anti-inflammatory process.

Jula et al (2002) in a randomized controlled trial found that Simvastatin 20mg/day reduced serum CoQ<sub>10</sub> 225 in a short-term trial (38).

Human clinical trials almost across the board show a frequent and significant reduction in blood CoQ<sub>10</sub> by statin drugs when given in higher dose and to elderly patients. CoQ<sub>10</sub> supplementation with statin drug therapy prevents the depletion of plasma CoQ<sub>10</sub> without affecting the cholesterol lowering effects. Statin drug therapy in patients with pre-existing CHF may accelerate the degree of failure, and increase morbidity and mortality. The same may be true in patients with ischemic heart disease.

In the past decade, multiple animal studies (N=15) have also shown that statin drugs block HMG-CoA reductase thus inhibiting the synthesis of LDL cholesterol and CoQ<sub>10</sub>. These studies will not be presented in this review. The overall summary from the animal studies show that statin drugs adverse effects in animals parallel those found in man. CoQ<sub>10</sub> supplementation before or during statin drug administration shows that the depletion of CoQ<sub>10</sub> and the adverse side effects are parallel and completely preventable.

## **SAFETY of CoQ<sub>10</sub> and DRUG INTERACTION**

After some 35 years of clinical and basic research in CoQ<sub>10</sub> and its availability world wide as a bionutrient, no major safety or toxic issues have been found. There have been a few reports of some transient nausea experienced by individuals when taking the lipid solubilized CoQ<sub>10</sub> product form (39). There have been published reports that address a potential interaction between CoQ<sub>10</sub> and the blood thinner Coumadin. These suggest a potential interaction due to the structure of CoQ<sub>10</sub> being very similar to that of vitamin K (40, 41). Other investigators that have followed larger groups of patients taking Coumadin and CoQ<sub>10</sub> for years have not supported this. In fact, this issue was addressed at the 2002 International Coenzyme <sub>10</sub> Association meeting in Frankfurt, Germany (42). In this study no interaction could be documented in a randomized double blind study protocol.

More than 35 placebo controlled clinical trials involving 2152 patients with cardiovascular disease have reported no CoQ<sub>10</sub> toxicity or drug interactions in the CoQ<sub>10</sub> treated compared to placebo treated heart failure patients (43). Other multiple open label trials support these observations. In all more than 5000 patients receiving CoQ<sub>10</sub> supplemental to various drugs have reported no major adverse side effects or drug interactions. The long-term tolerability and safety of CoQ<sub>10</sub> is undeniable from the large scale study results done in congestive heart failure (43, 39, 44, 45) and more recently in patients with Parkinson's disease (46), Huntington's disease (47), familial cerebellar ataxia (48) and in infants and children with Prader-Willi syndrome (49). Clearly safety should not be an issue since CoQ<sub>10</sub> is normal to the body and without toxicity even at doses above 1100mg/day.

## SUMMARY

Statin drug inhibition of the HMG-CoA reductase enzyme in the mevalonate pathway for the synthesis of cholesterol and CoQ<sub>10</sub> is well established. Younger patients with hyperlipidemia, in general, have little to no resting low energy syndrome when taking statins for two to five years at low to moderate doses. Older patients with age related decreased endogenous CoQ<sub>10</sub> synthesis experience resting fatigue, muscle cramps, muscle wasting, and heart failure when taking statin drugs. However, the adversities of statin drugs being given to more and more elderly patients is not just the high probability of induced low energy syndrome and a poor quality of life. This statin induces low energy transcends many clinical conditions with associated low energy. These include diabetes, age related CNS degenerative diseases, immune deficiencies, kidney failure, liver failure, inflammatory conditions, cancer and perhaps a host of other clinical conditions. Thus, the real issue is more than the effects of statin drugs on CoQ<sub>10</sub> related to heart failure. So as the number of Americans prescribed statin drugs by physicians increases three to four-fold in the next decade, it is likely that the epidemic in CHF may be increased. We will likely see more uncontrolled diabetic patients, more CNS degenerative disease, more kidney and liver failure, more inflammatory disease and more cancer leading to greater health care cost and mortality.

Since the statin drug lowering of cholesterol is so effective and its benefits relative to the morbidity and mortality related to heart attack and stroke is a clearly established, another direction must be taken for the millions of elderly Americans who will be given statins in the future. Since CoQ<sub>10</sub>'s essential role in energy synthesis, cell growth, cell repair, and cell protection is also clearly established and its role in reversing heart failure and other age related degenerative disease is well documented, the statin-low energy-CoQ<sub>10</sub> controversy should be easily resolved. Since CoQ<sub>10</sub> has not been shown to interfere with the cholesterol lowering effects of the statins, it is recommended that all patients receiving statin drugs also receive CoQ<sub>10</sub> daily as a means of maintaining endogenous CoQ<sub>10</sub> synthesis and energy production thereby securing a better quality of life for the aging American population.

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