The Role of Coenzyme Q10 in Statin-Associated Myopathy
A Systematic Review

Leo Maroff, MD,* Paul D. Thompson, MD†‡
New Haven, Hartford, and Farmington, Connecticut

Statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) are currently the most effective medications for reducing low-density lipoprotein cholesterol concentrations. Although generally safe, they have been associated with a variety of myopathic complaints. Statins block production of farnesyl pyrophosphate, an intermediate in the synthesis of ubiquinone or coenzyme Q10 (CoQ10). This fact, plus the role of CoQ10 in mitochondrial energy production, has prompted the hypothesis that statin-induced CoQ10 deficiency is involved in the pathogenesis of statin myopathy. We identified English language articles relating statin treatment and CoQ10 levels via a PubMed search through August 2006. Abstracts were reviewed and articles addressing the relationship between statin treatment and CoQ10 levels were examined in detail. Statin treatment reduces circulating levels of CoQ10. The effect of statin therapy on intramuscular levels of CoQ10 is not clear, and data on intramuscular CoQ10 levels in symptomatic patients with statin-associated myopathy are scarce. Mitochondrial function may be impaired by statin therapy, and this effect may be exacerbated by exercise. Supplementation can raise the circulating levels of CoQ10, but data on the effect of CoQ10 supplementation on myopathic symptoms are scarce and contradictory. We conclude that there is insufficient evidence to prove the etiologic role of CoQ10 deficiency in statin-associated myopathy and that large, well-designed clinical trials are required to address this issue. The routine use of CoQ10 cannot be recommended in statin-treated patients. Nevertheless, there are no known risks to this supplement and there is some anecdotal and preliminary trial evidence of its effectiveness. Consequently, CoQ10 can be tested in patients requiring statin treatment, who develop statin myalgia, and who cannot be satisfactorily treated with other agents. Some patients may respond, if only via a placebo effect. (J Am Coll Cardiol 2007;49:2231–7) © 2007 by the American College of Cardiology Foundation

CoQ10. Coenzyme Q10 was discovered by Crane et al. (6) in 1957. Coenzyme Q10 is a naturally occurring, fat-soluble quinone that is localized in hydrophobic portions of cellular membranes. Approximately half of the body’s CoQ10 is obtained through dietary fat ingestion, whereas the remainder results from endogenous synthesis (7). Coenzyme Q10 participates in electron transport during oxidative phosphorylation in mitochondria, protects against oxidative stress produced by free radicals (8), and regenerates active forms of the antioxidants ascorbic acid and tocopherol (vitamin E) (9,10). Statins block production of farnesyl pyrophosphate, an intermediate in the production of CoQ10 (Fig. 1). This fact plus the role of CoQ10 in mitochondrial energy production and the importance of mitochondria in muscle function has prompted the hypothesis that statin-induced CoQ10 deficiency participates in statin-associated myopathy.

Methods
English language articles relating statin treatment and CoQ10 levels were identified via a PubMed search through August 2006 and from reference citations in other articles. The PubMed search was performed using various combi-
Abbreviations and Acronyms

CK = creatine kinase
CoQ10 = coenzyme Q10
HMG-CoA = 3-hydroxy-3-methylglutaryl coenzyme A
LDL = low-density lipoprotein
RER = respiratory exchange ratio
\( \dot{V}_{O_2} \max = \) maximal oxygen uptake

nations of the terms myopathy, rhabdomyolysis, statin, HMG-CoA reductase inhibitor, CoQ10, ubiquinone, and skeletal muscle.

Abstracts were reviewed, and articles addressing the relationship between statin treatment and CoQ10 levels were examined in detail.

Effect of Statins on Circulating CoQ10 Levels

Statins have been known to reduce circulating CoQ10 levels in animal models (11) and humans (12) since at least 1990. Since that time and with rare exceptions (13,14) at least 9 observational studies (12,13,15–23) and 6 randomized controlled trials (7,24–28) have demonstrated that statins reduce plasma/serum levels of CoQ10 16% to 54% (Table 1). The largest trial (25) included 1,049 patients and noted reductions in plasma CoQ10 levels of 38% and 27% after treatment with atorvastatin 10 mg/day to 20 mg/day or lovastatin 20 mg/day to 40 mg/day, respectively. The decrease in blood CoQ10 levels with statin treatment is probably due to reductions in lower-density lipoproteins. Coenzyme Q10 is transported in low-density lipoprotein (LDL) (58 ± 10% of serum CoQ10), high-density lipoprotein (26 ± 8%), and very low-density lipoprotein + intermediate-density lipoprotein (16 ± 8%) particles (29). Normalizing CoQ10 concentrations for the reduction in LDL cholesterol or total cholesterol suggests that there is no change in CoQ10 lipoprotein particle concentration. For example, treatment with simvastatin 20 mg/day for 4 weeks (16) reduced serum total cholesterol and CoQ10 levels by 26% and 31%, respectively (p < 0.001), but the ratio of serum CoQ10 to total cholesterol decreased only 9% (p = NS). Similar apparently parallel reductions in total cholesterol have been reported by at least 7 other authors using a variety of statins (17–19,24–27) although 2 trials have not found reductions in circulating CoQ10 levels with statin treatment (14,30).

The hypothesis that a combination of ezetimibe with simvastatin would counteract the statin-induced decrease in circulating CoQ10 was tested in a recent trial (20). Ezetimibe inhibits intestinal absorption of dietary cholesterol and increases endogenous cholesterol synthesis. Seventy-two healthy men were randomized to receive either ezetimibe 10 mg/day, simvastatin 40 mg/day, or both for 2 weeks. Ezetimibe alone did not reduce plasma CoQ10 concentrations (+1.1 ± 21%). The combination of simvastatin and ezetimibe reduced plasma CoQ10 levels as did simvastatin alone (−28 ± 12% and −16 ± 16%, respectively). The decrease in LDL cholesterol correlated with the decrease in plasma CoQ10 levels in all 3 groups (R = 0.67, p < 0.0001). In addition, the ratios of plasma CoQ10 to LDL cholesterol concentrations were increased in all groups (p < 0.0001).

Few studies have examined the effect of statins on nonlipoprotein CoQ10 levels in the circulation, although at least 1 study (24) reported 12.5% reductions in platelet CoQ10 levels. The mechanism and significance of this finding are unclear, however, because platelets do not contain mitochondria.

Effect of Statins on Skeletal Muscle CoQ10 Levels

Animal studies document that statins can reduce ubiquinone levels in cardiac muscle and liver (11,31–33). If CoQ10 deficiency contributes, at least in part, to statin-associated myopathy, CoQ10 levels in skeletal muscle should also be reduced, but data from animal models are inconsistent. Whereas simvastatin or pravastatin decreased skeletal muscle ubiquinone up to 72% (p < 0.005) when administered to rabbits, other studies using rabbits do not support these results (34). High-dose statin treatment (50 mg/kg of simvastatin or pravastatin per day for 14 days) did not reduce skeletal muscle concentrations of ubiquinone in animals treated with either drug. Severe lesions in skeletal muscles developed in the simvastatin-treated rabbits, despite the absence of decreases in muscle ubiquinone levels (32). A recent animal study treated rats with various doses of cerivastatin for 15 days and demonstrated no significant
difference, in most cases, between skeletal muscle mean ubiquinone levels in statin-treated animals and nontreated difference, in most cases, between skeletal muscle mean ubiquinone levels in statin-treated animals and nontreated control animals (35). In humans, low-dose statin treatment does not appear to reduce intramuscular CoQ10 concentrations (Table 2). In the first human study to address this issue, skeletal muscle CoQ10 concentrations were actually 47% higher (p < 0.001) after 4 weeks of treatment with 20 mg of lovastatin daily. Longer treatment, also with simvastatin 20 mg daily, yielded similar results (18). Coenzyme Q10 levels in muscle obtained from hypercholesterolemic men at baseline and after 6 months of statin therapy showed virtually identical CoQ10 concentrations. These values were similar to those measured in 15 normolipidemic untreated subjects before and after 6 months of observation (88 vs. 95 μmol/kg, respectively).

### Table 1: Studies of Blood/Plasma/Serum CoQ10 Levels After Treatment With Statins

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Duration</th>
<th>Participants</th>
<th>%Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Folks et al. (12)</td>
<td>Lovastatin, 20–40 mg/day</td>
<td>7–18 months</td>
<td>5 cardiomyopathic patients, age 43–72 yrs</td>
<td>(−61.1–74.6)*</td>
</tr>
<tr>
<td></td>
<td>Lovastatin, 40 mg/day</td>
<td>29 days</td>
<td>1 hypercholesterolemic male volunteer, age 43 yrs</td>
<td>(−18.8)</td>
</tr>
<tr>
<td>Elmberger et al. (23) (RCT)</td>
<td>Pravastatin, 20–40 mg/day</td>
<td>12 weeks</td>
<td>12 patients with heterozygous FH, age 19–65 yrs</td>
<td>(−29†)</td>
</tr>
<tr>
<td>Watts et al. (15)</td>
<td>Simvastatin, 10–80 mg/day</td>
<td>15 ± 8 months</td>
<td>20 hyperlipidemic patients, age 55 ± 8.9 yrs</td>
<td>(−23.8±‡)</td>
</tr>
<tr>
<td>Ghirlanda et al. (7) (RCT)</td>
<td>Pravastatin, 20 mg/day</td>
<td>3 months</td>
<td>10 hypercholesterolemic patients, age 47 ± 8 yrs</td>
<td>(−50§)</td>
</tr>
<tr>
<td></td>
<td>Simvastatin, 20 mg/day</td>
<td>3 months</td>
<td>10 hypercholesterolemic patients, age 49 ± 10 yrs</td>
<td>(−54¶)</td>
</tr>
<tr>
<td>Bargossi et al. (24) (RCT)</td>
<td>Simvastatin, 20 mg/day</td>
<td>3 months</td>
<td>34 patients with primary hypercholesterolemia, age not reported</td>
<td>(−22.3†)</td>
</tr>
<tr>
<td>Laaksonen et al. (17)</td>
<td>Lovastatin, 20–40 mg/day</td>
<td>12 weeks</td>
<td>17 men with primary hypercholesterolemia, age 38–65 yrs, 4 weeks after stopping simvastatin (20–40 mg/day) therapy administered for 4.7 yrs</td>
<td>(−25§)</td>
</tr>
<tr>
<td>Laaksonen et al. (16)</td>
<td>Simvastatin, 20 mg/day</td>
<td>4 weeks</td>
<td>22 hypercholesterolemic men, age 25–55 yrs</td>
<td>(−32§)</td>
</tr>
<tr>
<td>Laaksonen et al. (18)</td>
<td>Simvastatin, 20 mg/day</td>
<td>6 months</td>
<td>19 hypercholesterolemic men, age 25–55 yrs</td>
<td>(−27.3)</td>
</tr>
<tr>
<td>De Pinieux et al. (21)</td>
<td>Simvastatin/pravastatin/fluvastatin, doses not reported</td>
<td>NR</td>
<td>40 hypercholesterolemic patients, age 21–76 yrs</td>
<td>(−21†‡)</td>
</tr>
<tr>
<td>Davidson et al. (25) (RCT)</td>
<td>Atorvastatin, 10–20 mg/day</td>
<td>1 yr</td>
<td>1,049 patients with primary hypercholesterolemia, age 18–80 yrs</td>
<td>(−38†)</td>
</tr>
<tr>
<td></td>
<td>Lovastatin, 20–40 mg/day</td>
<td>18 weeks</td>
<td>45 hypercholesterolemic patients, age 30–75 yrs</td>
<td>(−28.8§)</td>
</tr>
<tr>
<td>Mortensen et al. (26) (RCT)</td>
<td>Lovastatin, 20–80 mg/day</td>
<td>14 weeks</td>
<td>25 FH patients, age 35.9 ± 11.8 yrs</td>
<td>(−25.6¶)</td>
</tr>
<tr>
<td></td>
<td>Pravastatin, 10–40 mg/day</td>
<td>8 months</td>
<td>21 non-FH patients, age 52.5 ± 8.9 yrs</td>
<td>(−26)</td>
</tr>
<tr>
<td>Human et al. (22)</td>
<td>Simvastatin, 10–20 mg/day</td>
<td>NR</td>
<td>97 diabetic patients, age 58.1 ± 10 yrs</td>
<td>NS¶</td>
</tr>
<tr>
<td>Miyake et al. (13)</td>
<td>Pravastatin, 10–20 mg/day</td>
<td>Simvastatin, 5 mg/day</td>
<td>97 diabetic patients, age 58.1 ± 10 yrs</td>
<td>NS¶</td>
</tr>
<tr>
<td>De Lorgeril et al. (27) (RCT)</td>
<td>Simvastatin, 20 mg/day</td>
<td>12 weeks</td>
<td>32 patients with primary hypercholesterolemia and previous Q-wave MI, mean age 54.1 yrs</td>
<td>(−19.4§#)</td>
</tr>
<tr>
<td>Bleske et al. (14) (RCT)</td>
<td>Pravastatin, 20 mg/day</td>
<td>4 weeks</td>
<td>12 healthy volunteers, age 26 ± 5 yrs</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Atorvastatin, 10 mg/day</td>
<td>4 weeks</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Jula et al. (28) (RCT)</td>
<td>Simvastatin, 20 mg/day</td>
<td>12 weeks</td>
<td>120 hypercholesterolemic men, age 35–64 yrs</td>
<td>(−22.0§**</td>
</tr>
<tr>
<td>Runde et al. (19)</td>
<td>Atorvastatin, 80 mg/day</td>
<td>30 days</td>
<td>34 hypercholesterolemic patients, age 70 ± 7 yrs</td>
<td>(−52§)</td>
</tr>
<tr>
<td>Berthold et al. (20) (RCT)</td>
<td>Simvastatin, 40 mg/day</td>
<td>2 weeks</td>
<td>24 healthy men, age 31.9 ± 8.8 yrs</td>
<td>(−16§)</td>
</tr>
</tbody>
</table>

*Patients received CoQ10 supplementation before and during treatment with lovastatin; †p < 0.05; ‡compared to untreated group; §p < 0.01; ¶p < 0.001; §mean serum CoQ10 found to be similar in normocholesterolemic non–insulin-dependent diabetic patients with or without statin therapy; †compared to fenofibrate-treated group; **compared to placebo group. Note: age of participants is expressed as either range or mean ± SD.

CoQ10 = coenzyme Q10; FH = familial hypercholesterolemia; MI = myocardial infarction; NR = not reported; NS = not significant; RCT = randomized controlled trial.

### Table 2: Studies of Skeletal Muscle CoQ10 Levels After Treatment With Statins

<table>
<thead>
<tr>
<th>Study</th>
<th>Statin Dosage</th>
<th>Duration</th>
<th>Participants</th>
<th>[CoQ10]Pre</th>
<th>[CoQ10]Post</th>
<th>Change (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paiva et al. (5) (RCT)</td>
<td>Simvastatin, 80 mg/day</td>
<td>8 weeks</td>
<td>48 patients with hypercholesterolemia</td>
<td>39.7 ± 13.6 nmol/g</td>
<td>No reduction</td>
<td>(−33.3%)#</td>
</tr>
<tr>
<td></td>
<td>Atorvastatin, 40 mg/day</td>
<td></td>
<td></td>
<td></td>
<td>No reduction</td>
<td>NS</td>
</tr>
<tr>
<td>Laaksonen et al. (16)</td>
<td>Simvastatin, 20 mg/day</td>
<td>4 weeks</td>
<td>20 patients, age 25–55 yrs</td>
<td>0.060 mg/g (0.052–0.068)</td>
<td>95% CI</td>
<td>(−30%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.088 mg/g (0.083–0.093)</td>
<td>95% CI</td>
<td>(−57.1)†</td>
</tr>
<tr>
<td>Laaksonen et al. (18)</td>
<td>Simvastatin, 20 mg/day</td>
<td>6 months</td>
<td>19 patients, age 25–55 yrs</td>
<td>78 μmol/kg (70–85)</td>
<td>95% CI</td>
<td>85 μmol/kg (75–94)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>95% CI</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Lamperti et al. (37)</td>
<td>Variable</td>
<td>NR</td>
<td>18 patients with statin myopathy, age 31–76 yrs</td>
<td>29.5 μg/g (median in control group)</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

*p < 0.05; †p < 0.001.
CI = confidence interval; other abbreviations as in Table 1.
The effect of statins on muscle CoQ10 may be drug and dose dependent. In a recent trial using simvastatin 80 mg/day, atorvastatin 40 mg/day, or placebo for 8 weeks (5), mean muscle concentrations of CoQ10 in the simvastatin-treated patients decreased by 34%. To date, this is the only trial comparing intramuscular CoQ10 levels among the statins.

There are few published studies on intramuscular CoQ10 levels in subjects symptomatic from statin myopathy. Almost half (47% or 17 of 36 patients) of patients referred for myopathic complaints presumably due to statin-associated myopathy had intramuscular CoQ10 levels >2 standard deviations below the mean (G. Vladitu, personal communication, August 26, 2005). It is not clear, however, whether these decreased intramuscular CoQ10 levels produced statin myopathy or were simply associated with a reduction in mitochondrial volume associated with the statin myopathy itself (5) or associated with physical inactivity due to myopathic symptoms. A recent study (36) examined intramuscular CoQ10 levels in patients with statin-associated myopathy and found levels 2 standard deviations below the normal mean in 3 patients, below 1 standard deviation in 7 patients, normal levels in 4 patients, and increased levels in 4. No evidence of myocyte apoptosis was found, using terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate nick-end labeling assay and immunohistochemical studies with antibodies against Bax, Bcl-2, and caspase-3, although only 11 biopsies had enough tissue to perform the test.

**Effect of Statins on Mitochondrial Function**

If reduced CoQ10 levels mediate statin myopathy, not only should there be evidence of reduced intramuscular CoQ10 levels, but there should also be evidence of impaired mitochondrial function. One animal study (37) showed decreased phosphorylation potential of adenosine diphosphate in the cardiac mitochondria of guinea pigs treated with lovastatin 20 mg/kg twice daily. This correlated with a 37% and 31% decrease in CoQ10 concentration in cardiac mitochondria and myocardium, respectively. Curiously, these changes were observed in the older animals (2 years old), but not younger ones (2 to 4 months old), suggesting a possible age effect. Similarly, myocardium of dogs treated with simvastatin 2 mg/kg/day for 3 weeks contained lower concentrations of CoQ10 and decreased mitochondrial respiration during ischemia induced by left anterior descending coronary artery ligation, compared with untreated control patients or a pravastatin-treated group (38). In rats, pravastatin reduced mitochondrial complex I activity in the diaphragm and psoas major muscles in 35- to 55-week-old animals and decreased complex IV activity in 55-week-old animals (39). Various doses of cerivastatin (0.1, 0.5, or 1.0 mg/kg/day for 15 days) administered to rats did not produce morphologic abnormalities in skeletal muscle after 10 days of statin treatment (35). At 15 days, inflammation and necrosis with structurally altered mitochondria involving type II myofibers was observed in the mid/high dose groups. However, mitochondria in the unaffected adjacent muscle appeared normal, prompting the authors to conclude that mitochondrial damage did not precede myofiber degeneration. No significant changes in mitochondrial function were observed, and mitochondrial function did not correlate with changes in ubiquinone concentration. This study supports an earlier trial in rats (40) in which simvastatin treatment did not result in a significant change in ATP production in muscle, heart, liver, or brain, despite lower blood ATP levels.

Few studies have directly or indirectly addressed this issue in humans. de Pinieux et al. (21) examined the ratio of serum lactate to pyruvate as an indirect measure of mitochondrial function. Statin-treated hypercholesterolemic patients had 16% higher fasting, nonexercise, lactate:pyruvate ratios than untreated hypercholesterolemic patients (p < 0.05). In contrast mean lactate:pyruvate ratios with fibrates were not significantly higher than those of the untreated hyperlipidemic patients. Curiously, regardless of statin, fibrate, or no treatment, mean lactate:pyruvate ratios were higher in the hypercholesterolemic patients than in the normocholesterolemic control patients.

Others have also suggested that mitochondrial function may be impared by statin therapy. Muscle biopsies from 4 patients with statin-associated myopathy, despite normal creatine kinase (CK) levels, demonstrated findings consistent with mitochondrial dysfunction, including increased intramuscular lipid, diminished cytochrome oxidase staining, and ragged red fibers (3). Three of these patients had repeat biopsies performed after discontinuation of statin, which showed resolution of the pathologic abnormalities. These same investigators used respiratory exchange ratios (RER = VCO2/V O2) during exercise as a measure of exercise aerobic metabolism and an indirect measure of mitochondrial function (41). Sixteen healthy subjects received atorvastatin 5 to 10 mg for 6 weeks. Exercise results in these subjects were compared with those from 9 men and 2 women who developed muscle complaints plus CK elevations during statin alone (n = 6), statin and fibrate (n = 3), or statin and niacin (n = 2) therapy. There was no effect of statin therapy on maximal oxygen uptake (VO2 max), a measure of aerobic fitness, in the normal patients, but VO2 max was significantly lower in the myopathic patients, a finding the authors attributed to these patients’ physical inactivity due to their myopathy. Interestingly, the resting RER increased with statin therapy in the normal subjects (0.75 ± 0.02 to 0.86 ± 0.06), and was also elevated in the myopathic patients off statin therapy (0.90 ± 0.07). Respiratory exchange ratio decreases with fat oxidation and increases as carbohydrate is used as fuel, but is a crude measure of these processes. The authors interpreted their findings as demonstrating that statins impair fat metabolism in healthy patients and that victims of statin myopathy have a pretreatment abnormality in fat metabolism that is exac-
erbated by statin therapy leading to the muscle complaints. There was no apparent change in the onset of lactate accumulation or "anaerobic threshold" during the exercise test, however, which argues against an alteration in exercise fat metabolism with statin treatment. One additional study of 195 noninsulin diabetic patients noted a 6% increase in resting RER (0.78 to 0.83), which the authors attributed to improved glucose metabolism with statin treatment, but exercise parameters were not measured in that study (42). Consequently, these exercise results raise the possibility of mitochondrial dysfunction during exercise, a problem that could relate to CoQ10 depletion.

In contrast to these studies suggesting a mitochondrial problem in statin myopathy (13,21–23,41–48), muscle biopsies from 18 patients with statin-associated myopathy found only 2 patients with decreased intramuscular levels of CoQ10 and some morphologic evidence of mitochondrial dysfunction (36). Muscle biopsies from these patients revealed the presence of a few ragged red fibers or cytochrome c oxidase-negative fibers. It is not clear whether these changes were produced by the depletion of CoQ10 or were related to aging, given that both patients were older than 60 years old. In addition, the activity of complex III of the mitochondrial respiratory chain, which is dependent on CoQ10 activity, was normal in all participants.

Others have directly measured concentrations of high energy phosphates, including adenosine triphosphate and creatine phosphate, in the skeletal muscle of statin-treated patients and found no changes despite 6 months of treatment with 20 mg/day of simvastatin, suggesting that energy supply to the muscle was not compromised (18). These studies were performed at rest, however, and more subtle differences may be obvious with exercise or during exercise recovery.

**CoQ10 Supplementation**

A number of studies (12,13,24,30) have demonstrated that CoQ10 administration can increase CoQ10 blood levels in patients treated with statins. Coenzyme Q10 supplementation may also reduce the symptoms of statin-induced myopathy in patients treated with massive statin doses (43,44). Lovastatin was investigated as a potential cancer treatment in doses up to 45 mg/kg body weight. Among 56 cancer patients treated with monthly 7-day courses of high-dose (2 mg/kg/day to 45 mg/kg/day) lovastatin, over the course of 2 and a half years, CoQ10 supplementation (240 mg/day) did not reduce the frequency of lovastatin-induced myopathy compared with that in unsupplemented patients, but did decrease the severity of myopathic symptoms, judged by a grading scale that included duration of myalgia and degree of CK elevations. Interestingly, patients receiving lovastatin at doses <25 mg/kg/day did not develop musculoskeletal toxicity, and at higher doses there was no correlation between the incidence of myotoxicity and the dose of lovastatin (p = 0.24) (43). Another trial (44) treated 16 patients with advanced gastric adenocarcinoma with lovastatin 35 mg/kg/day for 7 consecutive days. All subjects received 240 mg of CoQ10 daily. Only 2 patients developed increased CK levels, myalgia, and muscle weakness. The authors reported that symptoms were successfully managed with CoQ10 and symptomatic treatment. The dose of CoQ10 required for this treatment was not specified nor was a control group without supplementation included.

There are only 2 randomized trials, both in abstract form, that were designed to evaluate CoQ10 as a treatment for statin-associated myopathy (45,46). The first treated 41 patients with statin-associated myalgia with either 400 IU of vitamin E or 100 mg of CoQ10 daily for 30 days. Preliminary results suggest a significant improvement in pain scores in patients treated with CoQ10, with 18 of 21 reporting improvement in symptom severity and a reduction in mean pain scores (6.2 ± 1.7 to 3.1 ± 2.2 at baseline using a 10-point scale (p < 0.001). By comparison, only 3 of 20 patients on vitamin E reported improvement in their symptoms, and there was no change in this group’s mean pain score (3.9 ± 2.2 vs. 3.1 ± 2.2, p = NS). These results require confirmation.

A more recent trial (46) randomized 44 dyslipidemic patients with prior statin-induced myalgia to 12 weeks of treatment with escalating doses of simvastatin (10 mg/day to 40 mg/day) and CoQ10 200 mg/day or placebo. Plasma CoQ10 levels increased with CoQ10 supplementation, but there were no differences in myalgia scores (p = 0.63) or in statin tolerance between the 2 treatment groups. Specifically, similar numbers of patients in both groups were able to tolerate simvastatin 40 mg (p = 0.34) and 10 mg (p = 0.35) daily.

**Conclusions and Clinical Implications**

Statins are the most effective medications for reducing LDL cholesterol concentrations. They have been proven to decrease the incidence of adverse cardiac events in diverse patient populations. The primary adverse effect limiting their use is myopathy, ranging from benign myalgias to rare cases of fatal rhabdomyolysis. Statins’ interference with the production of CoQ10 prompted the hypothesis that CoQ10 deficiency may play a role in statin-associated myopathy. Although statins reduce circulating levels of CoQ10, this effect is nullified by normalizing CoQ10 concentrations for the reduction in LDL cholesterol or total cholesterol. Low-dose statin treatment does not appear to reduce intramuscular levels of CoQ10 in humans. Few data are available regarding intramuscular CoQ10 levels in symptomatic patients with statin-associated myopathy. Mitochondrial function may be impaired by statin therapy, and this effect may be exacerbated by exercise, but confirmatory data are needed. Animal models of statin myopathy demonstrate similar results in that decreases in skeletal muscle ubiquinone levels and mitochondrial function are not consistent and skeletal muscle injury can occur without de-
creases in muscle CoQ10 concentrations. Supplementation can raise the circulating levels of CoQ10, but whether or not this relieves myopathic symptoms is not clear. The 2 available double-blind studies report contrasting results and are only available in abstract form. Presently, insufficient evidence exists to implicate CoQ10 deficiency as the cause of statin-associated myopathy. Our evaluation of this data is that intramuscular CoQ10 depletion does not cause statin myopathy and that CoQ10 supplementation does not mitigate the symptoms of statin myopathy. Nevertheless, there are no known risks to this supplement. Also, reports from cancer trials using high-dose statins (44,45), results from 1 are no known risks to this supplement. Also, reports from myopathy and that CoQ10 supplementation does not mit-

tates or reduces statin myalgia in symptomatic patients. For example, there are at least 2 reported cases of mitochondrial encephalopathy lactic acidosis and stroke-like episodes temporally related to statin therapy that appeared to benefit from CoQ10 therapy (47,48). Consequently, although there is no definite evidence of its effectiveness, CoQ10 supplementation, 200 mg daily, can be trialed in patients requiring statin treatment, who develop statin myalgia, and who cannot be satisfactorily treated with other agents. Some patients may respond if only via a placebo effect.

Future Directions

Statin therapy is frequently limited by myopathic symptoms creating a critical need for strategies to prevent statin myopathy. Coenzyme Q10 supplementation is a simple, attractive therapy that requires an appropriately powered and randomized trial to determine whether CoQ10 eliminates or reduces statin myalgia in symptomatic patients. Simultaneous genetic studies should attempt to determine if genetic variants contribute to the variability in the response to CoQ10 therapy. Studies designed to determine if CoQ10 prevents the onset of myalgia in statin-naive patients are not practical because of the number of subjects that would be required in such a trial. In addition, the absence of pharmacologic grade CoQ10 supplement and a study sponsor makes such a trial difficult. Nevertheless, such trials are the only way to demonstrate conclusively whether or not clinicians should prescribe CoQ10 to their patients on statin therapy.

Reprint requests and correspondence: Dr. Paul D. Thompson, Cardiology, Hartford Hospital, 80 Seymour Street, Hartford, Connecticut 06102. E-mail: pthomps@harthosp.org.

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