## Coenzyme Q10

Nutrient Name: Coenzyme Q10.
Synonyms: Coenzyme Q, coQ10, ubidecarenone; co-enzyme Q10, coQ10-alpha-cyclodextrin, coenzyme Q (50), coQ, coQ(50), co-Q10, coQ-10, 2,3 dimethoxy-5 methyl-6-decaprenyl benzoquinone, mitoquinone, Q10, ubiquinone, ubiquinone-10, ubiquinone-Q10, vitamin q10, vitamin Q10.
Related Substance: Ubiquinol (QH).
Synthetic Analog: Idebenone (water soluble).
Trade Names: Andelir, Cavamax W8/CoQ10, Heartcin, Neuquinone, Taidecanone, UBTH, Udekinon.

### Summary

| Drug/Class Interaction Type | Mechanism and Significance | Management |
|---|---|---|
| Beta-1-Adrenoceptor Antagonists<br>Antihypertensive medications<br>☼/⊕ | Beta blockers and related agents inhibit, to varying degrees, coQ10-related mitochondrial enzymes in cardiac tissue. Resulting drug-induced depletion pattern can adversely affect cardiac patients who are, in general, characterized by compromised coQ10 status. CoQ10 does not appear to interfere with therapeutic action of these medications. | Coadminister oral coQ10. Monitor closely. |
| Chlorpromazine<br>Thioridazine<br>Phenothiazines<br>◈≈≈/☼ | Phenothiazines appear to inhibit NADH-oxidase and succinoxidase, coQ10-related enzymes, and thereby contribute to pattern of adverse myocardial depressant effects associated with these agents. CoQ10 appears to mitigate adverse effects without diminishing therapeutic action of these medications. | Coadminister oral coQ10. Monitor closely. |
| Doxorubicin<br>Anthracycline chemotherapy<br>◈≈≈/☼ | Oxidative stress caused by anthracyclines often results in cardiotoxicity and other adverse effects from competitive inhibition of coQ10. CoQ10 supplementation can reduce free-radical damage and prevent anthracycline-induced cardiotoxicity. Clinical evidence is lacking to suggest coQ10 might interfere with therapeutic effect of anthracycline chemotherapy agents. | Coadminister oral coQ10. Monitor closely within context of integrative oncology care. |
| HMG-CoA reductase inhibitors (statins)<br>◈≈≈/≈≈/☼/⊕⊕ | HMG-CoA reductase inhibitors lower coQ10 levels, to varying degrees, by directly interfering with coQ10 synthesis. Resulting depletion of coQ10 over time can potentially induce adverse effects on cardiac function, especially in individuals with susceptibility to or presence of chronic heart failure, but may be prevented with coQ10 coadministration, without diminishing therapeutic action of the statin. Research findings on clinical significance of statin-induced coQ10 depletion and potential benefits of coQ10 coadministration are mixed. | Consider coadministration of oral coQ10. Monitor closely within context of integrative cardiovascular care. |
| Sulfonylureas<br>Oral hypoglycemic agents<br>☼/◈≈≈/≈≈ | Hypoglycemic drugs may inhibit, to varying degrees, the coQ10 enzyme NADH-oxidase and thereby cause adverse effects on bioenergetics, ATP generation, and insulin biosynthesis. Diabetic individuals are more likely to be predisposed to compromised coQ10 status and elevated oxidative stress. CoQ10 support can mitigate drug-induced adverse effects and may enhance insulin function and cardiovascular health. | Coadminister oral coQ10. Closely monitor glucose levels. |
| Tricyclic antidepressants (TCAs)<br>◈≈≈/≈≈≈ | TCAs can interfere with NADH-oxidase and succinoxidase, coenzyme Q10 enzymes, and may induce coQ10 deficiency. These actions may contribute to well-known association with cardiac adverse effects. Concomitant coQ10 administration appears to mitigate adverse effects without diminishing antidepressant activity. | Coadminister oral coQ10. Monitor closely. |
| Warfarin<br>Oral vitamin K antagonist anticoagulants<br>?/✗/✗✗ | Available clinical trial evidence does not support concerns that coQ10 might interfere with warfarin function based on structural similarities to vitamin K and several anecdotal reports. Administration of coQ10 may be therapeutically appropriate for many individuals receiving coumarin therapy. Nevertheless, gradual changes in dosage levels of any medication or nutrient is critical to maintain INR within therapeutic range. | Coadminister oral coQ10 if indicated. Monitor INR closely within context of integrative cardiovascular care. |

*HMG-CoA*, 3-Hydroxy-3-methylglutaryl coenzyme A; *NADH*, reduced form of nicotinamide adenine dinucleotide; *ATP*, adenosine triphosphate; *INR*, international normalized ratio.

### NUTRIENT DESCRIPTION

*Chemistry and Form*

Coenzyme Q10 (coQ10) belongs to a family of compounds known as *ubiquinones*, all of which are characterized by a functional group known as a *benzoquinone*. Ubiquinones are fat-soluble molecules with between 1 and 12 isoprene (5-carbon) units. Among the 10 naturally occurring coenzyme Q compounds, the ubiquinone found in humans is known as coenzyme Q10 because of the distinctive "tail" of 10 isoprene units (containing 50 carbons in toto) attached to its benzoquinone "head."

### *Physiology and Function*

In humans, coQ10 is synthesized in most tissues throughout the body. Three major steps are involved in the endogenous synthesis of coQ10: (1) synthesis of the benzoquinone structure from tyrosine or phenylalanine, (2) synthesis of the isoprene side chain from acetyl coenzyme A (CoA) via the mevalonate pathway, and (3) the condensation or merging of these two structures. 3-Hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase is the critical enzyme regulating coQ10 synthesis as well as cholesterol synthesis.

Coenzyme Q is highly soluble in lipids and is found in virtually all cell membranes, as well as lipoproteins. The primary biochemical action of coQ10 is as a coenzyme for numerous enzymes in the electron transport chain, a series of oxidation-reduction (redox) reactions involved in cellular respiration, where the presence of coQ in the inner mitochondrial membrane is required for the conversion of energy from carbohydrates and fats in the synthesis of adenosine triphosphate (ATP). Within the mitochondrial electron transport chain, coQ accepts electrons from reducing equivalents generated during fatty acid and glucose metabolism and transfers them to electron acceptors. Simultaneously, a proton gradient across that membrane results when coQ transfers protons outside the inner mitochondrial membrane. When the protons subsequently flow back into the mitochondrial interior, energy is released to form ATP.

Coenzyme Q10 has dual potential to enhance energy production by bypassing defective elements of the respiratory energy production chain and through its function as an antioxidant. Coenzyme Q can exist in three oxidation states: (1) the fully reduced ubiquinol form ($CoQH_2$), (2) the radical semiquinone intermediate (CoQH), and (3) the fully oxidized ubiquinone form (CoQ). Thus, in its central role as a pro-oxidant within mitochondria, coQ10 enables aerobic energy gain, promotes unilateral proton accumulation, and generates reactive oxygen species (ROS) involved in physiological signaling. Ubiquinone can execute reversible addition of single electrons and protons. Lysosomal membranes critical to cellular detoxification and recycling contain particularly high concentrations of coQ. Recent research indicates that lysosomal ubiquinone maintains the optimal pH for cellular recycling through its double function as proton translocator and radical source, particularly under certain metabolic conditions such as an acid pH. Alternately, a range of research demonstrates a pervasive and potent role of coenzyme Q10 in protecting membranes and DNA from oxidative damage from free radicals directly and through suppression of the formation of oxidized lipids and the consumption of alpha-tocopherol. As a lipophilic molecule, the reduced form of coQ, $coQH_2$, along with enzymes that are capable of reducing oxidized coQ back to $coQH_2$, is particularly concentrated in mitochondrial cell membranes, where it acts as a key cellular antioxidant and provides protection against free-radical damage. However, the type of biomembrane where ubiquinone exerts its free-radical, chain reaction–breaking activity can significantly affect this action's efficiency. Furthermore, $coQH_2$ regenerates alpha-tocopherol radicals back to the chain-breaking (i.e., antioxidant) form of vitamin E and thereby further contributes to the control of lipid peroxidation. This ability to counteract oxidative stress is particularly evident in its support of healthy cardiac tissue and its protection of endothelial function. Thus, coQ10's unique chemistry enables it to function both as a pro-oxidant and as an antioxidant.

## NUTRIENT IN CLINICAL PRACTICE

### *Known or Potential Therapeutic Uses*

Coenzyme Q10 can be synthesized in vivo by all living organisms, including humans, and thus is not defined as a vitamin. However, in some situations, the need for coQ10 may surpass the body's ability to synthesize it, so it may be regarded as "conditionally essential." CoQ10 is well absorbed by oral administration, as evidenced by significant increases in serum, plasma, and lipoprotein concentrations of coQ10 after oral intake.[1,2] However, evidence from animal and human research is mixed as to the degree to which oral intake elevates levels in various target tissues, and how that effect might vary depending on state of health, influence of aging, and presence of dysfunction, depletion, or pathology in particular tissues and systems.[3-7]

In 1958, Professor Karl Folkers elucidated the chemical structure of coQ10 and noted its potential in the treatment of cardiovascular disease. However, his employer, Merck, chose to sell the formula and patent to a Japanese firm in favor of promoting Diuril, a new product at the time aimed at the cardiovascular drug market. Thus, although coQ10 developed a strong presence in medical and supplement markets in Japan, its entry into clinical use in the United States has been delayed but is steady growing.

### *Possible Uses*

Alzheimer's disease, angina, arrhythmia, breast cancer, cardiac bypass surgery, cardiomyopathy, cardiovascular disease, cerebellar ataxia (familial), chemotherapy support, chronic fatigue, chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF), diabetes mellitus, diastolic dysfunction, fibromyalgia, gingivitis, human immunodeficiency virus (HIV) support, Huntington's disease, hypertension, immune deficiencies, insulin resistance syndrome, ischemia, lung cancer, male infertility, mitochondrial diseases, mitral valve prolapse, muscular dystrophies, myocardial infarction, neurodegenerative diseases, Parkinson's disease, periodontal disease, prostate cancer, renal failure, rhabdomyolysis.

Oral administration may also enhance aerobic capacity and muscle performance, especially in sedentary and elderly individuals. Conclusive evidence from large clinical trials has yet to be carried out to investigate this proposed action.

### *Deficiency Symptoms*

The deficiency pattern associated with coQ10 has not been clearly defined, and it is widely assumed that endogenous production and a varied diet provide adequate coQ10 for most individuals. A deficiency may result from impaired synthesis caused by nutritional deficiencies, acquired defect in synthesis or utilization, or increased tissue needs resulting from illness. Most coQ10 in humans is internally synthesized. Genetic defects in coQ10 synthesis and metabolism are considered rare at this time. Deficiency can be caused or aggravated by depletion or deficiency of any of the many nutrients required within this 17-stage synthetic pathway, including riboflavin (vitamin $B_2$), niacinamide (vitamin $B_3$), pantothenic acid (vitamin $B_5$), pyridoxine (vitamin $B_6$), cobalamin (vitamin $B_{12}$), folic acid, vitamin C, and several trace elements. As might be expected, given the central role of the HMG-CoA reductase enzyme in the coQ10 synthetic pathway, HMG-CoA reductase inhibitors ("statins"), which are widely prescribed for management of dyslipidemias and cardiovascular disease,

have been implicated as an iatrogenic cause of coQ10 deficiencies.

CoQ10 concentrations in various tissues decline with advancing age, and elderly individuals are known generally to have lower levels of coQ10.[8,9] Likewise, researchers have observed that the patient populations exhibiting many of the conditions coQ10 is used to treat more often demonstrate low levels of coQ10; these include cardiomyopathy, gingivitis and periodontal disease, heart failure, and HIV/AIDS. Many researchers and clinicians consider at least a CHF subset to represent a coQ10 deficiency disease, to a significant degree. Decreased plasma levels of coQ10 have also been observed in individuals with diabetes and cancer. Lastly, individuals with the genetic polymorphisms called the LPL and NQO1 genotypes exhibit decreased coQ10 redox ratios, reflective of impaired ability to convert ubiquinone to ubiquinol.[10]

### *Dietary Sources*

Coenzyme Q10 is widely distributed in foods but in such small amounts that extraordinary serving sizes would be required to obtain intake levels typically provided by commercial preparations (e.g., 100 mg daily).

Organ meats (e.g., heart, liver), meat, poultry, and fish are the richest dietary sources of coenzyme Q10. Nuts provide relatively high levels, as do soybean and canola oils. Vegetables, fruits, eggs, and dairy products contain moderate levels of coQ10, with broccoli and spinach being relatively richer.

Studies in Denmark conducted during the 1990s found that average dietary intake of coQ10 was 3 to 5 mg per day.[11,12] Overall, dietary sources appear to provide most individuals with less than 10 mg/day. Foods are estimated to provide an average of 25% of plasma coQ10 in most individuals. Boiling appears to have little adverse effect, but frying destroys 14% to 32% of coQ10 in foods thus prepared. The precise dietary contribution to plasma coQ10 concentration is unknown in any given individual but is estimated to be approximately 25%.

### *Nutrient Preparations Available*

Microcrystalline cellulose-coQ10 complex.

Complexing coenzyme Q10 with alpha-cyclodextrin may enhance bioavailability of coQ10 by approximately 35% compared to a microcrystalline cellulose-coQ10 complex.[13]

Ubiquinol (QH) is the converted active form of coQ10. The conversion rate of coQ10 (ubiquinone) to ubiquinol tends to decline with age, rendering lowered serum levels of ubiquinol. Furthermore, LPL and NQO1 genotypes are associated with impaired ability to conduct this conversion.[10] However, outside the body, ubiquinol is extremely unstable without certain stabilizing procedures because it will convert to coQ10 on exposure to oxygen.[14] Since ubiquinone must be reduced to become active, oral ubiquinol may provide bioavailability up to eight times as great as that of oral ubiquinone.

### *Dosage Forms Available*

Powder-filled hard-shell capsule, soft-gel capsule, liposomal spray, tablet, chewable wafer.

Oral coenzyme Q10 should be taken with a meal with some fat content since it is fat-soluble. Absorption decreases in the absence of lipid. Some experts suggest taking coQ10 with a small amount of olive oil to increase absorption. There is some evidence that coQ10 in oil suspension provides better bioavailability than granular form.[15-17] Chewable forms may also provide greater bioavailability than capsules or tablets.

### *Source Materials for Nutrient Preparations*

Yeast fermentation, or semisynthetic process.

Kaneka Corporation of Japan, which is the only company to use yeast fermentation in the production of coQ10, produces the natural all-*trans* Q, which is identical to the coQ10 occurring in nature and has succeeded in obtaining "generally recognized as safe" (GRAS) status from the U.S. Food and Drug Administration (FDA).[18]

### *Dosage Range*

#### Adult

Dietary: No level has been established for optimal dietary intake of coenzyme Q10.
Supplemental/Maintenance: 25 to 60 mg twice daily.
Pharmacological/Therapeutic: Ranging from 30 to 60 mg twice daily to 50 to 100 mg two to three times daily, depending on condition and in concert with a health care professional trained in nutritional therapies. Daily dosage levels of 300 to 600 mg have been used in clinical and research settings in the treatment of conditions such as severe cardiovascular disease and advanced breast cancer. Administration of 60 to 100 mg per day will usually double plasma levels of coQ10 in adults. Evidence indicates that oral intake does not impair endogenous coQ10 synthesis.
Toxic: None established.

#### Pediatric (< 18 Years)

Coenzyme Q10 is usually not prescribed for infants or children.

### *Laboratory Values*

Plasma and lymphocyte coenzyme Q10 and coenzyme $Q10H_2$ levels.

## SAFETY PROFILE

### *Overview*

All available evidence indicates that coenzyme Q10 is generally safe. No significant adverse effects or toxicities have been reported as being associated with oral intake of coQ10. CoQ10 in doses up to 900 mg daily is safe and well tolerated in healthy adults for 4 weeks.[19] Even continued doses of 600 mg/day for 30 months and 1200 mg/day for up to 16 months have not been associated with significant adverse effects.[20,21]

### *Nutrient Adverse Effects*

#### General Adverse Effects

Occasional reports of mild nausea, gastrointestinal (GI) discomfort, anorexia, or skin eruptions have been reported with oral intake of coQ10. Other reported adverse effects include fatigue, insomnia, headache, dizziness, irritability, photosensitivity, dyspepsia, vomiting, diarrhea, dermatitis, or flulike symptoms. Reported adverse effects typically receded when oral coQ10 was stopped or dosage levels or format were modified. Dividing daily intake into two or three dosages may eliminate adverse effects, especially if more than 100 mg/day is being used.

### Pregnancy and Nursing

Adverse effects are not predicted, and reports are lacking. However, the lack of controlled studies involving pregnant or lactating women precludes claims of safety and suggests that oral intake should be avoided during such life cycles.

### Infants and Children

Adverse effects are not predicted, and reports are lacking. CoQ10 administration is not recommended unless otherwise indicated as essential.

### *Contraindications*

No contraindications have been established for coQ10.

### *Precautions and Warnings*

No precautions or warnings are known at this time for healthy individuals. Individuals with CHF or other serious cardiovascular conditions should only discontinue coQ10 under the supervision of the prescribing health care professional; withdrawal of coQ10 intake could potentially contribute to relapse.

Cautions have been voiced regarding coQ10 use by individuals with diabetes, hypoglycemia, hypertension, or liver disease. Evidence to substantiate clinically significant adverse events is limited. Supervision and appropriate monitoring are usually adequate in most cases.

## INTERACTIONS REVIEW

### *Strategic Considerations*

The primary clinical uses of coenzyme Q10 supported by human trials are in the treatment of CHF, angina pectoris, mitochondrial encephalopathies, mitochondrial cytopathies, chronic myalgic conditions, dystrophies, fibromyalgia, and Parkinson's disease. In such conditions characterized by mitochondrial dysfunction, the functions of coQ10 in mitochondrial bioenergetics and protection against oxidative stress appear to be paramount. CoQ10's strong antioxidant activity also enables it to function as an effective therapeutic ally when administered in conjunction with medications, such as doxorubicin, that cause adverse effects as a result of inducing oxidative damage. Virtually all antioxidants are capable of functioning as pro-oxidants, either when present in overwhelming quantity (e.g., high-dose intravenous ascorbate) or when present with inadequate antioxidant network partners in an environment of high oxidative stress (e.g., smokers with poor dietary antioxidant intake who are supplemented with synthetic beta-carotene). Perhaps the unique aspect of coQ10 is that it functions physiologically both as a pro-oxidant and antioxidant and can be regenerated back to its reduced or antioxidant form through normal cellular enzymatic processes.

Many pharmacological agents inhibit coQ10 synthesis, interfere with its function, and induce coQ10 deficiency states. In such circumstances, coadministration of coQ10 can prevent or reverse adverse drug effects, often in a manner that enhances therapeutic efficacy and improves clinical outcomes. In these situations, coQ10 carries no significant risks, and controversy as to its use is minimal.

Coenzyme Q10 is most widely used in the prevention and treatment of heart disease, more recently incorporated into acute cardiac care. For example, in an innovative placebo-controlled randomized trial involving 49 patients, Damian et al.[22] found that combining liquid coQ10 (250 mg followed by 150 mg three times daily for 5 days) with mild hypothermia immediately after out-of-hospital cardiac arrest and cardiopulmonary resuscitation (CPR) appears to improve survival and may prevent reperfusion injury and neurological damage in survivors. The astroglial protein S100 is an established biochemical marker of central nervous system (CNS) injury. Mean serum S100 protein 24 hours after CPR was significantly lower in the coQ10 group (0.47 vs. 3.5 ng/mL). Three-month survival in the coQ10 group was 68% versus 29% in the placebo group, and nine coQ10 patients survived with a Glasgow outcome scale of 4 or 5 (vs. five placebo patients). As for chronic cardiovascular conditions and attendant mortality risk, evidence is not unanimously in support of its efficacy, but as part of a lifestyle that includes regular exercise and a healthy diet (particularly omega-3 oils), coQ10 may help significantly decrease cardiovascular risk.[23] In particular, chronic CHF has reached epidemic proportions and is the single most common cause for hospitalization among individuals over age 65 in the United States; in more than half these patients, impaired left ventricular (LV) diastolic function plays a major role. CoQ10 appears to provide particular benefit in reversing diastolic impairment, including adverse effects on LV diastolic function associated with atorvastatin therapy.[24] This therapeutic action, as well as the broader role of coQ10 in the treatment of chronic cardiovascular conditions, leads directly into what may become a major controversy within medicine.

The issue of the interaction between statin drugs and coenzyme Q10 presents some of the most complex and timely clinical issues affecting coQ10 and its role in human health. HMG-CoA reductase inhibitors have demonstrated important and substantial cardiovascular clinical benefits, including reducing mortality; however, the impact of coQ10 depletion with long-term statin therapy (≥20 years) is only beginning to be considered in a substantive manner, particularly concerning patients with heart failure. Nevertheless, in the first clinical research addressing some of these concerns, Go et al.[25] conducted a propensity-adjusted cohort study of all-cause death and hospitalization for heart failure during a median of 2.4 years of follow-up after initiation of statin therapy. They reported that among "adults diagnosed with heart failure who had no prior statin use, incident statin use was independently associated with lower risks of death and hospitalization among patients with or without coronary heart disease." Although encouraging, the short duration of follow-up in this study precludes any substantive conclusions regarding long-term safety of statin therapy.

The medical literature currently portrays statin therapy as a virtual "panacea" for prevention and treatment of cardiovascular conditions (and a multitude of other pathologies), but the parameters of the statin discussion have yet to expand beyond cholesterol and inflammation and incorporate comprehensive functional assessment of all risk factors. In a paper with potentially disturbing implications, Getz et al.[26] discussed the issue of estimating the high-risk group for cardiovascular disease in a well-defined Norwegian population according to European guidelines and the systematic coronary risk evaluation system. They raised concerns regarding the efficacy of applying the current cholesterol reduction goals (of total cholesterol below 180 mg/dL) being established as public policy in Europe and the United States. They noted that, in Norway, one of the world's healthiest countries, 85% of the men and more than 20% of the women over age 40 would need to be treated for high cholesterol under the American recommendations. Thus, in this population with relatively low rates of heart disease, "implementation of the 2003 European guidelines on

prevention of cardiovascular disease in clinical practice would classify most adult Norwegians at high risk for fatal cardiovascular disease.''[26] These observations prompted provocative responses in the scientific literature questioning the necessity, safety, and prudence of broad-based implementation of aggressive lipid-lowering standards. In particular, Ravnskov et al.[27] pointed out that application of these recommendations would result in the majority of the world's adult population being treated with statin drugs; to which they added, ''As the risk to benefit ratio for a more drastic lowering of low density lipoprotein cholesterol is unknown, we question the wisdom of this advice.'' Notably, May et al.[28] found that a total cholesterol level approaching 200 mg/dL is associated with higher survival in patients with heart failure than levels below 140 mg/dL.

Paradoxical evidence showing both reduced cardiovascular risk, including heart attack and stroke, and stress on cardiac tissue induced by the inherent action of HMG-CoA reductase inhibitors has yet to withstand the test of time over decades. Although 20 years may be required for ongoing inhibition of endogenous ubiquinone synthesis resulting in mitochondrial interference and diastolic dysfunction to manifest as impaired hepatic, neurological, and cardiac dysfunction or frank cardiomyopathy resulting in chronic CHF, long-term statin use could represent a significant iatrogenic risk factor for some patients, particularly those with baseline coQ10 levels that are suboptimal or compromised by aging, malnutrition, drug depletions, genotypic susceptibility, and other adverse influences. Thus, for example, Tsivgoulis et al.[29] found that patients with asymptomatic neuromuscular disorders may have their condition precipitated by statin use.

Although statin therapy may reduce inflammation, as reflected by reduced C-reactive protein (CRP) concentrations, other critical cardiovascular risk factors such as lipoprotein(a), homocysteine, and fibrinogen are not modified to any significant degree by inhibition of HMG-CoA reductase. Moreover, preliminary research indicates that hypotheses of reduced atherosclerosis and calcific aortic stenosis through aggressive lipid-lowering therapies using statins may have been premature and overly optimistic in the face of mixed findings; in fact, statins appear to block the beneficial effects of exercise on intimal thickening.[30,31] Likewise, in the IDEAL study comparing high-dose atorvastatin with usual-dose simvastatin for secondary prevention after myocardial infarction (MI), Pedersen et al.[32] found that although aggressive lipid lowering significantly reduced the risk of other composite secondary endpoints and nonfatal acute MI, intensive lowering of low-density lipoprotein (LDL) cholesterol did not reduce coronary death or cardiac arrest with resuscitation, and that there were no differences in cardiovascular or all-cause mortality.

Thus far, the potential for integrative clinical strategies based on synergistic activities has been neglected and may be most deserving of thorough investigation. A thorough review of the literature of statin therapy that incorporates a frank appraisal of risk factors suggests that the growing enthusiasm for statin drugs over the past decade may eventually succumb to a harsh realization that they are appropriate for a relatively select patient population, specifically those with severe and recalcitrant hypercholesterolemia for whom other therapies have proved ineffectual. Notably, the issue of individual pharmacogenomic variability influencing efficacious or adverse responses to statin therapy is only beginning to be considered.[33] Furthermore, until continued concerns about neuropathies, skeletal myopathies, and cardiomyopathies known or suspected to be associated with long-term statin therapy, as well as their potential for enhancing growth of subclinical malignancies through angiogenic and possibly immunomodulating mechanisms, are more fully investigated, the use of these widely prescribed, arguably overprescribed, medications should be more carefully considered, given the paucity of long-term studies of these agents, which, once instituted, will often be consumed for the lifetime of most patients. For example, in a retrospective case-control study, Wilke et al.[34] found that CYP3A genotype was associated with increased severity of atorvastatin-induced muscle damage, but not an increased risk for development of such adverse effects, as indicated by elevated serum creatine kinase (CK) levels. Thus, individuals who were homozygous for CYP3A5*3 demonstrated greater serum CK levels than patients who were heterozygous for CYP3A5*3, when concomitant lipid-lowering agents (gemfibrozil with or without niacin) were sequentially removed from the analysis. Similarly, in comparing nine haplotypes in the gene that carries the code for HMG-CoA reductase within both Caucasian and African Americans, Krauss et al.[35] found that treatment with simvastatin (40 mg) demonstrated significant genetic differences in statin response in lowering LDL cholesterol levels. Consequently, individuals who have a genetic problem with metabolizing statins could have a larger depletion of coQ10 (because of a higher level of the statin drug) and thus could have more problems. conversely, individuals who tolerate statins better may be metabolizing them faster, and thus their Q10 may not become as depleted. Moreover, half of all individuals who have heart attacks do not have hypercholesterolemia.

Meanwhile, other methods of cardiovascular disease risk reduction, such as a healthy and balanced diet, regular exercise, and omega-3 fatty acid supplementation, should be pursued vigorously as a coordinated broad response to multiple risk factors. In such an integrative approach, for example, the therapeutic benefits of statin therapy can be complemented or enhanced through coadministration of fish oil or L-carnitine.[36-43] Nevertheless, when Studer et al.[23] conducted a review of data on the efficacy and safety of different antilipidemic agents and diets on mortality, they found that fish oil and statins were the most effective interventions for lowering cardiac mortality risk, fish oil being superior to statin therapy in terms of lowering all-cause mortality, despite very modest effects on lipids.

However, other evidence has emerged that could complicate the picture. In a 6-year, randomized, controlled trial involving 140 middle-aged men, Rauramaa et al.[30] found that men undergoing statin treatment are significantly less likely to exhibit benefit from exercise in slowing atherosclerosis than those exercising but not taking statins. Intermittent exercise enhances coQ10 biosynthesis, resulting in higher coQ10 levels, and this could be a factor in the well-known health benefits of exercise. The findings from this study suggest that statins may neutralize the beneficial effect of exercise, at least in part, through their blocking of coQ10 biosynthesis. Levy and Kohlhaas[44] conducted a review of studies examining the effects of statin drugs, prescribed for reduction of cholesterol levels, on plasma concentrations of coQ10 and considerations regarding coadministration of coQ10 and concluded that ''statin drug therapy does indeed reduce blood concentrations of coenzyme Q10.'' However, the authors determined that ''due to the small number and dissimilar nature of studies available, the ability of the reviewers to draw any strong conclusions was limited.'' Nevertheless, ''results from isolated studies suggest that statin drugs may induce mitochondrial dysfunction.'' Furthermore, ''limited data suggest

that supplementation with coenzyme Q10 may be beneficial in patients taking statin drugs who 1) have a family history of elevated cholesterol levels, or 2) have a family history of heart failure, or 3) are over 65 years of age. Further studies investigating the effects of statin drugs on the development of myotoxicity are warranted, particularly among high-risk populations."[44] Continued research is needed to investigate the long-expressed hypothesis that many of the other adverse effects associated with statins derive from its interference with coQ10 synthesis and function.

Administration of coQ10 alone or in conjunction with other agents, as part of an integrative therapeutic strategy, offers significant potential for enhancing clinical outcomes in individuals with a range of cardiovascular conditions. In particular, numerous researchers and clinicians have reported many cases of extraordinary clinical improvement in individuals with conditions such as CHF in which the expected progression is characterized by steady worsening and morbidity within 2 years under conventional therapy. At the least, incorporation of coQ10 into the therapeutic repertoire presents an opportunity to correct myocardial deficiency of coQ10 and enhance synthesis of coQ10-requiring enzymes, thereby extending the duration and enhancing the quality of life of such patients.

## NUTRIENT-DRUG INTERACTIONS

### Beta-1-Adrenoceptor Antagonists (Beta-1-Adrenergic Blocking Agents) and Related Antihypertensive Medications

Evidence: Metoprolol (Lopressor, Toprol XL), propranolol (Betachron, Inderal LA, Innopran XL, Inderal).
Extrapolated, based on similar properties: Acebutolol (Sectral), atenolol (Tenormin); combination drugs: atenolol and chlorthalidone (Co-Tendione, Tenoretic); atenolol and nifedipine (Beta-Adalat, Tenif); betaxolol (Kerlone), bisoprolol (Zebeta), carteolol (Cartrol), esmolol (Brevibloc), labetalol (Normodyne, Trandate); metoprolol combination drug: metoprolol and hydrochlorothiazide (Lopressor HCT); nadolol (Corgard), nebivolol (Nebilet), oxprenolol (Trasicor), penbutolol (Levatol), pindolol (Visken); propranolol combination drug: propranolol and bendrofluazide (Inderex); sotalol (Betapace, Betapace AF, Sorine), timolol (Blocadren).
Similar properties but evidence lacking for extrapolation: Other antihypertensive drugs.

#### Interaction Type and Significance

☼ **Prevention or Reduction of Drug Adverse Effect**
⊕ **Potential or Theoretical Beneficial or Supportive Interaction, with Professional Management**

Probability: **3. Possible**

Evidence Base: ◉ **Emerging**

#### Effect and Mechanism of Action

Coenzyme Q10 plays a central role in energy production within the mitochondria of all cells but most critically in muscle cells, especially those of the heart. Propranolol and some other beta blockers inhibit, to varying degrees, enzymes in cardiac muscle, particularly NADH-oxidase and succinoxidase, that are dependent on coQ10 and indispensable for the bioenergetics of the myocardium.[45,46] Kishi et al.[47] reported that adrenergic blockers for beta receptors inhibited mitochondrial coQ10 enzymes to varying degrees.

#### Research

Kishi, Kishi, Folkers, et al.[46-49] have demonstrated with both in vitro and human studies and through reviews of the scientific literature that individuals with myocardial failure (dilated and restrictive cardiomyopathy and alcoholic heart disease) exhibit significantly decreased coQ10 levels compared to those with healthy myocardial tissue. Further, a strong association has been observed between the severity of the pathology and the degree of coQ10 deficiency.[46] Conversely, enhancement of coQ10 levels in the myocardium appears to counteract energy deficiency and reduce the tendency to and severity of myocardial dysfunction.

A range of antihypertensive medications have exhibited inhibitory effects on enzymes containing coQ10 in assays using mitochondrial preparations from beef myocardium.[47] Among beta blockers, propranolol demonstrates the most active inhibition of NADH-oxidase. Researchers have reported that adverse reactions related to depressed myocardial function associated with propranolol occurred in approximately 10% of 268 hospitalized patients receiving propranolol; adverse effects were reported at dosage levels as low as 30 mg daily or less.[47] In vitro research indicates that metoprolol is approximately 25% as inhibitory as propranolol; clonidine and hydralazine (both alpha-adrenergic blockers) exerted similar levels of effect. Timolol showed negligible inhibition of NADH-oxidase and exerted pharmacologically low cardiac-depressant effects. Five alprenolols showed inhibition that approached that of propranolol. The 1-isomer of alprenolol showed weak inhibition of another coQ10 enzyme, succinoxidase, but the other beta blockers were essentially noninhibitory to this enzyme.[48]

The common pattern of fatigue associated with beta-blocker drugs, particularly in the elderly and individuals with preexisting coQ10 deficiency, may derive from diminished myocardial contractility, decreased cardiac output, and other coQ10-related depression of myocardial function.[47] In an open study of 40 patients in severe heart failure (classes III and IV), almost two-thirds showed objective and subjective improvement when treated with 100 mg of coQ10 daily. Individuals with hypertension demonstrate coQ10 deficiencies regardless of whether or not they are taking antihypertensive agents.[47] In a small open study, three of five subjects taking propranolol complained of general malaise, whereas none of seven subjects receiving both propranolol and coQ10 reported similar adverse effects.[49] Hamada et al.[50] found that adverse effects on myocardial contractility (and coQ10 levels) associated with propranolol therapy in hypertensive patients were reduced when 60 mg of coQ10 daily was integrated into the treatment plan. In parallel research, Takahashi et al.[51] conducted a trial with 16 glaucoma patients in which they coadministered coQ10 (90 mg/day) during treatment with timolol eye preparation for 6 weeks. They reported that this complementary therapeutic approach reduced timolol-induced cardiovascular adverse effects while preserving intended effects on intraocular pressure.

#### Nutritional Therapeutics, Clinical Concerns, and Adaptations

Physicians prescribing beta blockers or related antihypertensive medications are advised to discuss adverse effects associated with these medications and the potential compensatory benefits of concomitant coQ10. Nutritionally oriented physicians and other health care providers often prescribe coQ10 for patients with cardiovascular conditions, or to prevent the occurrence of such in those concerned with or predisposed to such diseases. Therapeutic dosages of coQ10 for cardiovascular conditions range from 50 mg daily to 100 mg or more

three times daily; such dosage levels would be appropriate within the context of conventional treatment of hypertension with beta blockers and most other antihypertensive medications.

## Chlorpromazine, Thioridazine, and Related Phenothiazines

Evidence: Chlorpromazine (Largactil, Thorazine), thioridazine (Mellaril).
Extrapolated, based on similar properties: Acetophenazine (Tindal), fluphenazine (Modecate, Permitil, Prolixin, Prolixin Decanoate, Prolixin Enanthate), mesoridazine (Serentil), methotrimeprazine (levomepromazine; Nozinan), pericyazine (Neuleptil), perphenazine (Trilafon); combination drug: perphenazine and amitriptyline (Etrafon, Triavil, Triptazine); prochlorperazine (Compazine, Stemetil), promazine (Sparine), promethazine (Phenergan, Promacot, Promethegan), propiomazine (Largon), thiethylperazine (Torecan), thioproperazine (Majeptil), trifluoperazine (Stelazine), triflupromazine (Vesprin).

Interaction Type and Significance
**⟐≈≈ Drug-Induced Adverse Effect on Nutrient Function, Coadministration Therapeutic, with Professional Management**
☼ **Prevention or Reduction of Drug Adverse Effect**

Adverse Effect Probability: **3. Possible**
Evidence Base: **◉ Emerging**

Nutrient Benefit
**3. Possible**
**○ Preliminary**

Effect and Mechanism of Action
Phenothiazines are associated with adverse effects on cardiac function in some individuals. In vitro, phenothiazines inhibit NADH-oxidase and succinoxidase. Furthermore, chlorpromazine has strong alpha-adrenergic blocking activity and can induce orthostatic hypotension.

Research
Folkers, Kishi, and other researchers demonstrated that thioridazine and related phenothiazine agents can induce adverse changes in cardiac activity in some individuals. Inhibition of myocardial respiration, particularly NADH-oxidase and succinoxidase, by phenothiazines and other psychotherapeutic drugs contributes significantly to these adverse myocardial depressant effects. Research indicates that coadministration of coQ10 can prevent or reverse these changes, but conclusive evidence from large, well-designed clinical trials is lacking.[49,52]

Nutritional Therapeutics, Clinical Concerns, and Adaptations
Current use of phenothiazines has largely moved beyond the more obvious adverse effects and nutrient depletion patterns associated with prescribing patterns of prior decades. However, pending further research, physicians prescribing thioridazine and related phenothiazine agents are advised to inform patients of potential adverse effects and the possible benefit of reducing adverse effects through coadministration of coenzyme Q10. A typical oral dose of 30 to 50 mg twice daily would generally be appropriate but should be tailored to the particular characteristics and evolving needs of the individual patient. No evidence is available and no suggestion has been made that such nutrient support introduces any significant risk directly or through interference with the medication.

## Doxorubicin and Related Anthracycline Chemotherapy

Evidence: Doxorubicin (Adriamycin, Rubex).
Extrapolated, based on similar properties: Daunorubicin (Cerubidine), epirubicin (Ellence, Pharmorubicin), idarubicin (Idamycin, Zavedos), mitoxantrone (Novantrone, Onkotrone).
Similar properties but evidence lacking for extrapolation: Daunorubicin, liposomal (DaunoXome); doxorubicin, pegylated liposomal (Caelyx, Doxil, Myocet).

Interaction Type and Significance
**⟐≈≈ Drug-Induced Adverse Effect on Nutrient Function, Coadministration Therapeutic, with Professional Management**
☼ **Prevention or Reduction of Drug Adverse Effect**

Probability: **1. Certain**
Evidence Base: **● Consensus**

Effect and Mechanism of Action
Anthracyclines generate free radicals that cause oxidative damage, particularly microsomal lipid peroxidation, through an iron-dependent process, which results in cardiotoxicity and adverse effects on other tissues. Doxorubicin also causes several other adverse effects, including (1) reduction of the coQ10 content within mitochondrial membranes, (2) inhibition of mitochondrial biosynthesis of coQ10, and (3) inhibition of mitochondrial synthesis coQ10-dependent enzymes, particularly succinoxidase and NADH-oxidase. Evidence indicates that such interference with coQ10 metabolic processes and depletion of coQ10 constitutes a major factor in the acute and chronic adverse effects associated anthracyclines, particularly doxorubicin-induced cardiotoxicity.[52-54]

The acute and chronic forms of cardiomyopathy induced by doxorubicin appear to derive from its specific effects on coQ10 synthesis and function, both immediate interference and metabolic sequelae. A single dose of doxorubicin causes inhibition of respiratory enzymes and rapidly induces a characteristic, acute cardiotoxicity.[55] Furthermore, not only can the cardiotoxicity of doxorubicin be of rapid onset, but it also can endure for decades, often absent cardiac complaints. Thus, in a longitudinal assessment of cardiac function in 22 patients treated with anthracyclines for osteogenic sarcoma or malignant fibrous histiocytoma, Brouwer et al.[56] found systolic dysfunction in more than a quarter of the patients and diastolic dysfunction in almost half after two decades (median, 22 years). Moreover, cardiac dysfunction was progressive, as measured at 9, 14, and 22 years.[56] This effect, sometimes reversible, appears to result, at least in part, from competition between the drug and coQ10, both of which contain a quinone group, for the enzymatic sites of the coenzyme. Doxorubicin may also cause enzyme inhibition through oxidation of coQ10, directly and through doxorubicin-induced ROS. Subsequent depletion of coQ10, with attendant loss of its physiological functions in electron transport and mitochondrial respiratory energetics, plays a major role in the loss of mitochondrial integrity and necrosis of cardiac myocytes characteristic of chronic doxorubicin-induced cardiotoxicity. Thus, coQ10 exhibits a unique ability to reduce free-radical formation induced by doxorubicin and to prevent resultant toxicity, particularly the chronic form; other antioxidants, such as vitamin C and alpha-tocopherol, do not provide a similar protective effect.[57]

Cardiac toxicity is similar between equipotent doses of doxorubicin and daunorubicin, slightly lower for epirubicin, and only one-sixth that of doxorubicin for equipotent doses of mitoxantrone. Doxil and DaunoXome (liposome-encapsulated doxorubicin and daunorubicin, respectively) exhibit negligible cardiotoxicity, presumably because of minimal cardiac exposure to the active drug with the pharmacokinetics of the liposome-encapsulated preparation.

### Research

A broad consensus exists regarding the cardiotoxic effects of doxorubicin and its adverse effects on coQ10. Confirmatory evidence as to the extent to which introduction of exogenous coQ10 might mitigate such damage has developed more gradually.

Animal studies using rabbits found that mitochondrial degeneration is the most immediate and characteristic ultrastructural damage associated with the nonreversible cardiomyopathy induced by repeated exposure to doxorubicin.[58] All anthracyclines share cardiotoxicity to differing degrees, probably by the same mechanism. Using a rodent model, Shinozawa et al.[59] observed that among anthracyclines, aclarubicin had the smallest effect on rat liver microsomal lipid peroxidation, and the degree of this effect increased in the order of pirarubicin, doxorubicin, daunorubicin, and epirubicin.

Coenzyme Q10 demonstrated a protective effect against doxorubicin-induced damage to cardiac tissue in numerous animal experiments using mice, rats, and rabbits.[59-67] However, after confirming protective activity of coQ10 in conjunction with intraperitoneal administration of doxorubicin in mice, Schaeffer et al.[65] found that coQ10 failed to exhibit such a protective effect with intravenous anthracycline, as typical in clinical application with humans.

In reporting the findings of an experiment using a mouse model, Shinozawa et al.[68] observed that pretreatment with alpha-tocopherol significantly increased the tissue concentration of aglycone I (the major metabolite of doxorubicin) compared with saline placebo. They concluded that caution was required in the concomitant application of coQ10 and alpha-tocopherol with antitumor drugs, especially doxorubicin.[68] Some derivative literature has interpreted this statement as a contraindication of concomitant doxorubicin and coQ10 use. However, in two subsequent papers, these researchers noted that coadministration of coQ10 was associated with improved myocardial mitochondrial functions and "showed a significant decrease in mouse liver and heart microsomal lipid peroxidation" compared with doxorubicin-administered controls.[59,67]

In two studies (one in vitro and the other using rats) the addition of carnitine enhanced the protective effect of coQ10 in preventing anthracycline-induced cardiac damage.[69,70]

Iarussi et al.[71] demonstrated the protective effect of coQ on anthracycline-induced cardiotoxicity in a small study involving children being treated for acute lymphoblastic leukemia and non-Hodgkin's lymphoma.

### Nutritional Therapeutics, Clinical Concerns, and Adaptations

Although further research with large, well-designed clinical trials is essential, coQ10 is already playing a role in many cancer treatment protocols employing multiple therapeutic modalities within an integrative clinical strategy. Administration of coQ10 before, during, and after chemotherapy with anthracyclines, particularly doxorubicin, is supported by scientific evidence and experienced clinicians; evidence of any interference by the nutrient on the therapeutic effect of the drug(s) is lacking and generally considered as unlikely. The usual dosage of coQ10 ranges from 50 to 100 mg orally twice daily and inherently requires close supervision and regular monitoring. Physicians and other health care professionals may consider reviewing the potential for such synergistic therapies with appropriate patients and provide referral information to centers specializing in such integrative approaches.

## HMG-CoA Reductase Inhibitors (Statins)

Evidence: Atorvastatin (Lipitor), lovastatin (Altocor, Altoprev, Mevacor), combination drug: lovastatin and niacin (Advicor), pravastatin (Pravachol), simvastatin (Zocor); combination drug: simvastatin and extended-release nicotinic acid (Niaspan). Extrapolated, based on similar properties: Fluvastatin (Lescol, Lescol XL), rosuvastatin (Crestor).

### Interaction Type and Significance

⟐≈≈ **Drug-Induced Adverse Effect on Nutrient Function, Coadministration Therapeutic, with Professional Management**

≈≈ **Drug-Induced Nutrient Depletion, Supplementation Therapeutic, with Professional Management**

☼ **Prevention or Reduction of Drug Adverse Effect**

⊕⊕ **Beneficial or Supportive Interaction, with Professional Management**

Probability: **2. Probable**

Evidence Base: ● **Consensus**

### Effect and Mechanism of Action

3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) is normally converted to mevalonate, the substrate for biosynthesis of both cholesterol and coQ10. Coenzyme Q10 is a component of the LDL and VLDL fractions of cholesterol. Statin drugs exert their action in lowering cholesterol synthesis by competitively inhibiting hepatic synthesis of HMG-CoA reductase, the rate-limiting step of mevalonate synthesis, and thereby limiting conversion of HMG-CoA to mevalonate. Thus, HMG-CoA reductase inhibitors lower coQ10 (ubiquinone) levels, in a dose-dependent relationship, as they lower cholesterol.[72-79] Statins are the only class of lipid-lowering agents that are known to block the synthesis of mevalonate.

### Research

Researchers have developed a consistent body of evidence over time demonstrating the adverse effects of HMG-CoA reductase inhibitors on the synthesis and function of coQ10 and determining the variables influencing this depletion pattern and its clinical significance. The emerging research demonstrating the central importance of coQ10 in myocardial and endothelial function underlies the growing concern for adverse effects on cardiovascular function, particularly among individuals who have developed or are susceptible to coronary artery disease and heart failure, especially within the context of aging and associated tendencies to coQ10 deficiency.[79-82] Significantly, Langsjoen and Langsjoen[69] have noted that all large clinical trials of statin therapy have excluded patients with "class III and IV heart failure such that long term safety of statins in patients with heart failure has not been established."

Beginning with Willis et al.[82a] in 1990, animal studies have evaluated the effects of statins on coQ blood and tissue levels. In addition to documenting the adverse effects of statin-induced depletion of coQ9 and coQ10 (species dependent) on ATP and creatinine phosphate in myocardium, these researchers also investigated prevention or reversal of resultant deficiency states through coadministration of exogenous

ubiquinone. Researchers further established that statins are the only class of lipid-lowering agents that directly impede the synthesis of mevalonate and therefore most directly interfere with coQ10 synthesis. Lipid-soluble statins (atorvastatin, cerivastatin, simvastatin, fluvastatin) showed more toxicity in this regard than water-soluble/hydrophilic statins (pravastatin).[83,84] In all animal studies where coQ10 was administered to the animals before initiation of statin therapy, the coQ10 blood and tissue depletion was completely prevented.

In 1990, Folkers et al.[72] first reported the interaction between statins and coQ10 in a small human trial that documented depletion of coQ10 by lovastatin and concluded that oral administration of coQ10 increased blood levels of coQ10 and was generally accompanied by an improvement in cardiac function. These researchers further suggested that coQ10 depletion might play a significant role in or be responsible for abnormal liver function and other adverse effects associated with statin use. Studies published in 1993 by Watts et al.[73] and Ghirlanda et al.[74] and later by De Pinieux et al.[75] (1996) confirmed the effects of HMG-CoA reductase inhibitors on blood levels of ubiquinone.

Nevertheless, some researchers have interpreted as clinically insignificant the degree of coQ10 depletion in some patient populations and questioned the need for compensatory coQ10 administration. In 1994, Laaksonen et al.[85] conducted inquiries into the effects of lovastatin and simvastatin on serum ubiquinone concentrations and found that after short-term lovastatin treatment, and after long-term simvastatin treatment, average serum ubiquinone levels were similar to those observed in a group of apparently healthy middle-aged men. However, in 1997, Mortensen et al.[76] conducted a randomized, double-blind clinical trial where serum levels of coQ10 were measured over a period of eighteen weeks in forty-five hypercholesterolemic individuals who had been prescribed the statin drugs lovastatin and pravastatin. A dose-related significant decline of the total serum level of coQ10 was found in both groups, with those taking lovastatin (20-80 mg/day) demonstrating the more pronounced decline. Likewise, Paloma'ki et al.[86] conducted a double-blind, placebo-controlled, crossover trial with 27 hypercholesterolemic men with coronary heart disease. During the 6-week treatment period using lovastatin (60 mg/day), ubiquinol content diminished by 13%, as measured by LDL phosphorus. However, in a later randomized, double-blind, placebo-controlled, crossover trial, Paloma'ki et al.[87] found that 180 mg coQ10 daily did not convincingly correct impaired defense against initiation of oxidation of LDL due to lovastatin treatment at 60 mg/day. They concluded that concomitant coQ10 only partially restored the drug-induced depletion of LDL ubiquinol and questioned the clinical benefits of coQ10 coadministration in individuals taking HMG-CoA reductase inhibitors, specifically lovastatin.

Bleske et al.[88] reported a lack of significant decline in measurable coQ10 in a randomized crossover study involving 12 healthy young normolipidemic volunteers treated with either pravastatin or atorvastatin for 4 weeks despite a significant decrease in LDL levels. Despite the short period involved and the dissimilarity between the test subjects and the typical patient population, these authors concluded: ''Routine supplementation of CoQ10 may not be necessary when HMG-CoA reductase inhibitor therapy is administered.'' In contrast, Rundek et al.[89] conducted a prospective blinded study involving 34 subjects eligible for statin treatment according to standard criteria. After assessing baseline coQ10 status, investigators found that a decline in blood concentration of CoQ10 was already detectable after 14 days and had dropped by approximately 50% (mean, 1.26 μg/mL vs. 0.62 μg/mL) after 30 days. ''Even brief exposure to atorvastatin causes a marked decrease in blood CoQ10 concentration,'' the authors observed, and further noted: ''Widespread inhibition of CoQ10 synthesis could explain the most commonly reported adverse effects of statins, especially exercise intolerance, myalgia, and myoglobinuria.'' These researchers proposed that future research might benefit from measurement of tissue levels of cQ10 and concluded by suggesting that coadministration with coQ10 may be appropriate.[89]

Thus, coQ10 depletion appears to be well tolerated in younger and healthier patients, particularly in the short term, but the collected data demonstrate detrimental cardiac effects, especially with preexisting cardiac dysfunction, when subjected to this drug-induced depletion pattern. Some evidence indicates that pravastatin may reduce coQ10 levels to a lesser degree than other HMG-CoA reductase inhibitors.[74,76] Of particular concern to many clinicians and coQ10 investigators are the statin-induced changes in diastolic LV performance because myocardial diastolic function is highly ATP dependent and therefore particularly susceptible to coQ10 depletion. In November 2002, at the third conference of the International Coenzyme Q10 Association, Silver et al.[77] presented the results of a small pilot study involving six hyperlipidemic patients undergoing statin therapy. They reported that after 6 months of statin therapy, 67% demonstrated abnormalities of diastolic function.

The effect of statins on coQ10 is not paralleled by similar adverse impact on other antioxidant substances. Yoshida et al.[90] reported that LDL cholesterol (LDL-C) levels declined with low-dose simvastatin, with no attendant drop in the antioxidant levels of LDL or elevation of oxidative susceptibility of LDL. Subsequently, in a 3-month trial involving 42 hypercholesterolemic male patients treated with different doses of atorvastatin, simvastatin, and pravastatin, Passi et al.[78] observed not only the desired drop in total cholesterol and LDL-C, but also a significant dose-dependent plasma (and lymphocyte) depletion of $coQ10H_2$ and coQ10, although no accompanying change in the $coQ10H_2$/coQ10 ratio. Other antioxidants, both lipophilic (alpha- and gamma-tocopherol, lycopene, beta-carotene) and hydrophilic (vitamin C, uric acid) as well as glutathione, polyunsaturated fatty acid (PUFA), copper, and zinc–superoxide dismutase, were spared drug-induced depletion. Concomitant vitamin E may partially offset the loss of coQ10 caused by lovastatin.[91]

Following up on the early work of Folkers et al.,[72] human studies by Bargossi et al.[92] and Miyake et al.[93] found that coadministration of 90 to 100 mg daily of coQ10 protects against declining blood levels of coQ10 caused by statins without interfering with lipid-lowering activity. Pettit et al.[94] demonstrated reversal of statin toxicity to human lymphocytes in tissue culture. Significantly, in terms of clinical strategy, both coQ10 and statins appear to have a protective effect on endothelial function.[84,95-97] Wong et al.[98] found that concurrent coQ10 did not diminish the anti-inflammatory effect attributed to statins.

Brady et al.[99] and Goldman et al.[100] conducted surveys investigating the use of statins among general practitioners in the United Kingdom. They found that 80% believed that 80% of their patients had achieved target cholesterol levels ($\leq$5 mmol/L). However, such outcomes were achieved in only 65% of patients initially, with that rate increasing to 78% after uptitrations and switching medication. Moreover, only 46% of patients demonstrated cholesterol reduction of 25% to the target levels, increasing to 56% after uptitrations or

switching medication. Notably, in response to such failure to achieve intended clinical outcomes, these practitioners stated that they would continue the unsuccessful therapy in 23.2% of such cases. These findings indicate that clinical guidelines are not being followed by many primary care physicians and that a significant gap exists between expectation and actual clinical results in statin prescribing. The issues of patient skepticism and compliance further complicate the realities of clinical application of statin therapy and reveal a significant departure from the scenarios envisioned in clinical trials and academic reviews.

### Nutritional Therapeutics, Clinical Concerns, and Adaptations

Concomitant administration of coQ10 during statin therapy offers the opportunity to derive benefits from HMG-CoA reductase inhibitors while counteracting some of their more direct potential adverse effects and supporting broader clinical outcomes. Therapeutic dosages of coQ10 for cardiovascular conditions range from 50 mg daily to 100 mg or more three times daily. CoQ10 support is more important in elderly persons and those with a high susceptibility to or known history of cardiovascular disease, particularly heart failure. Genomic testing may be appropriate to elicit patterns of increased susceptibility to adverse effects of a particular statin drug or to impaired conversion of ubiquinone to ubiquinol. The need for coQ10 coadministration is dose dependent and should be initiated with statin therapy, if not earlier. Individuals prescribed statins that have a greater impact on coQ10, such as atorvastatin, may benefit from higher coQ10 dosage levels. A collaborative approach involving health care professionals trained and experienced in cardiology, nutrition, and other relevant modalities can provide optimal care for each individual through a customized and evolving program of integrative care. Thus, more broadly, strong emphasis needs to be placed on a comprehensive approach using proactive interventions that are safe and effective, such as regular exercise, stress reduction, healthy diet, omega-3 oils, L-carnitine, magnesium, L-taurine, and nutrient support emphasizing a network of antioxidant substances; consideration might also be given to potentially beneficial plant medicines, including *Crataegus* (hawthorn), garlic, and *Ginkgo biloba*.

It is noteworthy that, in apparent recognition of the significant adverse effects associated with statin-induced coQ10 depletion, two patents were awarded to Merck and Co. (now Merck, Sharp and Dohme) in 1990 for the combination of Mevacor in particular and statins in general with 1000 mg of coQ10. U.S. Patent No. 4,933,165 was issued for the following therapy: ''A method of counteracting HMG-CoA reductase inhibitor-associated skeletal muscle myopathy in a subject in need of such treatment which comprises the adjunct administration of a therapeutically effective amount of HMG-CoA reductase inhibitor and an effective amount of Coenzyme Q10 to counteract said myopathy.''[101] Merck is also the assignee for U.S. Patent No. 4,929,437, which applies to a pharmaceutical composition and method of counteracting elevated transaminase levels associated with HMG-CoA reductase inhibitor. The method described comprises the adjunct administration of an effective amount of a statin inhibitor and an effective amount of coQ10.[102] These actions indicate that Merck was convinced of the clinical value and market potential of administering coQ10 in conjunction with statins, at least enough to apply for and receive patents for that combination of therapies. Merck's patents would preclude other companies from combining coQ10 with other statins in a single-dose form. It is not clear why Merck thus far has chosen not to market such a combination with Mevacor (lovastatin).

## Sulfonylureas and Related Oral Hypoglycemic Agents

Evidence: Acetohexamide (Dymelor), glyburide (glibenclamide; Diabeta, Glynase Prestab, Glynase, Micronase, Pres Tab), phenformin (Debeone, Fenformin), tolazamide (Tolinase)
Related but evidence lacking for extrapolation: Glimepiride (Amaryl), metformin (Dianben, Glucophage, Glucophage XR); combination drugs: glipizide and metformin (Metaglip); glyburide and metformin (Glucovance).
Similar properties but evidence indicating no or reduced interaction effects: Chlorpropamide (Diabinese), glipizide (Glucotrol, Glucotrol XL), tolbutamide (Orinase, Tol-Tab).

### Interaction Type and Significance

☼ **Prevention or Reduction of Drug Adverse Effect**
◈≈≈ **Drug-Induced Adverse Effect on Nutrient Function, Coadministration Therapeutic, with Professional Management**
≈≈ **Drug-Induced Nutrient Depletion, Supplementation Therapeutic, with Professional Management**

| Probability: | Evidence Base: |
|---|---|
| **2. Probable** | ◉ **Emerging** |

### Effect and Mechanism of Action

Certain hypoglycemic drugs inhibit the coQ10 enzyme NADH-oxidase.

### Research

Numerous studies have reported that coQ10 levels tend to be lower in individuals with type 2 diabetes mellitus than in the general population. For example, comparing the activity of succinate dehydrogenase–coQ10 reductase in leukocytes from blood samples, Kishi et al.[103] found that the mean percent deficiency of coQ10 was significantly greater (20% ± 0.7%) in 120 patients with diabetes than in healthy controls (16% ± 1.0%). Likewise, a mean percentage deficiency of approximately 20% was observed in 37 individuals whose condition was being treated by diet alone.

Kishi et al.[103] reported that acetohexamide, glyburide, phenformin, and tolazamide inhibit NADH-oxidase in vitro; however, tolbutamide, glipizide, and chlorpropamide had no inhibitory effect on NADH-oxidase or succinoxidase. In assessing patients under treatment, they further found that coQ10 deficiency was greater in individuals taking phenformin and tolazamide than in controls. Based on these observations, an even greater depletion pattern would theoretically occur in individuals administered acetohexamide and glyburide because they exert more potent inhibitory activity on coQ10 enzymes. Overall, the evidence thus far available suggests that the added effect of oral hypoglycemic agents on compromised coQ10 levels often characteristic of individuals with diabetes mellitus might exert a further adverse effect on bioenergetics, ATP generation, and insulin biosynthesis.

Concern has been raised that coadministration of coQ10 might destabilize patients under treatment for diabetes. In a randomized, double-blind trial involving hypertensive patients with coronary artery disease, Singh et al.[104] found that coadministration of 60 mg coQ10 twice daily in 30 of 59 total patients was associated with a significant decline in fasting and 2-hour plasma insulin and glucose levels, compared with controls receiving a B-vitamin complex. These researchers interpreted their findings as suggesting that ''treatment with

coenzyme Q10 decreases blood pressure possibly by decreasing oxidative stress and insulin response in patients with known hypertension receiving conventional antihypertensive drugs.'' Subsequently, in a randomized, double-blind, placebo-controlled, $2 \times 2$ factorial intervention involving 74 subjects with uncomplicated type 2 diabetes and dyslipidemia, Hodgson et al.[105] found that subjects who received 100 mg coQ orally twice daily (200 mg/day), with 200 mg fenofibrate each morning, for 12 weeks demonstrated a threefold increase in plasma coQ concentration and improved blood pressure and long-term glycemic control. Although not associated with reduced oxidative stress (assessed by plasma F2-isoprostane levels), as hypothesized, the primary effects attributable to coQ10 were significant decreases in systolic and diastolic blood pressure and hemoglobin $A_{1c}$.

### Nutritional Therapeutics, Clinical Concerns, and Adaptations

Health care professionals treating individuals with diabetes and especially those being prescribed oral hypoglycemic agents, particularly acetohexamide and glyburide, are advised to consider coadministration of coenzyme Q10 (30-100 mg twice daily) as adjunctive therapy for the primary condition (and typical comorbid conditions) and to mitigate adverse effects of the medications. Close supervision and regular monitoring of glucose levels and blood pressure are warranted, especially while introducing coQ10 or changing dietary programs or dosage levels of any relevant medication. After a period of stabilization, gradual, staged reduction in dosage of oral hypoglycemic agents may be possible and appropriate with continued coadministration of coQ10. Attending health care providers are also encouraged to advise patients to be watchful for changes indicative of unstable blood glucose levels, especially acute fatigue, malaise, difficulty focusing, agitation, irritability, lethargy, cravings for sweets, and other characteristics of hypoglycemia.

## Tricyclic Antidepressants (TCAs)

Evidence: Amitriptyline (Elavil).
Extrapolated, based on similar properties: Amitriptyline combination drug: amitriptyline and perphenazine (Etrafon, Triavil, Triptazine); amoxapine (Asendin), clomipramine (Anafranil), desipramine (Norpramin, Pertofrane), doxepin (Adapin, Sinequan), imipramine (Janimine, Tofranil), nortriptyline (Aventyl, Pamelor), protriptyline (Vivactil), trimipramine (Surmontil).

### Interaction Type and Significance

⟐≈≈ **Drug-Induced Adverse Effect on Nutrient Function, Coadministration Therapeutic, with Professional Management**
≈≈≈ **Drug-Induced Nutrient Depletion, Supplementation Therapeutic, Not Requiring Professional Management**
☼ **Prevention or Reduction of Drug Adverse Effect**

Probability: **3. Possible**
Evidence Base: ◉ **Emerging**

### Effect and Mechanism of Action

Tricyclic antidepressants (TCAs) are antagonistic to coenzyme Q10 enzymes NADH-oxidase and succinoxidase.[49] Furthermore, these agents are class I antiarrhythmics.[106] Drug-induced coQ10 deficiency may be a contributing factor to the cardiac adverse effects associated with TCAs.

### Research

Tricyclic antidepressant drugs, including amitriptyline, particularly when given in high doses, have been reported to produce arrhythmias, sinus tachycardia, and prolonged conduction time.[49] TCAs inhibit NADH-oxidase and succinoxidase in vitro.[52] Myocardial infarction and stroke have also been reported with TCAs.[107,108] At this time, direct evidence of the frequency, circumstances, and severity of this interaction from large-scale, randomized human trials is lacking. However, the pharmacological principles of this interference/depletion pattern is widely accepted, particularly inhibition of myocardial respiration by psychotherapeutic drugs and its prevention by coQ10, as is restoration of healthy coQ10 levels through oral administration.[52]

### Nutritional Therapeutics, Clinical Concerns, and Adaptations

Coadministration of coQ10 may prevent myocardial depression and other adverse effects on cardiac function associated with use of TCAs. Physicians prescribing TCAs are advised to discuss these risks and the potential benefits of concomitant coQ10 with their patients. CoQ10, 20 to 100 mg three times daily, can offset depletion resulting from TCA use and may reduce adverse effects and attendant cardiac risks.

## Warfarin and Related Oral Vitamin K Antagonist Anticoagulants

Warfarin (Coumadin, Marevan, Warfilone).
Similar properties but evidence lacking for extrapolation: Anisindione (Miradon), dicumarol, ethyl biscoumacetate (Tromexan), nicoumalone (acenocoumarol; Acitrom, Sintrom), phenindione (Dindevan), phenprocoumon (Jarsin, Marcumar).

### Interaction Type and Significance

? **Interaction Possible but Uncertain Occurrence and Unclear Implications**
✗ **Potential or Theoretical Adverse Interaction of Uncertain Severity**
✗✗ **Minimal to Mild Adverse Interaction—Vigilance Necessary**

Probability: **5. Improbable**
Evidence Base: ▽ **Mixed** or ☐ **Inadequate**

### Effect and Mechanism of Action

Warfarin exerts its therapeutic effect by interfering with vitamin K metabolism. As quinones, coenzyme Q10 and various forms of vitamin K share a chemical structure. As a result of this vague structural similarity, coQ10 could theoretically interfere with the action of warfarin.[109,110]

### Research and Reports

Although often presented as well documented and almost self-evident in derivative literature, the evidence supporting this proposed interaction is at best suggestive and fragmentary. The available data are lacking in substantive information necessary to predict the character and severity of any such adverse event. Furthermore, the frequency of alleged incidence is far below what would be predicted based on known usage patterns.

The medical literature contains at least four case reports describing decreased international normalized ratios (INRs) subsequent to the introduction of coQ10 in patients previously stabilized on warfarin therapy. When the individuals stopped taking the coQ10, their previous responsiveness to warfarin

resumed.[111,112] Heck et al.[113] (2000) published a cautionary review of this potential interaction based on these available case reports.

Engelsen et al.[113a] conducted a small, randomized, double-blind, placebo-controlled, crossover trial in which patients stabilized on long-term warfarin therapy were administered coQ10. Concomitant use of warfarin and coQ10 did not significantly alter the warfarin dosage needed to maintain an INR in the acceptable range of 2.0 to 4.0 in these patients.

Emerging knowledge of the significant pharmacogenomic variability that influences warfarin activity, sensitivity, and resistance suggests that such possible interactions may occur only in patients with certain genotypes and that inconsistencies in the literature may reflect such variability.[114]

#### Nutritional Therapeutics, Clinical Concerns, and Adaptations

The clinical significance and frequency of occurrence of this interaction are uncertain, even though the theoretical foundation for this interaction is plausible and several case reports have appeared. Grounds for concern are amplified because of the high probability of overlap among the patient populations interested in coQ10 for cerebrovascular benefits and those being treated for the disorders for which warfarin is often prescribed. Physicians prescribing of warfarin should be aware of the possible risk of treatment effect alteration when coQ10 is coadministered and closely monitor any such patients for reduced effects. INR levels and prothrombin time (PT) should be checked with greater frequency during the first 2 weeks after either starting or stopping coQ10 to verify that the risk of bleeding or clotting (as reflected by INR value) is not being affected by the coQ10 doses. In general, it is important always to monitor PT twice weekly when medications, supplements, and diet are changed in any significant way; this is the safest and most reliable method of compensating for unexpected or idiosyncratic interactions in patients undergoing treatment with coumarin derivatives.

## THEORETICAL, SPECULATIVE, AND PRELIMINARY INTERACTIONS RESEARCH, INCLUDING OVERSTATED INTERACTIONS CLAIMS

### Fenofibrate, Gemfibrozil, and Related Fibrates

Bezafibrate (Bezalip), ciprofibrate (Modalim), clofibrate (Atromid-S), fenofibrate (Tricor, Triglide, Lofibra), gemfibrozil (Apo-Gemfibrozil, Lopid, Novo-Gemfibrozil).

No mechanism of action has been articulated for the phenomena reported in the available research, nor has available evidence indicated a consistent effect. It is generally accepted that the mechanism of action of fibrates in lowering cholesterol does not involve direct inhibition of mevalonate, the substrate for biosynthesis of both coenzyme Q10 and cholesterol.[73]

The evidence for this interaction is in preliminary stages, and understanding of its clinical implications is. In a randomized, placebo-controlled, crossover study involving 21 men with combined hyperlipidemia, Aberg et al.[115] found that 10 to 12 weeks of gemfibrozil treatment reduced serum coQ10 levels by more than 40%; alpha- and gamma-tocopherol as well as serum antioxidant levels also dropped. Also, normolipemic control subjects had significantly lower levels of ubiquinone and other antioxidants than placebo-treated patients, as part of an association between antioxidants and lipoprotein lipids. The authors concluded that the mechanisms and clinical significance of this finding were ''unclear.'' In contrast, in a randomized, double-blind, placebo-controlled, $2 \times 2$ factorial intervention involving 74 subjects with uncomplicated type 2 diabetes and dyslipidemias, Hodgson et al.[105] found that subjects who received 100 mg coQ10 orally twice daily (200 mg/day), with 200 mg fenofibrate each morning, for 12 weeks demonstrated a threefold increase in plasma coQ concentration and improved blood pressure and long-term glycemic control. Although not associated with reduced oxidative stress, as hypothesized, the primary effects attributable to coQ10 were significant decreases in systolic and diastolic blood pressure and hemoglobin $A_{1c}$. The specific influence of fenofibrate on coQ10 levels and outcome measures was not determined.

Another factor involving the impact of fibrate derivatives on coQ10 derives from their use in combination with statin drugs (HMG-CoA reductase inhibitors). Gemfibrozil, in particular, inhibits the glucuronidation of most statins (especially cerivastatin), thereby increasing their levels and the attendant risks, including interference with coQ10 synthesis and function. Fluvastatin appears to be the only statin with which gemfibrozil does not increase drug levels.

The evidence for a direct interaction between fibrates and coQ10 remains unclear and lacking direct investigation. Nevertheless, such preliminary status does not contradict the therapeutic value of coQ10 (e.g., 30-100 mg twice daily) in individuals with or at significant risk for cardiovascular conditions, particularly heart disease. Concomitant administration of fibrates and coQ10 may be medically appropriate as a preventive measure or a treatment intervention for many such individuals. Health care providers are advised to discuss such integrative approaches with patients as part of a comprehensive review of options toward a personalized and evolving therapeutic strategy.

### Hydrochlorothiazide and Related Thiazide Diuretics

Hydrochlorothiazide (Aquazide, Esidrix, Ezide, Hydrocot, HydroDiuril, Microzide, Oretic).

Related: Bendroflumethiazide (bendrofluazide; Naturetin); combination drug: bendrofluazide and propranolol (Inderex); benzthiazide (Exna), chlorothiazide (Diuril), chlorthalidone (Hygroton), cyclopenthiazide (Navidrex); combination drug: cyclopenthiazide and oxprenolol hydrochloride (Trasidrex); hydrochlorothiazide combination drugs: hydrochlorothiazide and amiloride (Moduretic); hydrochlorothiazide and captopril (Acezide, Capto-Co, Captozide, Co-Zidocapt); hydrochlorothiazide and enalapril (Vaseretic); hydrochlorothiazide and lisinopril (Prinzide, Zestoretic); hydrochlorothiazide and losartan (Hyzaar); hydrochlorothiazide and metoprolol (Lopressor HCT); hydrochlorothiazide and spironolactone (Aldactazide); hydrochlorothiazide and triamterene (Dyazide, Maxzide); hydroflumethiazide (Diucardin), methyclothiazide (Enduron), metolazone (Zaroxolyn, Mykrox), polythiazide (Renese), quinethazone (Hydromox), trichlormethiazide (Naqua).

Hydrochlorothiazide exerts a mild to moderate inhibitory effect on NADH-oxidase.[47] Although preliminary indications suggest that a probable adverse effect of thiazide diuretics on coQ10 status, this interaction has not been investigated adequately to provide evidence sufficient to enable a well-founded assessment of its frequency, circumstances, severity, or clinical significance. Nevertheless, patients with chronic heart failure are consistently deficient in coQ10, typically proportionate to the severity of the cardiac dysfunction, and will generally benefit from coQ10 as part of a comprehensive therapeutic strategy.[46] No evidence is available to suggest that such nutritional support would interfere with the clinical effectiveness of diuretic therapy.

### Levothyroxine and Related Thyroid Hormones

L-Triiodothyronine ($T_3$): Cytomel, liothyronine sodium, liothyronine sodium (synthetic $T_3$), Triostat (injection).
Levothyroxine ($T_4$): Eltroxin, Levo-T, Levothroid, levothyroxine (synthetic), levoxin, Levoxyl, Synthroid, thyroxine, Unithroid.
L-Thyroxine and L-triiodothyronine ($T_4 + T_3$): animal levothyroxine/liothyronine, Armour Thyroid, desiccated thyroid, Westhroid.
L-Thyroxine and L-triiodothyronine (synthetic $T_4 + T_3$): Euthroid, Euthyral, liotrix, Thyar, Thyrolar.
Dextrothyroxine (Choloxin).

The physiological interrelationship between coenzyme Q10 and thyroid function is multifaceted and has been investigated in many contexts. In the literature, plasma coQ10 determination has been discussed as a potentially useful diagnostic tool in differential diagnosis of thyroid diseases. Kotake et al.[116] observed protective effect of exogenously administered coQ10 on thyrotoxic heart in rabbits. Mancini et al.[117] demonstrated that coQ10 levels have a significant inverse correlation with thyroid hormone concentration in patients with spontaneous hyperthyroidism or hypothyroidism. Furthermore, exogenous administration of coQ10 may be beneficial in hyperthyroid patients with risk factors for heart failure.

Given these and other known patterns of mutual influence between coQ10 and thyroid hormone, oral coQ10 theoretically may affect thyroid hormone levels and alter the effects of levothyroxine or other thyroid medications. Evidence of any such direct interaction of clinically significance is lacking. Nevertheless, physicians or other health care professionals recommending coQ10 to individuals taking thyroid medication are advised to monitor such patients regularly. Clinical investigation of potential interactions, their character, and clinical implications is warranted.

### Orlistat

Orlistat (alli, Xenical).

Depletion of coenzyme Q10 in individuals using orlistat has been suggested, but findings from clinical trials or other direct substantive evidence is lacking. Nevertheless, physicians prescribing orlistat as part of a comprehensive program for reducing obesity, hypercholesterolemia, or other cardiovascular risk factors are advised to consider and discuss with patients the potential benefits of 30 to 50 mg twice daily (or more) of coQ10. Further research is warranted to determine if the action of orlistat in interfering with fat digestion and assimilation might produce a substantial adverse effect on coQ10 synthesis and metabolism.

### Pentoxifylline

Pentoxifylline (Pentoxil, Trental).

Portakal and Inal-Erden[118] reported that combined pentoxifylline and coQ10 pretreatment reduced ischemia-reperfusion damage in the rat liver, as indicated by hepatic glutathione and malondialdehyde levels. Treatment with pentoxifylline alone did not produce beneficial results.

### Radiotherapy

Radiotherapy

Lund et al.[119] reported a reduced effect of radiation therapy on small cell lung cancer (SCLC) with concomitant coQ10 using a human SCLC xenograft into an immunodeficient nude mouse model. They observed interference with radiation therapeutic effect at 40 mg/kg coQ, but not at 10 mg/kg. The 10-mg/kg dosage would be 600 to 800 mg coQ10 in average-sized patients, which is a frequently used dose range in integrative care of cancer patients. The 40-mg/kg dosage is equivalent to 2.8 g for a 70-kg person, a dose infrequently, if ever, used in nutritional oncology.

### Zidovudine (AZT) and Antiretroviral Agents, Reverse-Transcriptase Inhibitor (Nucleoside)

Evidence: Zidovudine (azidothymidine, AZT, ZDV, zidothymidine; Retrovir); combination drugs: zidovudine and lamivudine (Combivir); abacavir, lamivudine and zidovudine (Trizivir).
Extrapolated, based on similar properties: Abacavir (Ziagen), didanosine (ddI, dideoxyinosine; Videx), dideoxycytidine (ddC, zalcitabine; Hivid), lamivudine (3TC, Epivir), stavudine (D4T, Zerit), tenofovir (Viread).

Zidovudine (AZT/ZDV) has been associated with "ragged-red" fiber myopathy because of its effects on myocyte mitochondria; this condition typically is reversible with cessation of the drug. Rosenfeldt et al.[120] reported the case of a 52-year-old male who first developed ragged-red fiber myopathy in 1985 while on effective ZDV-based combination antiretroviral therapy (ART), 14 years after diagnosis of HIV infection. The patient demonstrated "an excellent recovery" after administration of coQ10, known for its antioxidant activity in mitochondria, and was able to continue ART without disruption. The authors concluded that this response to coQ10 therapy "suggests a novel therapy for further investigation targeted at ZDV induced myopathy, potentially allowing continuation of antiviral treatments including ZDV."

## NUTRIENT-NUTRIENT INTERACTIONS

### L-Carnitine

Concomitant administration of coenzyme Q10 and L-carnitine may result in an additive effect.[69,70] Such a potential interaction likely would be beneficial, but direct evidence from human trials is lacking. Close supervision and regular monitoring are warranted at the initiation of and through the course of any such coadministration, particularly in individuals with serious heart disease or other cardiovascular conditions. Clinical investigation of potential interactions, their character, and clinical implications is warranted.

### Vitamin $B_6$, Pyridoxine, Pyridoxal 5′-Phosphate

Pyridoxal 5′-phosphate is required in the conversion of tyrosine to 4-hydroxyphenylpyruvic acid; the formation of the quinone nucleus being the first step in coQ10 biosynthesis. Many researchers have noted the parallel decline in coQ10 and $B_6$ levels associated with aging. In a pilot study involving 29 patients and healthy volunteers, Willis et al.[121] observed strong positive correlations between blood levels of coQ10 and the specific activity of erythrocyte glutamine-oxaloacetic acid transaminase (EGOT) and between coQ10 and the percent saturation of EGOT with pyridoxal phosphate (PLP).[121] Further research is warranted to better understand this physiological relationship and the potential for synergistic therapeutics using nutritional interventions.

### Vitamin E, Alpha-Tocopherol

Vitamin E and coQ10 function in complementary roles within physiological antioxidant networks as the principal fat-soluble antioxidants in membranes and lipoproteins. In particular,

$coQH_2$, the reduced form of coQ, is capable of regenerating alpha-tocopherol. Alpha-tocopherol becomes oxidized whenever it neutralizes a free radical, such as a lipid hydroperoxyl radical, and consequently an alpha-tocopheroxyl radical appears. Subsequently, when $coQH_2$ reacts with the alpha-tocopheroxyl radical, alpha-tocopherol is regenerated and CoQH, the semiquinone radical, is produced. Thus, the formation of oxidized lipids and the consumption of alpha-tocopherol are suppressed while $CoQH_2$ is present.[122,123]

Some researchers have reported that vitamin E may reduce blood levels of coQ10. Coadministration of vitamin E and coQ10 would reasonably be predicted to have a mutually supportive effect, which would also enhance the broader activity of the physiological antioxidant network against oxidative stress. Further investigation into the physiological functions and therapeutic roles of vitamin E, coQ10, and other antioxidants is underway within both research and clinical settings and promises to deepen our understanding of their roles in physiology, health enhancement, and treatment of disease.

## HERB-NUTRIENT INTERACTIONS

### Ginkgo

Ginkgo *(Ginkgo biloba)*.

In an open, pilot study, Lister[124] reported significant improvements in the quality-of-life self-rating scores of 64% of individuals with clinically diagnosed fibromyalgia syndrome after administration of 200 mg coQ10 and 200 mg *Ginkgo biloba* extract daily for 84 days. Controlled clinical trials involving larger number of subjects with a placebo group are warranted to further investigate this potential therapeutic synergy and assess its clinical implications, particularly in treating individuals with mitochondrial dysfunction.

The 126 citations for this monograph, as well as additional reference literature, are located under Coenzyme Q10 on the CD at the back of the book.

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