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COENZYME Q-10: EFFICACY, SAFETY, AND USE

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OBJECTIVES

Upon completion of this article, participants should be able to do the following:

1. Comprehend the functions of CoQ-10 in mammalian metabolism.
2. Evaluate the preclinical and clinical literature on CoQ-10 supplementation that supports (or in some cases does not support) its therapeutic uses.
3. Apply this knowledge of potential therapeutic applications and health benefits of CoQ-10 supplementation to clinical practice.
4. Understand the dosage, formulation and safety issues related to the use of CoQ10 as a supplement.

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In 1957, Crane and coworkers isolated from mitochondrial lipids in bovine heart a compound they named "coenzyme Q," which they proposed was a mediator of electron transport within the cellular respiratory chain.[1] Subsequent structural determination revealed that the compound was identical to an earlier described quinone, named *ubiquinone* because of its widespread occurrence.[2]

In 1975, the International Union of Pure and Applied Chemistry and International Union of Biochemistry and Molecular Biology (IUPAC-IUB) Commission on Biochemical Nomenclature established this name as the "official" scientific designation for the compound, referring to its quinoid structure. This permitted easy reference to the partially reduced (ubisemiquinone) and fully reduced (ubiquinol) forms of the compound that reversibly interconvert via redox reactions. This property is key to ubiquinone's roles in electron and proton transport in mitochondrial respiration coupled to synthesis of adenosine triphosphate (ATP) and its use as a powerful lipophilic antioxidant.[2]

CHEMISTRY

More commonly known as CoQ-10, ubiquinone is widely distributed in nature, where it is biosynthesized de novo in animals (including humans), plants, and microbes. Additionally, several homologues of CoQ-10 are known from various organisms. The homologues differ from CoQ-10 in the length of the lipophilic isoprenoid side chain.[3] In birds, fish, and most mammals, only CoQ-10 itself is found. The major exception is a rodent that has the major CoQ-10 homologue called coenzyme Q-9 (the homologue of CoQ-10 containing 9 isoprene units) in addition to smaller amounts of CoQ-10. Rodent CoQ-10 biochemistry differs in that it also features shorter homologues of CoQ-10, including coenzyme Q-7 and coenzyme Q-8 in various tissues.[4]

CoQ-10 biosynthesis in mammals is characterized by the convergence of 2 metabolic pathways. The quinone moiety is derived from tyrosine or phenylalanine, which are converted over several steps to 4-hydroxy-benzoate. The isoprenoid side chain is biosynthesized from acetyl-Coenzyme A (acetyl-CoA) via

the mevalonate pathway, through which cholesterol is produced as well. Acetyl-CoA is converted via several enzymatic steps to farnesyl-pyrophosphate, the common precursor to both CoQ-10 and cholesterol. Farnesyl-pyrophosphate is then converted to decaprenyl-pyrophosphate (or solanesyl-pyrophosphate in rodents) and condenses with 4-hydroxy-benzoate, producing decaprenyl-4-hydroxy-benzoate, which results in CoQ-10 after several more biosynthetic steps.[2]

As noted previously, CoQ-10 is a fundamental redox component of the respiratory chain within inner mitochondrial membranes. All respiratory chain enzymes except cytochrome oxidase require CoQ-10 as a coenzyme.[3] As lipophilic, freely diffusible components of the mitochondrial membrane, both CoQ-10 and cytochrome-*c* mediate the electron transfer between complexes. This flow of electrons (from redox pairs with a more negative redox potential to pairs with a more positive redox potential) drives proton pumps that generate an electrochemical gradient (via the flow of protons from the mitochondrial matrix). The resulting "proton motive force" across the inner mitochondrial membrane is used to drive ATP synthase (complex V of the respiratory chain), whereby the protons are channeled back into the mitochondrial matrix where ATP, the "cellular currency of energy," is produced.[3]

THERAPEUTIC APPLICATIONS

In one study, CoQ-10 status was determined to be inadequate in 40% of women and 24% of healthy people more than 90 years of age.[5] An experimental study of aging in the rat has shown some decrease of mitochondrial CoQ-10 content in the heart, and even greater decrease in the liver and skeletal muscle. The authors reason that CoQ-10 administration may be beneficial in the elderly because of the aging body's increased demand for antioxidants.[6]

Mitochodrial CoQ-10 levels are influenced by numerous factors, including dietary fat and physical exercise. A study conducted by Mataix et al[7] suggests monounsaturated dietary fats increase CoQ-10 mitochondrial contents, whereas polyunsaturated fats decreased CoQ-10 levels. Another study found that the highest mitochondrial CoQ-10 content was found in a diet supplemented with corn oil.[8] A possible interpretation is that oil subjected to thermal treatment represents an oxidative insult, subsequently provoking a net decrease in endogenous CoQ.[7] Only in the polyunsaturated fat diet were CoQ-10 levels elevated in response to aerobic performance.[7]

New studies have shown that CoQ-10's unique biochemistry has diverse applications in all cellular membranes. One important function of CoQ-10 is in plasma membrane electron transport. CoQ-10 potentiates the activation of signaling protein kinases related to gene expression in cellular proliferation. In addition, CoQ-10 has recently been found to function as a co-antioxidant with tocopherol (within membranes) and ascorbate (both intracellularly and extracellularly, via CoQ-10's ability to maintain both of these compounds in their reduced states).[1]

The ubiquinol/ubiquinone ratio in plasma has been proposed as a marker of oxidative stress.[9] Oxidative stress has been defined as a disturbance in pro-oxidant/antioxidant balance, which is biased toward greater pro-oxidant activity. Pro-oxidant activity is alleged to be a factor in aging as well as in various pathological conditions. Patients who experience oxidative stress have more CoQ-10 than ubiquinol compared to healthy patients.[10] CoQ-10 levels reach their peak in most tissues by the time a person reaches the age of 20 and then fall slowly thereafter. This decrease in CoQ-10 content during aging is consistent with the "free-radical theory of aging," as demonstrated by the inverse correlation between longevity and peroxide-producing potential in mammalian tissues. Disorders observed during the process of aging may relate to the diminished capacity of an organism to maintain adequate ubiquinol levels in relation to the necessity for protection from oxidative insult.[2]

The role of the ubisemiquinone radical in respiratory chain redox cycling has raised the question of the possible role of this compound in the generation of oxygen radicals; that is, a pro-oxidant effect.[2] An increasing body of evidence, however, refutes the assumption that free-radical generation is an inevitable side effect of respiration.[11] Schnurr and colleagues have reported another type of pro-oxidant effect for CoQ-10 that involves 15-lipoxygenase in the biologically programmed degradation of mitochondria during the maturation of red blood cells.[11]

To date, the main application of CoQ-10 has been the treatment of cardiological disease, including congestive heart failure, hypertension, angina pectoris, and arrhythmias.[12,13] Doses were usually 100 mg/d,[13] and in some trials up to 240 mg/d.[12] Male patients with effort angina and ischemic heart disease have shown normal levels of CoQ-10 in muscles of the diaphragm, gastrocnemius, and vastus lateralis, but levels in intercostal muscles were lower compared to those of healthy individuals.[14] Levels of endogenous CoQ-10 and succinate-CoQ-10 oxidoreductase, key components of complex II of the mitochondrial respiratory chain, are reported to be depressed in myocardial tissue and blood samples of patients with cardiomyopathy and other cardiac diseases. The magnitude of these deficiencies is proportionate to the severity of disease, and decreasing levels of CoQ-10 are correlated with a decline in patient status.[13] Data on the effective treatment of cardiomyopathy with CoQ-10 suggest that a myocardial deficiency of CoQ-10 may be one cause of cardiac dysfunction.

PRECLINICAL STUDIES

Cardiovascular and Circulatory Functions

Hypertension. In stroke-prone, spontaneously hypertensive rats, CoQ-10 treatment attenuated the blood pressure elevation, the degradation of membrane phospholipids, and the enhanced phospholipase A_2 activity in the renal membrane. Researchers speculated that these effects were due to a renal membrane-stabilizing activity of CoQ-10.[15]

Ischemia-Reperfusion Injury. Several reports exist in the literature indicating a protective role of CoQ-10 against ischemia-reperfusion injury. A study was conducted in swine hearts to determine the mechanism of action by which CoQ-10 protects heart tissue. The results of the study demonstrated that pigs fed CoQ-10 (5 mg/kg/d) for 30 days fared significantly better: they had less

myocardial infarction and less creatine kinase release. The hearts of animals fed CoQ-10 had higher levels of CoQ-10, higher levels of the intracellular antioxidants ascorbate and thiol, and an increased amount of ubiquitin gene expression, all of which may contribute to the observed increased resistance to ischemic injury.[18] Results of of this study suggest that nutritional supplementation with CoQ-10 renders the heart resistant to ischemia-reperfusion injury, probably by reducing oxidative stress.

In addition to swine hearts, the effects of CoQ-10 on ischemia-reperfusion injury have also been studied in rat livers. Pentoxifylline (PTX) is a hemorrheologic drug that improves capillary blood flow by increasing erythrocyte flexibility and reducing blood viscosity. Portakal et al[19] have investigated whether the addition of CoQ-10 to PTX treatment affects the outcome of laboratory-induced ischemia-reperfusion injury. Whereas PTX treatment alone did not cause beneficial effect in the measured outcome variables, the combination of CoQ-10 and PTX pretreatment proved useful. This combination prevented glutathione depletion and curbed the elevation of malondialdehyde, catalase, and superoxide dismutase typically seen in ischemia-reperfusion injury.

Thrombosis, Hemostasis, and Embolism. In a randomized, placebo-controlled study in female pigs, Serebruany et al[20] found that CoQ-10 (100 mg twice a day for 20 days) decreased levels of eicosanoids and endothelin-1, a potent endothelium-derived vasoconstrictor. Abnormal hemostasis plays an important role in the pathogenesis of coronary artery disease, and free radicals have strong platelet proaggregatory properties. Dietary CoQ-10 supplementation was examined in experiments using swine (chosen for their hemostatic parameters, which are similar to those of humans). Serum levels more than doubled after 20 days of supplementation with 200 mg of oral CoQ-10. This was correlated with decreases in ADP-induced platelet aggregation, eicosanoid levels, and levels of endothelin-1. Researchers surmised that some of the reported clinical benefits with regard to cardiovascular morbidity and mortality of CoQ-10 supplementation may be due to improved hemostatic profile and a reduction in possible thrombotic and thromboembolic complications.

The effect of CoQ-10 was assessed on aortic lipoprotein lipid peroxidation and atherosclerosis in apolipoprotein-E −/− mice fed a high-fat diet. CoQ-10 treatment significantly decreased atherosclerotic lesions in the aortic root and descending aorta and decreased the absolute concentrations of hydroperoxides of cholesteryl esters and triacylglycerols.[21]

Rabbits fed a diet rich in trans fatty acids were supplemented with 3 mg/kg/d of CoQ-10 in a randomized, single-blind, controlled trial. Intervention with CoQ-10 was associated with changes indicative of decreased oxidative damage. The aortic and coronary artery plaque sizes and the atherosclerosis scores of each were significantly lower in the CoQ-10 group verses placebo. Aortic and coronary plaque frequencies, as well as frequencies of ulceration, thrombosis, or hemorrhage and cracks and fissures, were also significantly lower in the CoQ-10 group. These and other markers from the study suggest that CoQ-10 can have a beneficial effect on the chemical composition of atheroma.[22]

Metabolic and Nutritional Functions

Antioxidant Activity. CoQ-10 potentiates the antioxidant efficacy of vitamins E and C via its ability to recycle them from their oxidized states (ie, to reduce the oxidized forms of both). Vitamin E is recycled within membranes and low-density lipoproteins (LDL), and vitamin C from inside and outside the cell.[1,2]

Subarachnoid hemorrhage in humans can be complicated by the development of a delayed cerebral vasospasm (an arteriopathy), which can result in ischemic brain damage and permanent neurological deficits.[23] Putative causal mechanisms for this kind of vasospasm include immunologically mediated inflammatory changes as well as epithelial damage to cerebral arteries via hemoglobin-generated free-radical peroxidation of membrane lipids. Researchers also have noted similarities between atherosclerosis and arteriopathy that occurs after subarachnoid hemorrhage, suggesting a common mechanism involving free-radical-induced peroxidation of low-density lipoprotein (LDL). A rabbit model of subarachnoid hemorrhage uses carotid artery ligation, followed at 2 weeks by injection of autologous blood into the subarachnoid space. Using this system, Grieb et al[24] treated rabbits with oral CoQ-10 (10 mg/kg/d) or inactive fluid. A third of the untreated group died before the end of the experiment, and all surviving rabbits showed moderate to severe neurological deficits. All untreated animals had widespread brain lesions associated with disappearance of neurons and loss of myelin. All CoQ-10-treated animals survived, no brain lesions could be found, and no neurological deficits could be observed. The researchers surmised that the central nervous system damage in this model was due to free radicals generated from autooxidation of hemoglobin in the autologous blood injection, rather than the initial ligation, and that the resulting peroxidized plasma LDL was the ultimate mediator of the brain damage. Grieb et al[24] inferred that the affinity of CoQ-10 for LDL and its antioxidant activity were responsible for the observed positive effects in this model.

CoQ-10 has been shown to occur throughout all mammalian cells, where it likely has a membrane-stabilizing function in addition to its redox and antioxidant activities.[4] CoQ-10 is discharged to a limited extent into the blood, where it is bound to serum lipoproteins.[2]

CoQ-10 inhibits initiation and propagation of lipid peroxidation as well as oxidation of proteins and DNA.[2] The antioxidant efficacy of CoQ-10 is due to its access to the proton motive cycle within the mitochondrial respiratory chain. After quenching a free radical, CoQ-10 may be recycled within plasma membranes and cytosol by quinone reductases.[2,25,26]

Unlike cholesterol, endogenous CoQ-10 is not distributed among different tissues via circulation.[2] In the tissues of humans and other mammals, a portion of the endogenous CoQ-10 (ubiquinone) is found as ubiquinol, the reduced form in which it is active as an antioxidant. The ratio of reduced to oxidized species varies from one tissue type to another. In humans it can range from as low as ~25% in lung and brain to 95% to 100% in intestine, liver, and pancreas.[2] Quinone reductases have been identified in cytosol and plasma membranes, which function to maintain CoQ-10 in the reduced state.[25,26]

Studies in rats with altered oxidative metabolism (eg, low-temperature acclimation or thyroid hormone treatment) revealed changes in CoQ-10 levels in highly aerobic tissues that paralleled the increases in metabolic rate and resultant free-radical production. The increase in CoQ-10 levels following thyroid hormone treatment paralleled the increase in metabolic rate, suggesting that the increase was an adaptation to the oxidative rate increase rather than the cause of it.[2]

Pharmacokinetics. CoQ-10 pharmacokinetics were investigated in rat tissues after oral treatment. CoQ-10 passed quickly from plasma into tissues such as the liver, which showed maximal CoQ-10 concentrations. The results indicated that oral treatment makes it possible to obtain good tissue levels of CoQ-10 that might be of clinical value against endogenous CoQ-10 insufficiencies due either to pathological alterations or to drug administration.[27] More recently, researchers reported that a 2-month treatment with orally administered CoQ-10 increases cerebral cortex concentrations in rats by 30%.[28,29]

Kommuru et al[30] examined the bioavailability of a commercially marketed CoQ-10 oil-based formulation and powder-filled capsule products in beagle dogs in an open, randomized, multiple-dose crossover design study. The oral absorption of both formulations proved slow and poor, and while not significantly different in terms of pharmacokinetic parameters, the results were in agreement with bioavailability studies in humans that showed a lack of significant difference between oil-based and granular (soft gelatin and tablet, respectively) forms of CoQ-10. In shelf-life tests, most degradation of CoQ-10 occurred at temperatures of 45°C and 55°C (113°F and 131°F). Stability was improved more by the addition of EDTA (.1%) and ascorbic acid (5%) than by the addition of propyl gallate (PG), butylated hydroxy anisole (BHA), or butylated hydroxy toluene (BHT). Kommuru et al noted that when BHA concentrations were increased by 400% or PG concentrations by 300%, degradation of CoQ-10 accelerated. They added that CoQ-10 appears yellow upon exposure to light and turns a dark yellow as it decomposes. Preparations of CoQ-10 in solution are more prone to degradation in light than are solid preparations. Shelf life at room temperature was 6.3 years, based on time to reach 90% potency, and no degradation occurred at 37°C (98.6°F) for a period of 12 months. Preliminary (unpublished) studies by Kommura and colleagues indicate that some commercial CoQ-10 products lack a stable shelf life. In conclusion, they suggest that stable formulations of the supplement may be possible by formulating with EDTA (.1%) and ascorbic acid (5%).

Protection from Adriamycin-induced Cardiotoxicity. Doxorubicin (adriamycin), an anthracycline type of antimalignant tumor agent, is widely used in chemotherapy regimes, but the severity of side effects, such as cardiotoxicity and suppression of bone marrow functions, limits its clinical use. The mechanism of adriamycin (ADM)-induced toxicity may be mediated by microsomal lipid peroxidation resulting from cell membrane damage.[31] CoQ-10 may stabilize the heart microsomal membrane lipid or may improve the myocardiac mitochondrial functions under such insult.[32]

When CoQ-10 was given to rats in conjunction with ADM treatment, no significant change in mitochondrial electron transport chain was observed in cardiac cells. Without CoQ-10, significant decreases were noted in complex I activity of the transport chain.[33] Other research suggests that the beneficial effect of CoQ-10 against ADM-induced cardiotoxicity appears not to be the result of its role in the respiratory chain, but a consequence of its antioxidant action.[34]

Neurological, Psychological, and Behavioral Functions

Neurotoxicity and Neuroprotection. Matthews et al[29] reported neuroprotective effects from CoQ-10 powder in studies with 12- and 24-month-old male rats given a high dose (200 mg/kg/d orally for 2 months) as part of their normal diet. The 12-month-old rats experienced an increase in cerebral cortex levels of CoQ-10 of about 30%, levels usually found in animals 2 to 3 months old. Cerebral cortex mitochondrial levels of CoQ-10 also showed a significant increase after 60 days, compared to controls. An increase in CoQ-10 levels of about 8% in the 24-month-old rats after 1 month of the diet was also significant ($P<.05$). Rats that received the same diet for 1 week before receiving 3-nitropropionic acid–induced striatial lesions (resembling those of Huntington's) disease developed lesions significantly reduced in size compared to controls ($P<.001$). Using a transgenic model of familial amyotrophic lateral sclerosis in transgenic mice (of the G1 line) that express high levels of human superoxide dismutase, the same diet resulted in a significant increase in animal survival ($P<.05$) compared to controls on the same diet without CoQ-10 supplementation. Similar effects were not found with vitamin E supplementation, though vitamin E does reduce disease onset in these mice. Matthews et al concluded that CoQ-10 might be a useful adjunct in treating Huntington's disease and other neurodegenerative diseases.

The symptoms of Huntington's disease might arise from glutamate-mediated excitotoxicity and abnormalities in mitochondrial energy production. Using a mouse model, Shilling et al[35] determined that supplementation with a combination of CoQ-10 and remacemide hydrochloride produced a transient improvement in motor performance 3 weeks after therapy was initiated. The combination therapy was ineffective at prolonging survival time in this study.[35]

CLINICAL STUDIES

Cardiovascular and Circulatory Disorders

Cardiotonics and Cardioprotection. From a meta-analysis of the main placebo-controlled clinical trials on CoQ-10 (1986-1995), Soja and Mortensen[36] concluded that scores for various parameters of cardiac function were significantly better for patients treated with CoQ-10 than for patients given placebo. An average 73% of patients treated with CoQ-10 displayed improved cardiac output ($P<.05$), 76% ($P<.005$) had increased stroke volume, cardiac index was improved in 87% ($P<.001$), diastolic index in 88% ($P<.001$), and ejection fraction in 92% ($P<.001$).

Watson et al[37] reported no significant benefit from CoQ-10 in 30 men with congestive heart failure (aged 44 to 66 years)

diagnosed with chronic left-ventricular dysfunction (echocardiography less than 35%) secondary to idiopathic or ischemic dilated cardiomyopathy. The randomized, double-blind, placebo-controlled, crossover trial found no difference of any significance after treatment with CoQ-10 compared to placebo in functional capacity, well-being (quality of life according to the Minnesota Living With Heart Failure questionnaire), cardiac volumes, or left-ventricular ejection fraction; nor were changes of any significance evident in the hemodynamic data. Watson et al noted that both the dosage and duration of the therapy (33 mg orally 3 times daily for 3 months) were comparable to those used in other trials of CoQ-10. The patients had a history of chronic heart failure of 6 months to 6.25 years, left-ventricular dysfunction for 3 months or more, and were clinically stable on angiotensin-converting enzyme inhibitor. Daily medications taken concurrently with CoQ-10 during the trial by the vast majority of patients consisted of digoxin, nitrates and hydralazines, and frusemide. Watson et al commented that resting left ventricular ejection fraction did not improve under therapy with CoQ-10. However, no adverse events occurred, no altered hematologic parameters or deleterious changes in renal or hepatic function were found, and the patients achieved plasma levels of CoQ-10 of about double their baseline readings.

Singh and Niaz[38] examined the effect of CoQ-10 (Hydrosoluble Q-gel; Tishcon Corp, Westbury, NY) on serum alpha-lipoprotein in a randomized, double-blind, placebo-controlled trial in 35 patients diagnosed with acute coronary artery disease and a moderate elevation of alpha-lipoprotein. Alpha-lipoprotein is associated with both the occurrence and recurrence of cardiac death and myocardial infarction. The placebo group received a vitamin B-complex while the CoQ-10 group received a dose of 120 mg twice daily for the same 28 days. The results showed that, compared to placebo, there was a significant increase in the CoQ-10 group in levels of high-density lipoprotein (HDL) cholesterol and significant decreases in fasting blood glucose, malondialdehyde (MDA), diene conjugates, lipid peroxides, and especially alpha-lipoprotein ($P<.001$), which dropped by 31.0%, versus 8.2% in the placebo group. LDL and total cholesterol showed no change. Adverse events, mostly nausea (36%), vomiting (24%), and hypotension in the first week of therapy (24%), occurred in 30 subjects in the CoQ-10 group, compared to 13 subjects in the placebo group, and were assessed as mild.[38]

Taggart and colleagues[39] studied the effects of short-term supplementation of CoQ-10 on myocardial protection during cardioplegia in a double-blind, placebo-controlled study of patients having well-preserved ventricular function. The CoQ-10 treatment group received 2 oral doses of 300 mg, the first on the evening before and the second on the morning of the cardiopulmonary bypass operation. These researchers found no difference between treated and untreated groups with regard to biochemical markers of cardiac injury, and no cases of low cardiac output requiring inotropic support; however, preoperative blood tests revealed no difference in plasma CoQ-10 levels between treated and untreated groups. These researchers suggested that this was due to rapid uptake of exogenous CoQ-10 into plasma lipoproteins and subsequent concentration in liver, myocardium, and other sites, and that longer treatment durations led to a greater steady-state concentration of CoQ-10 in plasma. They also noted that their patient groups had relatively well-preserved ventricular function and short ischemic times. Taggart and colleagues concluded that patients whose myocardial function was the most impaired, with clear evidence of a deficiency in endogenous CoQ-10 such as those in heart failure or undergoing valve replacement, would benefit most from CoQ-10 supplementation.[39]

Hofman-Bang et al[40] examined the effect of CoQ-10 in a double-blind, crossover, placebo-controlled study in which the treatment was an adjunct to conventional therapy. Patients were all diagnosed with stable chronic congestive heart failure. Thirteen of the patients were diagnosed at class II on the New York Heart Association (NYHA) functional scale, 60 at class III, and 6 at class IV. The vast majority were receiving treatments with diuretics, digitalis, and angiotensin-converting enzyme inhibitors. Hofman-Bang and colleagues reported that in their 3-month trial, compared to placebo, 100 mg/d of CoQ-10 (Pharmacia, Stockholm, Sweden) produced no significant differences in measurements of the ejection fraction, the primary endpoint of their study. However, CoQ-10 produced a significant increase ($P<.05$) in ejection fraction during the volume-load test with legs up, as well as significant improvement ($P<.05$) in maximum exercise tolerance. Also significant ($P<.05$) was the decrease in the end-of-exercise score for leg fatigue and dyspnea, and the difference in the quality-of-life questionnaire total score versus placebo ($P<.05$), in which life satisfaction and physical activity scores were significantly higher than those in the placebo group. No significant changes were found in blood specimens, and no patients were changed from their initial NYHA classification. An insignificant difference was found in the number of patients in each phase of the study who reported side effects, none of which could reasonably be ascribed to CoQ-10. The authors concluded that, though the changes were significant in quality of life and exercise capacity, these were still only slight improvements, and the clinical importance of these differences remained unclear.[40]

Langsjoen et al[41] recorded the clinical outcomes of 424 cardiovascular disease patients who received CoQ-10 as an adjuvant therapy over a period of 8 years. Doses averaged 242 mg/d (75 to 600 mg/d), and in many cases the goal was to reach a whole-blood level of ≥2.0 mg/mL. An average whole-blood level of 2.92 mg/mL was achieved in 297 subjects. Regardless of the different categories of patients, clinical responses were evaluated according to the NYHA functional scale. Compared to baseline readings, significant improvements were recorded in the majority in fatigue, chest pain, palpitations, and dyspnea, along with improvements in the NYHA functional scale according to classes of function; 247 subjects improved by 1 class; 120 subjects improved by 2 classes. The authors point out that, apart from 1 subject reporting transient nausea, there were no side effects from CoQ-10, and improvements were gradual and sustained.[42] It is interesting to note that these researchers found that over time, absorption of CoQ-10 commercial products

could be enhanced by chewing and swallowing a fat-containing food; for example, peanut butter.

Cardioplegia is the process by which cardiac function is temporarily arrested via hypothermia, medication, or electrical stimuli to reduce myocardial oxygen demand during cardiopulmonary bypass. Chen et al[43] reported that a double-blind trial of the effectiveness of oral CoQ-10 pretreatment (150 to 200 mg/d for 5 to 7 days, 1000 mg total) on myocardial preservation during cardioplegia revealed the following:

- Treated patients displayed better preservation of myocardial function, as demonstrated by a slightly decreased incidence of low cardiac output and wider pulse pressure.
- Treated patients' right and left ventricular myocardial structure was better preserved.
- No demonstrable benefit could be found regarding preservation of atrial myocardium.

Chen and coworkers noted that in both groups, atrial function was less well preserved because of the following:

- Topical cooling of the atrium was less effective because of its position during cardioplegia (maintenance of profound hypothermia is paramount in protecting myocardial tissue).
- Noncoronary collateral blood flow caused early washout of the cardioplegia solution.
- Cardioplegic solution was delivered differentially; all atrial regions received approximately half as much solution per gram of tissue as did the ventricles.

Chen et al[43] concluded that CoQ-10 helps preserve ventricular myocardial function during cardioplegic arrest, most likely via its effects on cellular energetics, membrane stability, and myocardial oxidative load.

Permanetter and colleagues[44] conducted a placebo-controlled, double-blind, crossover study with CoQ-10 (33.3 mg given orally 3 times/day) in 25 chronic heart failure patients (aged 31 to 71 years) diagnosed with dilated cardiomyopathy. Four patients were symptom free at NYHA class I, 7 were at class II, and 15 were at class III. The 2 groups of patients were well-balanced except that 15 patients in group 2 were taking digitalis, compared to 8 patients in group 1. CoQ-10 was suspended in soya oil and provided in capsules (Zyma GmbH; Munich, Germany). The other accompanying medications were diuretics, nifedipine, and nitrates. Results showed that while only 1 patient had to be excluded because of the need for a heart transplant, there were no significant differences between placebo and CoQ-10 in any measurements, either in the cardiothoracic ratio, maximum exercise capacity, exercise tolerance, echocardiography of the left ventricle, left ventricle ejection time, stroke volume index, or cardiac index. No side effects could be ascribed to CoQ-10, and function tests of liver and kidneys, blood count, and serum levels of electrolytes showed nothing out of the ordinary. The authors commented that 1 reason for the equivalent results might have been that other trials involved patients in worse condition than theirs.[44]

Judy et al[45] recorded improved long-term survival for patients with NYHA class IV congestive heart failure who were treated with CoQ-10, when compared with a conventionally treated control group. Congestive heart-failure patients on CoQ-10 were also found to relapse when taken off this treatment. Judy et al studied the short-term effect of CoQ-10 (100 mg/d for 90 days) in 14 NYHA class IV patients, aged 52 to 76 years, who had been diagnosed with cardiac failure. The randomized, double-blind, placebo-controlled, crossover study found that patient response to CoQ-10 varied, with some patients showing improvements in cardiac function after 30 to 45 days and others showing improvements after 60 to 90 days. CoQ-10 treatment for 90 days resulted in patients' cardiac index attaining normal levels; however, left ventricular end diastolic volume index and ejection fraction showed no normalization, nor was there improvement after a year of treatment with CoQ-10 in these patients. Judy et al concluded that their results supported previous findings with CoQ-10 in congestive heart failure, adding that if CoQ-10 treatment is stopped, a gradual decrease in cardiac function ensues at variable rates from 1 patient to the next. Patients who showed declining cardiac function during the placebo phase showed improvement when they were treated again with CoQ-10 after 180 days.

Poggesi and colleagues[46] conducted a double-blind, placebo-controlled, crossover study of the effects of CoQ-10 (100 mg/d orally for 60 days) in patients with dilative cardiomyopathy. Significant improvement in left ventricular systolic function was noted following CoQ-10 treatment. After a 30-day washout period, effects returned to baseline levels, indicating that functional improvement was linked to drug administration and, therefore, to serum and myocardial levels of CoQ-10. Since the improved function was seen in both ischemic and idiopathic cardiomyopathies, the therapeutic efficacy of CoQ-10 was independent of coronary blood flow. These researchers concluded that oral CoQ-10 is a safe and effective treatment for dilative cardiomyopathies of different etiology and that this efficacy may be due to CoQ-10's supportive and enhancing effect on myocardial tissue energetics.[46]

Serra et al[47] reported beneficial results from CoQ-10 (60 mg/d orally for 28 days) added to "usual treatment" in a randomized, double-blind, crossover, placebo-controlled study of 20 chronic ischemic heart disease outpatients (aged 44 to 70 years, with 15 in NYHA class II and 5 in class III) diagnosed with symptoms of stable-effort angina, sinus rhythm, and mild or moderate heart failure. The condition of 13 of the patients resulted from chronic artery disease; the condition of the remainder was from left ventricular hypertrophy resulting from left ventricular hypertension. Study results showed that, compared to placebo, CoQ-10 produced a significant improvement in heart failure scores, cardiothoracic ratio, number of angina attacks per week, stroke volume, cardiac output, exercise duration (26 minutes versus 3 minutes for placebo, $P < .01$) and endpoint, workload, and a significant reduction in the number of nitrate tablets consumed per week ($P < .01$). At the end of the treatment period, 4 of the 5 patients in NYHA class III were diagnosed class II, and 4 of the 15 NYHA class II patients improved to NYHA class I. Side effects from CoQ-10 were insignificant, with 3 patients reporting slight gastralgia.[47]

A double-blind, double-crossover, placebo-controlled trial involving 19 patients with chronic, stable, moderately advanced myocardial disease found that treatment with oral CoQ-10 (33 mg