Advances in Heart Failure

Coenzyme Q10 and Heart Failure
A State-of-the-Art Review

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Abstract—Heart failure (HF) with either preserved or reduced ejection fraction is associated with increased morbidity and mortality. Evidence-based therapies are often limited by tolerability, hypotension, electrolyte disturbances, and renal dysfunction. Coenzyme Q10 (CoQ10) may represent a safe therapeutic option for patients with HF. CoQ10 is a highly lipophilic molecule with a chemical structure similar to vitamin K. Although being a common component of cellular membranes, CoQ10's most prominent role is to facilitate the production of adenosine triphosphate in the mitochondria by participating in redox reactions within the electron transport chain. Numerous trials during the past 30 years examining CoQ10 in patients with HF have been limited by small numbers and lack of contemporary HF therapies. The recent publication of the Q-SYMBIO randomized controlled trial demonstrated a reduction in major adverse cardiovascular events with CoQ10 supplementation in a contemporary HF population. Although having limitations, this study has renewed interest in evaluating CoQ10 supplementation in patients with HF. Current literature suggests that CoQ10 is relatively safe with few drug interactions and side effects. Furthermore, it is already widely available as an over-the-counter supplement. These findings warrant future adequately powered randomized controlled trials of CoQ10 supplementation in patients with HF. This state-of-the-art review summarizes the literature about the mechanisms, clinical data, and safety profile of CoQ10 supplementation in patients with HF. (***Circ Heart Fail***. 2016;9:e002639. DOI: 10.1161/CIRCHEARTFAILURE.115.002639.)

Key Words: coenzyme Q10 ■ drug interactions ■ electrolytes ■ heart failure ■ hypotension

Despite numerous evidence-based medical and device therapies for patient with heart failure (HF) and reduced ejection fraction (HFrEF), the outcomes of these patients remain poor. HF is an energy-depleted state associated with low myocardial adenosine triphosphate (ATP) production, mitochondria dysfunction, abnormal calcium handling, increased reactive oxygen species generation, and endothelial dysfunction. Many of the disease modifying therapies in chronic HF act by modulation of maladaptive neurohormonal pathways, such as the renin–angiotensin–aldosterone axis. Such therapies are limited by side effects, including hypotension leading to calls for new drugs with hemodynamically neutral profiles.[1] Coenzyme Q10 (CoQ10) may represent a therapeutic option to treat individuals with HF. Preclinical data suggest that CoQ10 has a critical role in ATP production, a potent anti-inflammatory agent, and may improve endothelial function. Lower CoQ10 levels are seen in patients with advanced HF symptoms and with lower ejection fractions. A recent randomized controlled trial has suggested that there may be a mortality benefit in patients with HFrEF with CoQ10 supplementation. Furthermore, there does not seem to be an adverse hemodynamic profile or safety concern about CoQ10 use.[2] This review summarizes the literature about the mechanisms, clinical data, and safety profile of CoQ10 supplementation in HF.

Mitochondria, Energy, and HF
Patients with chronic HF typically have a relapsing and remitting disease course, with periods of decompensation causing worsening symptoms, such as dyspnea and peripheral edema, resulting in increases in therapy or hospitalization.[3] Furthermore, despite drug therapies that can reduce morbidity and mortality, the management of chronic symptoms such as fatigue and exercise intolerance remains challenging. One novel therapeutic avenue is to modulate cardiac energetics. Regardless of cause, it has been hypothesized that the failing heart is energy starved.[4,5] HF is associated with abnormal calcium handling,[6] ATP depletion,[4] and mitochondria dysfunction[7] within cardiomyocytes leading to a perturbation of the cardiac metabolic pathways.[6] These alterations result in energy depletion and negatively affects on cardiac contractile function.[6] Therapies that can prevent cardiac energy depletion may play a role in the treatment and management of HF.

Physiological Role of Coenzyme Q10:

Coenzyme Q10 (CoQ10) or ubiquinone can potentially enhance cardiac function through a variety of mechanisms (Figure 1). CoQ10 is highly lipophilic molecule composed of a 1,4-benzoquinone. The Q refers to the quinone chemical groups and the 10 refers to the number of isoprenyl chemical subunits in its tail. CoQ10 belongs to a group of compounds that are characterized by their quinone moieties in addition to the length and composition of their hydrophobic tails. Although being a common component of most cellular membranes, CoQ10's most prominent role is to facilitate the production of ATP by participating in redox reactions within the electron transport chain in the mitochondria.[8] Within the electron transport chain, CoQ10 accepts electrons from complexes I and II and transports them to complex III. At this point, it is ready to be reduced by complexes I and II again (Figure 2).

In addition to its critical role as a component of the electron transport chain, CoQ10 is a potent antioxidant.[10] CoQ10 has been shown to inhibit the peroxidation of cell membrane lipids and reduces the oxidation of circulating lipolipids.[11–13] In vitro analysis demonstrated that supplementation with CoQ10 inhibited low-density lipoprotein oxidation to a significantly greater degree compared with other natural antioxidants, such as β-carotene or α-tocopherol.[12] In apolipoprotein E–deficient mice fed with a high-fat diet, CoQ10 supplementation decreased the concentration of lipid hydroperoxides in atherosclerotic lesions and minimized the size of atherosclerotic lesions in the aorta.[14]

In addition to its antioxidant activity, CoQ10 also seems to improve endothelial function. In vitro analyses on human umbilical vein endothelial cells demonstrated that CoQ10 supplementation reduced oxidized low-density lipoprotein–induced endothelin-1 (a known potent vasoconstrictor) secretion.[15] Furthermore, CoQ10 supplementation increased nitric oxide bioavailability and decreased cytochrome c (required for activation of proapototic proteins) secretion.[15]

Preclinical Data With CoQ10 in HF

Preclinical data has provided information across a variety of models that support the pathophysiological role of CoQ10 depletion in HF and other cardiovascular diseases and the concept of improved outcomes with CoQ10 supplementation.[16]

Zebrafish models have identified UBIAD1 (which is conserved across multiple species including humans) as a nonmitochondrial CoQ10-forming enzyme. Loss of UBIAD1 results in a depletion of cytosolic CoQ10 and mutations in the *ubiad1* gene results in cardiovascular failure because of oxidative stress and reactive oxygen species-mediated cellular damage. Furthermore, UBIAD1 and nonmitochondrial CoQ10 play a critical role in NO signaling. These provide evidence of the cardiovascular protective effects of CoQ10 against oxidative stress and reactive oxygen species-mediated cellular damage.[17]

In isoproterenol-induced HF model in dogs, CoQ10 levels were significantly reduced, whereas supplementation in rat models of isoproterenol-induced HF improved left ventricular function.[18] Transgenic diabetic mice created to exaggerate diabetic cardiomyopathy through inhibition of phosphoinositide 3-kinase p110a signaling demonstrated attenuated LV diastolic dysfunction, cardiomyocyte hypertrophy and fibrosis, atrial natriutretic peptide with CoQ10 supplementation.[19]

Measurement of CoQ10 Levels

The hydrophobicity of CoQ10 and the rapid rate of oxidation make measurement of CoQ10 challenging. Furthermore, lack of commercially available internal standards remain a major issue as other naturally occurring ubiquinones and vitamins (such CoQ9[20] or vitamin K) are used as internal standards for CoQ10 measurements. Extraction of serum is traditionally conducted using hexane or hexane with methanol; however, recent reports have used 1-Propanol.[20] Measurement of total CoQ10 represents the sum of the reduced form (Ubiquinol-10) and the oxidized form (Ubiqinone-10). In human plasma, CoQ10 is predominantly found in the ubiquinol-10 (reduced) form.[21] Ubiquinol-10 can be oxidized into ubiqinone-10 at room temperature so blood samples should be collected in heparinated tubes and immediately placed on ice. Subsequently, the sample should be centrifuged to extract the plasma which should be stored at −80° (to prevent oxidation of ubiquinol-10 to ubiquinone-10) until the sample is ready to be measured. CoQ10 level measurement in most publications have used reverse-phase high performance liquid chromatography with electrochemical detection.[20,22] Reference levels for CoQ10 in serum have demonstrated a range of values (Table 1). Because CoQ10 is known to bind
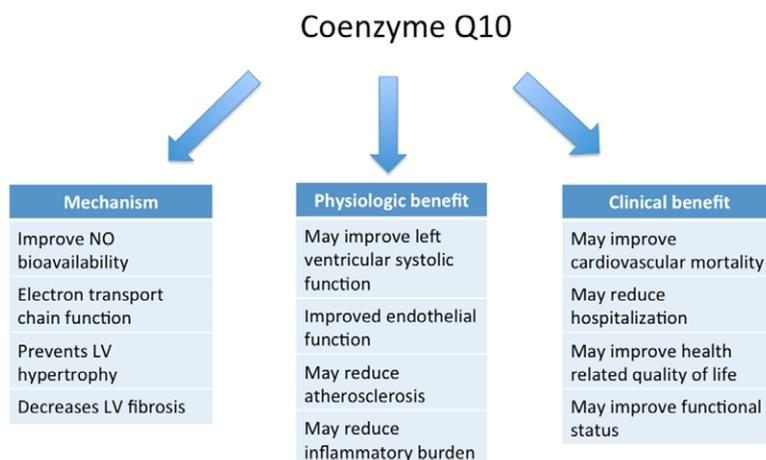
Figure 1. Summary of potential mechanistic, physiological, and clinical benefits of Coenzyme Q10. LV indicates left ventricle; and NO, nitrous oxide.
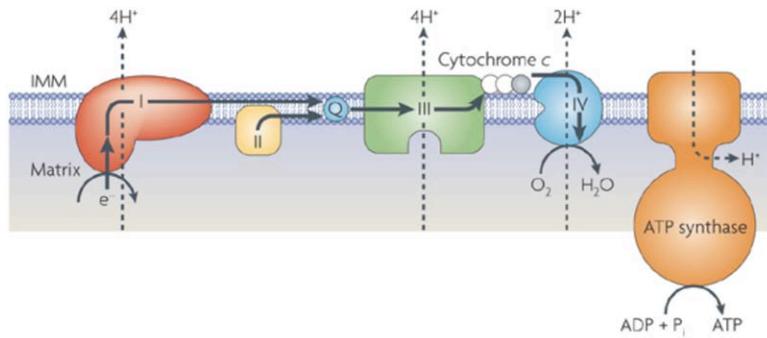
Figure 2. Role of coenzyme Q10 (CoQ10) in the electron transport chain. CoQ10 plays a critical role in ATP generation by accepting electrons from complexes I and II and transporting them to complex III. At this point, it is ready to be reduced by complexes I and II again. The electron transportation allows hydrogen ions (H+) to be pumped across the inner mitochondrial membrane (IMM), which finally drives the synthesis of ATP via ATP synthase. Reprinted from Ow et al[9] with permission of the publisher. Copyright © 2008, Macmillan Publishers Ltd.

to lipoproteins, CoQ10 levels maybe indexed to LDL or total cholesterol (Table 1).

CoQ10 Levels in HF

Lower CoQ10 levels are associated with increasing severity of HF symptoms. In 43 patients with heterogenous causes of cardiomyopathy, endomyocardial biopsies demonstrated significant differences in CoQ10 depending on New York Heart Association (NYHA) class: patients with NYHA class I and II (0.4±0.06 µg/mg and 0.34±0.6 µg/mg), respectively, had significantly higher myocardial CoQ10 levels than patients with NYHA class III and IV (0.28±0.05 µg/mg and 0.28±0.06 µg/mg, respectively; $P<0.001$).[28] Supplementation with CoQ10 resulted in significant increases in both myocardial and serum CoQ10 levels.[28] The association between CoQ10 and HF symptoms have been seen in other populations.[29,30] A total of 1191 patients from the Controlled Rosuvastatin Multinational Study in HF (CORONA) trial demonstrated that those in the lowest tertile of CoQ10 had significantly lower left ventricular ejection fractions (LVEFs) and higher N-terminal prohormone of brain natriuretic peptide levels.[30]

Despite the association of worse HF-related clinical status with lower CoQ10 levels, the prognostic use of CoQ10 is controversial. In 236 patients with HF hospitalizations, elevated CoQ10 levels (independent of risk factors such as N-terminal prohormone of brain natriuretic peptide), conferred an increased risk of mortality (hazard ratio, 2.0; 95% confidence interval [CI], 91.2–3.3).[29] However, there was no association between CoQ10 and mortality or other outcomes in the CORONA trial (n=1191).[30] Rosuvastatin did reduce CoQ10 levels but there was no interaction between CoQ10 and rosuvastatin use for any outcome.[30] These results suggest that CoQ10 levels do not have prognostic use but may indicate severity of disease.

Clinical Data on CoQ10 Supplementation in HF

There have been a large number of trials examining the effect of CoQ10 in HF conducted during the past 30 years. To date, these trials have predominantly evaluated patients with HFrEF. Despite pathophysiological rationale,[31] there are no trials evaluating CoQ10 in patients with HF with preserved ejection fraction (HFpEF). There is 1 trial evaluating CoQ10 in patients with hypertrophic cardiomyopathy and diastolic dysfunction.[32] Modest sample size with few events, heterogenous populations and outcomes, varying trial design, duration of follow-up, varying doses of CoQ10, and lack use of contemporary HF

drugs contribute to the difficulty in evaluating these trials. The most contemporary trials are highlighted in Table 2.

There are 2 meta-analyses that have examined data ≤2012[41] and 2013.[2] Fotino et al[41] using pooled data from 13 trials and 395 patients demonstrated an improvement in LVEF of 3.67% (95% CI, 1.6%–5.74%) in those receiving CoQ10 versus placebo. The majority of benefit of LVEF improvement was in trials published before 1993 (7/13). Madmani et al[2] using 7 studies and data from 914 patients did not show any significant improvement in LVEF or exercise capacity. Given the significant heterogeneity of the data, it was not possible to make any significant conclusions on any other clinically relevant outcomes.

The largest randomized trial to date (completed in 1993 and enrolled 641 patients) demonstrated that compared with placebo, CoQ10 reduced the risk of HF hospitalization (73 versus 118, $P<0.001$) and complication of HF, such as pulmonary edema and cardiac asthma (20 versus 51 and 97 versus 198, $P<0.001$). Lack of contemporary cardiovascular drugs and devices, and use of more subjective outcomes (such as hospitalizations and symptoms) limit the strength of these findings.[33] The most contemporary trial (Q-SYMBIO [Coenzyme Q10 as Adjunctive Treatment of Chronic Heart Failure: A Randomised, Double-blind, Multicentre Trial With Focus on Symptoms, Biomarker Status]; completed 2014 and enrolled 420 patients[40]) demonstrated that compared with placebo, CoQ10 at 100 mg orally 3× a day reduced the primary 2-year end point of cardiovascular death, hospital stays for HF, or mechanical support or cardiac transplant (30 versus 57, $P=0.005$; hazard ratio, 0.5; 95% CI, 0.32–0.80), death from cardiovascular causes (18 versus 34, $P=0.039$; hazard ratio, 0.51; CI, 0.28–0.92), and all-cause mortality (21 versus 39, $P=0.036$; hazard ratio, 0.51 95% CI; 0.30–0.89).

Table 1.   CoQ10 Levels in Healthy Populations

Study	Reference, Mean±SD (µmol/L)	Indexed to LDL (µmol/mmol)	Index to Total Cholesterol (µmol/mmol)
Niklowitz et al[23] (n=10)	1.11±0.24	N/A	N/A
Sohmiya et al[24] (n=29)	0.75±0.22*	N/A	0.16±0.05
Miles et al[25] (n=106)	1.04±0.33	0.33±0.1	0.20±0.05
Duncan et al[26] (n=24)	0.675±0.315	N/A	N/A
Niklowitz et al[27] (n=14)	1.02±0.3	N/A	0.24±0.07

CoQ10 indicates Coenzyme Q10; and LDL, low-density lipoprotein.
*units in µmol.

Table 2.   Summary of Contemporary Clinical Trials of CoQ10 Supplementation in Heart Failure

Trial	Population	Design	CoQ10 Dose and Duration	Results
Morisco et al[33]	641 patients with HFrEF (mixed pathogeneses) NYHA III or IV heart failure	Double-blind placebo-controlled trial	CoQ10 50 mg orally 2× or 3× a day versus placebo for 1 y	Decreased admission for heart failure in CoQ10 group (n=73) vs placebo (n=118; $P<0.001$). Decreased episodes of pulmonary edema in CoQ10 group (n=20) vs placebo (n=51; $P<0.001$). Decreased episodes of cardiac asthma in CoQ10 group (n=97) versus placebo (n=198; $P<0.001$)
Munkholm et al[34]	22 patients with ischemic or dilated cardiomyopathy, NYHA II or III	Double-blind placebo-controlled randomized trial	CoQ10 100 mg orally twice a day versus placebo for year.	Improvement in stroke index from baseline to 12 wk in CoQ10 group: 31.28±3.43–36.2±2.72 mL/stroke per m² ($P<0.005$). No change seen in placebo group. Reduction in pulmonary capillary wedge pressure from baseline to 12 wk in CoQ10 group: 40±16–32±15 mm Hg ($P<0.02$). No change in PCWP seen in placebo group. Improvement in mean pulmonary artery pressure from baseline to 12 wk in CoQ10 group: 27±10 to 21±7 mm Hg ($P=0.02$). No change seen in placebo. No change in echocardiographic parameters in COQ10 or placebo group
Khatta et al[35]	55 patients with HFrEF (mixed pathogeneses), NYHA III or IV CHF symptoms	Randomized, double-blind placebo-controlled trial	CoQ10 200 mg orally daily versus placebo for 6 mo	No improvement in ejection fraction, peak oxygen consumption, or exercise duration
Keogh et al[36]	39 patients with HFrEF (mixed pathogeneses) and class II or III heart failure	Randomized, double-blind placebo-controlled trial	CoQ10 50 mg PO 3× a day versus placebo for 3 mo	Improvement in NYHA score in CoQ10 group between baseline and end of study (2.9±0.06 to 2.4±0.12, $P=0.001$). No change in placebo group NYHA score. Between group $P=0.01$. No difference in CoQ10 group versus placebo in Canadian-specific activity scale score ($P=0.29$), 6-min walk test ($P=0.29$) or fractional shortening ($P=0.9$).
Berman et al[37]	32 patients with HFrEF awaiting heart transplantation	Randomized controlled trial	CoQ10 60 mg oral twice daily compared to placebo for 3 mo	Improvement in 6-min walk test in CoQ10 from baseline to study completion: 269.5–382.2 mo ($P<0.0001$). Placebo group decreased, 254–177 mo ($P<0.001$). Between group $P<0.0001$. Improvement in NYHA classification in CoQ10 group from baseline to study completion (3.1–2.4, $P=0.01$). No changes in placebo group. Between group $P=0.01$. No improvement in echocardiography parameters (fractional shortening). No improvement in 6-wk ANF blood levels in CoQ10 group (185.2±21.6 pg/mL) vs placebo (260.2±23.8 pg/mL). No improvement in 6-wk TNF blood levels in CoQ10 group (10.5±3.1 pg/mL) vs placebo (16.1±3.5 pg/mL)
Kocharian et al[38]	38 patients; <18 y of age with IDCM	Double-blind placebo-controlled trial	2 mg/kg/d over 2 or 3 doses increased to 10 mg/kg/d according to tolerance or side effects for 6 mo	Improvement in cardiac index score in CoQ10 (5.8) versus placebo (9.0) after 6 mo (between group $P=0.024$). Improvement in diastolic grade on echocardiography in CoQ10 versus placebo (between group $P=0.01$)
Pourmoghaddas et al[39]	62 patients with HFrEF (mixed pathogeneses) with NYHA II–IV	Double-blind placebo-controlled randomized trial	CoQ10 100 mg and orally twice daily with atorvastatin 10 mg orally daily versus placebo for 4 mo.	Improved ejection fraction in CoQ10 group from baseline to 4 mo (18.7±10.3 arm to 24.2±14.5, $P=0.003$) versus placebo (26.2±9.1 to 25.8±9.7, $P=0.23$; between group $P=0.006$). Improve NYHA classification from baseline to 4 mo in CoQ10 group (2.7±0.7 to 2.3±0.7, $P=0.025$) versus placebo (2.9±0.8 to 2.7±0.7, $P=0.17$; between group $P=0.002$). No significant change in biomarkers between CoQ10 and placebo (NT-proBNP, ESR, and CRP)
Mortensen et al[40]	420 patients with HFrF (mixed pathogeneses) and NYHA I–II symptoms	Double-blind placebo-controlled randomized trial	CoQ10 100 mg orally 3× a day versus placebo for 2 y	Reduced risk of all-cause death in CoQ10 group: HR, 0.51 (95% CI, 0.30–0.89; $P=0.018$). Reduced risk of composite including unplanned hospital stay resulting from worsening HF, cardiovascular death, mechanical assist implantation, or urgent cardiac transplantation: HR, 0.50 (95% CI, 032–0.80; $P=0.003$). No difference between groups for NYHA functional class, 6-min walk test, or functional status with a visual analogue scale for symptoms

There were no adverse drug reactions (or were not reported) in these studies except for Berman et al,[37] where 1 patient withdrew because of gastrointestinal side effect. ANF indicates atrial natriuretic factor; CI, confidence interval; CoQ10, coenzyme Q10; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HFrEF, heart failure with reduced ejection fraction; HR; hazard ratio; IDCM, idiopathic dilated cardiomyopathy; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; NYHA, New York Heart Association; PCWP, pulmonary capillary wedge pressure; and TNF, tumor necrosis factor.

The results of the Q-SYMBIO highlight a potential avenue for further study. However, this study had significant limitations. Q-SYMBIO required an extended period of time (an 8-year period >17 centers in 9 countries) to complete enrollment. It is unclear if this was because of investigator or site-specific limitations, patient acceptance of drug intervention, competing trials, or other causes. The large treatment effect (a 50% reduction in the primary end point and a 49% reduction in all-cause mortality) is striking and unexpected. The small number of events with an annualized mortality rate of 7% for the entire trial population and the small number of total patients recruited should prompt further caution in interpreting the trial results.

In terms of CoQ10 dosing, a majority of the trials used doses from 60 to 300 mg orally daily. An open label study of 143 patients with NYHA III, IV used CoQ10 100 mg daily and demonstrated an increase in CoQ10 levels from 0.85 mg/L to 2 mg/L in association with an improvement in LVEF and NYHA symptoms in the absence of adverse effects.[42] CoQ10 level of 2 mg/L was selected as the target in the Q-SYMBIO trial, which used CoQ10 at 300 mg orally per day. CoQ10 levels of 3.25 mg/L (±1.57) were seen in the only RCT that investigated invasive hemodynamics, which demonstrated that compared with placebo, CoQ10 reduction in stroke index, pulmonary artery pressure, and pulmonary capillary pressure.[34] A double-blind RCT of CoQ10 at 300 mg/d for 3 months (compared with placebo) in patients with ischemic heart disease demonstrated a significant reduction of inflammatory markers, such as tumor necrosis factor-α and interleukin-6.[43] In terms of duration of dosing, a majority of trials have given CoQ10 for 3 months, whereas the longest administration of CoQ10 was 2 years (Q-SYMBIO trial).

HFpEF ultimately arises when ventricular compliance decreases in diastole, resulting in increased left ventricular end-diastolic pressure in the absence of left ventricular systolic dysfunction. Ventricular diastole requires ATP hydrolysis for myofilament detachment and subsequent ventricular relaxation to occur, suggesting that HFpEF represents a disorder of abnormal energetics.[44] Increased inflammatory mediators (such as tumor necrosis factor-α, interleukin-6, soluble ST2, and pentraxin-3) seen in HFpEF may cause reactive oxygen species elevation and subsequent endothelial dysfunction.[45] This can drive adverse cardiac remodeling and subsequent adverse ventricular relaxation. Given the mechanistic and preclinical data on CoQ10's role in energetics, the ability to ameliorate proinflammatory mediators, and possibly improve endothelial dysfunction, there is rationale for examining CoQ10 as a possible treatment of HFpEF.[25] To date, there is no randomized controlled trial specifically evaluating CoQ10 supplementation in HFpEF. Given the current lack of treatments that alter mortality in patients with HFpEF, future trials of CoQ10 should consider the inclusion of these patients.

Formulation and Cost of CoQ10 Supplementation

CoQ10 is available commercially as either ubiquinol (reduced form) or ubiquinone (oxidized form). There is currently no intravenous formulation. Supplements are available as solubilized tablets, oil suspensions, tablets, chewable tablets, and powder-filled capsules.[21] Regardless of whether the formulation contains ubiquinol or ubiquinone, after ingestion CoQ10 seems in the plasma circulation as ubiquinol. It is likely that conversion from oral ubiquinone to ubiquinol occurs after intestinal absorption but before CoQ10 entering the lymphatic system.[21] The solubilized formulation of CoQ10 results in the greatest increase in plasma CoQ10 levels. Furthermore, the ubiqinol containing formulation may result in a greater increase in plasma CoQ10 levels compared with ubiquinone formulations.[21]

CoQ10 is readily available over the counter in supermarkets, pharmacies, health food stores, and online. A survey of the most popular online vendors in the United States (Amazon, Walmart, and Costco) identifies that the solubilized form of CoQ10 at 100 mg cost ≈$ 0.13 to $0.33 (USD) per tablet. At doses used in the Q-SYMBIO trial, patients would have to pay ≈$142 to $364 per year.

Safety Concerns and Side Effect Profiles

Outside of the clinical trials, little published data are available on the adverse effects of CoQ10 in HF. The largest evaluation of adverse events comes from a 3-month postmarketing study of 2664 patients with HF from 173 Italian centers.[46] Using CoQ10 doses from 50 to 150 mg orally/d, 38 adverse events from 36 patients (1.5% of all patients) were noted. Nausea was the most common symptom (n=30) followed by allergic maculopapular rash (n=3). Seven patients with nausea and 2 with an allergic maculopapular rash discontinued the drug, whereas the remainder of patients tolerated a reduced dose of CoQ10. Hematologic and biochemical laboratory evaluation before starting CoQ10 and 3 months later were unchanged. There was also a reduction in blood pressure (supine systolic 143.8 mm Hg versus 149.4 mm Hg, $P<0.05$) and heart rate (75.1 versus 78.4 beats per minute $P<0.05$). This has been seen in other smaller populations.[47] However, the Q-SYMBIO trial did not demonstrate any significant alteration in blood pressure or heart rate in those randomized to CoQ10 supplementation. Such changes were not reported in other CoQ10 trial in patients with HF. It is unclear whether other electrophysiological parameters such as QT interval of the ECG are affected in patients with HF taking CoQ10 but evaluation of a single dose of 50 mg CoQ10 in healthy volunteers did not demonstrate any significant ECG changes.[48] On the basis of the available literature, it seems that CoQ10 is well tolerated with an acceptable safety; however, larger studies will be needed to further evaluate the safety of CoQ10 in the setting of HF.

Among non-HF studies, CoQ10 doses of ≤3000 mg/d have been used in Parkinson patients.[49] Plasma levels reached 8 mg/L with a dose of 2400 mg/d but did not increase with doses of 3000 mg/d. No systematic pattern of adverse effects was found with gastrointestinal effects being no more common at daily intakes of 1200 mg than at a 60 mg.[50] In general, it seems that the maximum observed safety level of CoQ10 is at a dose of 1200 mg/d.[50]

Drug Interactions

Although the side effect profile of CoQ10 seems to be favorable, there are some reports of drug interactions. The most significant drug interaction seems to be with warfarin. CoQ10

Table 3.   Summary of Clinical Recommendations for CoQ10 Use in Patients With HF

Clinical Question	Recommendation
Should clinicians initiate CoQ10 in patients with HF?	ACC/AHA guidelines currently do not recommend initiation of nutritional supplementation as treatment (including CoQ10) in patients with current or previous symptoms of HFrEF (level of evidence B, class III recommendation). Although the results of Q-SYMBIO[29] have suggested an improvement in the primary MACE end point at 2 y, the small event numbers, difficulties in patient recruitment, and an unexpectedly large treatment effect with wide confidence intervals limits the interpretability of the results. At this time point, CoQ10 initiation cannot be recommended to patients with HF
Are there certain subgroups of patients with HF that may have significant benefit from CoQ10?	RCTs' evaluating CoQ10 in patients with HF have focused on HFrEF. The Q-SYMBIO trial did not suggest an interaction between CoQ10 therapy and subgroups. Currently, we do not recommendation for the use of CoQ10 in specific subgroups of patients with HF
If patients are already taking CoQ10, what should clinicians' recommend with regard to future use?	Given the absence of a signal to harm in Q-SYMBIO, a detailed discussion of the risks and benefits of CoQ10 should occur between the patient and the clinician. Given the similar molecular structure of CoQ10 to vitamin K, patients who are taking warfarin should have international normalized ratios carefully and potentially more frequently checked

ACC indicates American College of Cardiology; AHA, American Heart Association; CoQ10, coenzyme Q10; HF, heart failure; HFrEF, HF with reduced ejection fraction; and MACE major adverse cardiovascular events.

shares some structural similarity to vitamin K and may increase the metabolism of warfarin through selective interaction with the cytochrome p450 enzymes.[51,52] Multiple reports have demonstrated difficulties in achieving adequate anticoagulation targets in patients taking CoQ10 and warfarin.[53] This may be of concern in a population with HF where a significant proportion of patients have atrial fibrillation and may be anticoagulated with a warfarin strategy. Theophylline is also affected by cytochrome p450 enzymes and animal studies have demonstrated altered pharmacokinetics of theophylline with coadministration of CoQ10.[54]

Statin therapy may deplete CoQ10 levels.[55,56] Investigators of the CORONA trial evaluated CoQ10 levels in relation to statin therapy because of Food and Drug Administration regulatory requirements. A significant reduction of CoQ10 levels associated with statin therapy was identified.[11–13,30] Although lower levels were associated with worsened HF, it was not an independent predictor of adverse outcomes.

Practical Use of CoQ10

Current American Heart Association/American College of Cardiology HF guidelines do not recommend initiation of nutritional supplementation for the treatment of HF (levels of evidence B, class III).[57] Although the Q-SYMBIO trial was published after these guidelines were established, given the limitations of this trial (described previously),[58] CoQ10 initiation cannot currently be recommended as a guideline-based treatment for HFrEF. It should also be noted that Q-SYMBIO was not powered to evaluate for safety. The Q-SYMBIO trial did not suggest any specific interaction between subgroups and CoQ10, but there was trends toward benefit in elderly patients, male patients, patients in NYHA functional class III, patients with dilated cardiomyopathy, patients with N-terminal prohormone of brain natriuretic peptide ≥300 pg/mL, and patients with left ventricular EF of ≥30% (P=0.065). If patients are already taking CoQ10, a detailed discussion between the physician and patient about the risks and benefit of continuing CoQ10 should occur. Caution should be given to the patients who are taking Coumadin given the similarities of CoQ10 with vitamin K. The clinician should be vigilant in ensuring that the patient is appropriately anticoagulated if taking Coumadin. Clinical recommendations are highlighted in Table 3.

Conclusions

CoQ10 seems to be a potent antioxidant, may improve endothelial dysfunction, and can possibly enhance cardiac ATP production. A recent trial has suggested that CoQ10 may be an adjunctive therapeutic option for patients with HFrEF. Evidence to support its widespread use is limited by small, heterogenous studies. Dosing of CoQ10 suggests that serum targets of >2 mg/L are reasonable to achieve clinical benefit. Although available data suggest that CoQ10 has limited side effects, further studies are needed to ensure the safety of CoQ10 and to identify any additional drug interaction. Future adequately powered studies are warranted to adequately evaluate for clinical benefit in patients with HFrEF. Furthermore, the pathophysiological rationale for the use of CoQ10 in HEpEF exists and well-conducted RCTs will be required to demonstrate efficacy and safety in this population.

Disclosures

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