

## EDITORIAL COMMENT

# Time to Energize Coenzyme Q<sub>10</sub> for Patients With Heart Failure?\*



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*Nobody realizes that some people expend tremendous energy merely to be normal.*

Albert Camus, *Notebooks*, 1942-1951 (1)

## ENERGY GENERATION IN THE MITOCHONDRIA

Energy generation and utilization have been the focal points of many research groups trying to elucidate the pathways, deficiencies, and enhancement of the energy-generation centers of the cell, the mitochondria (2). In mitochondrial function, coenzyme Q<sub>10</sub> (CoQ<sub>10</sub>; ubiquinone) has a unique function in oxidative phosphorylation and the generation of adenosine triphosphate (3). The myocardial and skeletal muscle cells of patients with heart failure (HF) are in an energy-starved state; hence any increase in the ability to augment energy production or enhance efficient utilization is certain to have positive functional effects.

## COENZYME Q<sub>10</sub> AS A THERAPY

Few nutraceuticals (a type or subcategory of drug) have received as much attention as CoQ<sub>10</sub>. Consider the number of published articles (>10,000 on PubMed), the number of search results on [google.com](http://google.com) (~7 million), the number of supplements available and sold in stores on the Internet (>100), and the number of diseases it prevents or treats as advertised (nearly all!) or as approved by a regulatory agency (none). The market for CoQ<sub>10</sub> is estimated at ~\$1 billion annually, and the cost to patients is between

\$50 and \$100 per month for the doses used in clinical trials.

Now consider that there has been no major disease state in which a clinical trial has shown overwhelming and replicated efficacy using CoQ<sub>10</sub>. Has any “antioxidant” therapy shown benefit in the form of reduced mortality or serious morbidity for the treatment or prevention of HF? Does this therapy have value for a patient or a health system given the outcomes of the published data?

## OBSERVATIONAL DATA ON COENZYME Q<sub>10</sub> LEVELS IN HEART FAILURE

Although associations linking low levels of blood CoQ<sub>10</sub> levels to patients with HF have been present for many years, 2 more recent studies are important. In a study of 236 patients admitted to a hospital for HF, the median baseline CoQ<sub>10</sub> concentration was 0.68 μmol/l; lower levels conferred a 2-fold higher risk for short-term survival independent of other variables (4). However, a much larger cohort of 1,191 patients with chronic HF did not show this association with mortality (5). The median value was similar (0.72 μmol/l), and although it was significant with univariate analysis, it did not hold up when other important variables were included or when hospital stays, changes in New York Heart Association (NYHA) class, or composite outcomes were assessed. Essentially, there was no important relationship between CoQ<sub>10</sub> and clinically meaningful outcomes in patients with HF. Most importantly and not unexpectedly, low levels of CoQ<sub>10</sub> were linked with markers of the severity of the disease, but not the outcomes of interest. So where does that leave us?

## INTERVENTIONAL DATA ON COENZYME Q<sub>10</sub> THERAPY IN HEART FAILURE

Numerous systematic reviews have assessed the ~900 patients enrolled in short-term and medium-term

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clinical trials conducted over 30 years, using a variety of preparations and dosages of CoQ<sub>10</sub>, patients enrolled and outcomes assessed over varying degrees of follow-up time (6,7). There have been mixed results in clinically meaningful outcomes and no clear effect on mortality or hospital stay demonstrated. For example, in the first (and to date, the largest) trial of CoQ<sub>10</sub>, which was published in 1993, Morisco et al. enrolled 641 patients into a 12-month trial of CoQ<sub>10</sub>: 5% died in the CoQ<sub>10</sub> group and 6.5% in the placebo group (not statistically significant) (8). An interesting 50% reduction in hospital stay rate was observed, albeit in an era of few other therapies and during the emergence of therapies now considered standard (e.g., beta-blockers, angiotensin-converting enzyme [ACE] inhibitors, and mineralocorticoid antagonists).

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Fast forward to 2014, where the decade-long Q-SYMBIO trial is now complete (9), and outlined in this issue of *JACC: Heart Failure*. The investigators should be commended for completing a trial and committing to publishing it in its entirety. This randomized trial allocated 420 patients to CoQ<sub>10</sub> 100 mg or placebo 3 times daily and followed these patients for 2 years for the main outcome efficacy endpoints while still collecting early data to replicate prior studies that used surrogate endpoints.

The generalizability of the patients enrolled is of more than passing interest, given that the last major outcomes trial was published in 1993, and Q-SYMBIO ran over 8 years. The patients were mostly NYHA class III, 16% had atrial fibrillation, and the mean ejection fraction was 31% with median N-terminal pro-B-type natriuretic peptide (NT-proBNP) of ~750 pg/ml, similar to values in a contemporary trial of exercise (10). Nearly all patients in Q-SYMBIO were taking an ACE inhibitor, >70% were taking a beta-blocker, and one-third were taking a mineralocorticoid receptor antagonist. The mean heart rate was 80 beats per minute, a finding suggesting that inadequate dosing of beta-blockers was evident, and the high rate of use of digoxin (~45% of the cohort) likely reflects the locales of recruitment.

By 16 weeks, there was no difference between placebo and CoQ<sub>10</sub> groups in NYHA class, 6-min walk test, echocardiographic or physiologic measures, or NT-proBNP. Similarly, by 2 years, no difference was seen in the same parameters, with the exception of more patients with an improved NYHA class in patients taking CoQ<sub>10</sub> compared with placebo; this was a borderline result considering the multiplicity of testing.

However, and somewhat surprisingly, there was a large treatment effect for the outcome of mortality at 2 years: a 43% relative reduction in cardiovascular death, hospital stays for HF, or mechanical support or cardiac transplant. Considering all-cause mortality alone (a total of 60 deaths in the trial), there was an annualized mortality rate of 7% for the entire cohort, with a 42% relative reduction in favor of the CoQ<sub>10</sub> group. These striking results should be interpreted with caution given the small population and event numbers and the large treatment effect; many of these results were not replicated when a subsequent adequately powered trial was done (11).

Some other trial issues need consideration. This trial of chronic HF recruited 420 patients over an 8-year period in 9 countries in 17 centers, clearly, this trial had significant recruitment issues. It is unclear whether this situation resulted from patients' acceptance of the experimental therapy, the ability of the sites and investigators to conduct a trial, the intensity of follow-up, or other features that are not further elucidated.

#### WILL COENZYME Q<sub>10</sub> BECOME A GUIDELINE-DIRECTED MEDICAL THERAPY?

Enthusiastically, the investigators have said that CoQ<sub>10</sub> “should be added as standard therapy” based on these results, and additionally, it is a “natural and safe substance” (12). Perhaps this second statement is driven by the *fewer* side effects in the CoQ<sub>10</sub> group than in the placebo group (13% vs. 19%). Further study in adequately powered clinical trials is required because it is premature to suggest that this finding reaches the necessary efficacy or safety bar required to consider prescribing this drug. Additionally, Although CoQ<sub>10</sub> is widely available and taken as a supplement, safety cannot be assumed for any drug in this context, and so much broader and more detailed experience is required to declare this substance acceptably safe. Finally, CoQ<sub>10</sub> is natural, naturally made in a factory by pharmaceutical-grade processes of medicinal chemistry and yeast or bacterial fermentation. One could argue that the most natural and safe method to increase CoQ<sub>10</sub> levels in the body is through improved diet (13), which can act on more potential nutritional deficiencies than just the mitochondrial cycle. No information is required on the dietary intake of the groups and whether this differed over time, but presumably it is equally balanced between groups.

Nutraceutical manufacturers must step up and, like pharmaceutical and device companies, fund a trial for which an indication is sought or advertised, not

solely through governmental funding agencies. If 1% of the estimated \$1 billion annual market for CoQ<sub>10</sub> was reinvested into an adequately powered, appropriately designed, academically led trial to demonstrate the efficacy and safety of CoQ<sub>10</sub>, then perhaps we would have a scientific advance worth being excited about. After all, our patients with HF

are spending a lot of energy trying to be normal. Let us help them.

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