The benefit of coenzyme Q₁₀ supplements in the management of chronic heart failure: a long tale of promise in the continued absence of clear evidence¹–³

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Clinical studies of coenzyme Q₁₀ (CoQ₁₀) in chronic heart failure (CHF) date back more than 35 y (1), yet the role of CoQ₁₀ in the management of CHF remains controversial. CoQ₁₀ is essential for respiration because it is required for both the shutting of electrons from complexes I/II to complex III and the protonmotive Q cycle in mitochondria (2). CoQ₁₀ is synthesized in tissues, and under normal physiologic conditions, the bioavailability of dietary CoQ₁₀ is very low for most tissues including the heart (2). In situations of severe CoQ₁₀ deficiency such as genetic CoQ₁₀ deficiency, however, dietary supplements alleviate pathologic conditions and restore mitochondrial and other functions (2). The rationale for a potential benefit of CoQ₁₀ supplements in CHF is thus based on the well-established role of CoQ₁₀ in mitochondrial function, its antioxidant properties, and limited studies with biopsy samples from patients with cardiomyopathy that indicate that cardiac concentrations of CoQ₁₀ are decreased and may be increased by dietary supplementation with the lipid.

In this issue of the Journal, Fotino et al (3) report the results of a meta-analysis of 13 phase 2 placebo-controlled clinical trials of CoQ₁₀ supplementation in CHF. All trials included in the meta-analysis were small in size and short in duration of follow-up, which ranged from 2 to 28 wk. The endpoints examined in the individual trials and included in the meta-analysis were left ventricular ejection fraction (LVEF) and the New York Heart Association (NYHA) functional classification. The key findings of the meta-analysis (3) were a significant increase in LVEF of just under 4% and a nonsignificant trend toward improved NYHA class in response to CoQ₁₀. The authors then performed a series of post hoc analyses to explore variables that might affect the response to CoQ₁₀. Among the variables analyzed were year of publication, study design, baseline LVEF, median daily dose of CoQ₁₀, and duration of trial.

As the authors suggest (3), these post hoc analyses need to be interpreted with caution; however, they do raise some intriguing questions. For example, studies published before the end of 1993 were positive overall, whereas those published from 1994 onward were not. The authors speculate that this may be explained by recruitment of patients with more severely impaired LVEF in the more recent trials. Another or additional explanation is the major change in the treatment of CHF, which occurred in the mid-1990s with the increase in prescription of β-blockers, after the publication of large-scale clinical trials showing a survival benefit with this class of drug in CHF (4). Hence, it is possible that there is an incremental benefit of CoQ₁₀ when added to treatment that includes angiotensin-converting enzyme inhibitors but no or less incremental benefit of CoQ₁₀ in addition to angiotensin-converting enzyme inhibitors plus β-blockers.

Another intriguing finding of the current meta-analysis is the apparent lack of dose-response relation between CoQ₁₀ and LVEF. Studies published before 1994 used 100 mg CoQ₁₀ per day, whereas later studies commonly used >100 mg and ≤300 mg CoQ₁₀ per day. Given its low bioavailability and the recent experience with CoQ₁₀ supplements in the treatment of neurodegenerative diseases (5), one would have reasonably expected greater benefit with increasing concentrations of CoQ₁₀ supplements.

At first glance, the positive results of the meta-analysis by Fotino et al (3) suggest that CoQ₁₀ may be a beneficial adjunct treatment of patients with CHF. However, it is important to remember that improvements in LVEF and NYHA class after a short follow-up period do not establish that the therapeutic intervention is safe or effective during long-term administration. Positive inotropic drugs are the classic example of medicines that produce short-term benefits in LVEF and NYHA class but are associated with increased long-term morbidity and mortality (6). Whereas CoQ₁₀ clearly is not a positive inotropic agent, the lesson from the clinical trials of positive inotropic drugs in CHF is that only phase 3 clinical trials with “hard endpoints” including morbidity and mortality can establish the safety and efficacy of any new therapeutic intervention.

The largest published placebo-controlled trial of CoQ₁₀ in CHF by Morisco et al (7) was excluded from the current meta-

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⁴ Abbreviations used: CHF, chronic heart failure; CoQ₁₀, coenzyme Q₁₀; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

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analysis. A closer look at this trial arguably provides even more compelling evidence than that provided in the current meta-analysis to support a potential therapeutic role of CoQ10 in CHF. Morisco et al (7) enrolled 641 patients (compared with a total of 395 in the current meta-analysis), followed them for 1 y, and observed a highly significant reduction in major clinical events including hospitalizations and episodes of acute pulmonary edema and of "cardiac asthma" for CoQ10 compared with placebo. Also, the average age of patients in the study by Morisco et al (7) was 67 y. This is considerably closer to the average age of CHF patients in the general community compared with patients entered into the current meta-analysis whose median age was just over 60 y. However, a major limitation of the Morisco et al study (7) is that none of the CHF patients were receiving $\beta$-blockers. This is not surprising given that the trial was published almost 20 y ago! Indeed, a small percentage was receiving ibopamine, an inodilator drug later withdrawn due to its use being associated with excess mortality (8).

The preliminary results of the long-awaited Q-SYMBIO trial were presented recently at the 7th International Coenzyme Q10 Association Meeting in Seville, Spain (SA Mortensen, unpublished data, 2012). Q-SYMBIO is a randomized, double-blind, multicenter trial with CoQ10 as adjunctive treatment of CHF, with focus on SYMptoms, BIOmarker status, and long-term outcome (hospitalizations/mortality). At completion, 422 patients with CHF were recruited and CoQ10 (2 mg · kg$^{-1}$ · d$^{-1}$) was reported to significantly reduce all-cause mortality at 2 y compared with placebo (SA Mortensen, unpublished data, 2012). This important trial is still to be published, but it is likely to be an important addition to the evidence base supporting a role of CoQ10 in the management of CHF. Importantly, however, and regardless of the promising results of the Q-SYMBIO study, additional large-scale, placebo-controlled clinical trials will be needed to clearly determine the utility of CoQ10 in the management of CHF in addition to optimal medical therapy that includes $\beta$ blockade. This is where the biggest challenge lies: funding for such expensive large-scale, long-term clinical trials will be difficult to obtain given that CoQ10 is a dietary supplement rather than a registered drug—unless, of course, government organizations step in.

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REFERENCES


