The benefit of coenzyme \textsubscript{Q\textsubscript{10}} supplements in the management of chronic heart failure: a long tale of promise in the continued absence of clear evidence\textsuperscript{1–3}

Roland Stocker and Peter Macdonald

Clinical studies of coenzyme \textsubscript{Q\textsubscript{10}} (CoQ\textsubscript{10})\textsuperscript{3} in chronic heart failure (CHF) date back more than 35 y (1), yet the role of CoQ\textsubscript{10} in the management of CHF remains controversial. CoQ\textsubscript{10} is essential for respiration because it is required for both the shuttling of electrons from complexes I/II to complex III and the protonmotive Q cycle in mitochondria (2). CoQ\textsubscript{10} is synthesized in tissues, and under normal physiologic conditions, the bioavailability of dietary CoQ\textsubscript{10} is very low for most tissues including the heart (2). In situations of severe CoQ\textsubscript{10} deficiency such as genetic CoQ\textsubscript{10} deficiency, however, dietary supplements alleviate pathologic conditions and restore mitochondrial and other functions (2). The rationale for a potential benefit of CoQ\textsubscript{10} supplements in CHF is thus based on the well-established role of CoQ\textsubscript{10} in mitochondrial function, its antioxidant properties, and limited studies with biopsy samples from patients with cardiomyopathy that indicate that cardiac concentrations of CoQ\textsubscript{10} 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 CoQ\textsubscript{10} supplementation in CHF. All trials included in the meta-analysis were small in size and short term 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 CoQ\textsubscript{10}. The authors then performed a series of post hoc analyses to explore variables that might affect the response to CoQ\textsubscript{10}. Among the variables analyzed were year of publication, study design, baseline LVEF, median daily dose of CoQ\textsubscript{10}, 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 \textbeta-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 CoQ\textsubscript{10} when added to treatment that includes angiotensin-converting enzyme inhibitors but no or less incremental benefit of CoQ\textsubscript{10} in addition to angiotensin-converting enzyme inhibitors plus \textbeta-blockers.

Another intriguing finding of the current meta-analysis is the apparent lack of dose-response relation between CoQ\textsubscript{10} and LVEF. Studies published before 1994 used 100 mg CoQ\textsubscript{10} per day, whereas later studies commonly used \textgtr100 mg and \textless300 mg CoQ\textsubscript{10} per day. Given its low bioavailability and the recent experience with CoQ\textsubscript{10} supplements in the treatment of neurodegenerative diseases (5), one would have reasonably expected greater benefit with increasing concentrations of CoQ\textsubscript{10} supplements.

At first glance, the positive results of the meta-analysis by Fotino et al (3) suggest that CoQ\textsubscript{10} 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 CoQ\textsubscript{10} 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 CoQ\textsubscript{10} in CHF by Morisco et al (7) was excluded from the current meta-

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\textsuperscript{1} From the Vascular Biology Division (RS) and the Cardiac Physiology and Transplantation Division (PM), Victor Chang Cardiac Research Institute, Darlinghurst, Australia.

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\textsuperscript{3} Address correspondence to R Stocker, Vascular Biology Division, Victor Chang Cardiac Research Institute, Lowy Packer Building, 405 Liverpool Street, Darlinghurst NSW 2010, Australia. E-mail: r.stocker@victorchang.edu.au.

\textsuperscript{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 β-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 β 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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