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Coenzyme Q_{10} and congestive heart failure: an evolving evidence base

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THE Q-SYMBIO STUDY AND ITS IMPLICATIONS

The recently published Q-SYMBIO clinical trial has provided support that coenzyme Q_{10} (CoQ_{10}) supplementation should be considered as a part of the maintenance therapy of patients with chronic heart failure (CHF) [1]. The Q-SYMBIO study concluded that long-term CoQ_{10} treatment of patients with CHF is safe, improves symptoms, and reduces major adverse cardiovascular (CV) events [1].

This was a randomised, controlled, double-blind intervention trial (RCT), conducted in many centres in nine countries including Poland.

Q-SYMBIO was initiated with CoQ_{10} supplementation in CHF patients and focused on symptoms, biomarker status (BNP) and long-term outcomes.

A total of 420 patients with moderate to severe CHF were randomly assigned in a two-year prospective trial to either CoQ_{10} 100 mg three times daily or a placebo, in addition to standard therapy. There were no changes in primary end-points at 16 weeks. These included changes in New York Heart Association (NYHA) functional classification, six-min walk test, and levels of N-terminal pro-B type natriuretic peptide (NT-proBNP).

The primary long-term end-point (composite major adverse CV events as determined by a time-to-first-event analysis), was reached by 15% of the patients in the CoQ_{10} group vs. 26% in the placebo group (hazard ratio [HR] 0.50; 95% confidence interval [CI] 0.32–0.80; $p = 0.003$) by intention-to-treat analysis (Fig. 1). This included secondary end-points, which were significantly lower in the CoQ_{10} group compared to the placebo group: CV mortality (9% vs. 16%; $p = 0.026$), all-cause mortality (10% vs. 18%; $p = 0.018$), and incidence of hospital stays for heart failure (HF) ($p = 0.033$). In addition, a significant improvement of NYHA class was found in the CoQ_{10} group after two years ($p = 0.028$).

Q-SYMBIO is the first RCT with adequate size, dosage of CoQ_{10}, and duration of follow-up to evaluate the efficacy of CoQ_{10} on morbidity and most importantly, major clinical end-points such as mortality in CHF.

The findings have implications for clinical practice, by providing a more robust evidence base for CoQ_{10} intervention in CHF patients. In addition, it has a good safety profile and is readily available over the counter without prescription.

The present review examines the background as to why the Q-SYMBIO study came about. Starting with the role of CoQ_{10} in biological systems, it covers what previous studies have discovered about CoQ_{10} and cardiac function. This includes observational studies, intervention studies prior to Q-SYMBIO, meta-analyses [2–4] and a Cochrane review [5]. Statin drugs, used to lower cholesterol as part of CV prevention strategies, are also known to lower CoQ_{10} through their action on the mevalonate pathway [6]. The present review discusses the findings of studies with statin intervention in CHF and their implications. It also provides a commentary of Q-SYMBIO with *caveats* and recommendations for future studies.

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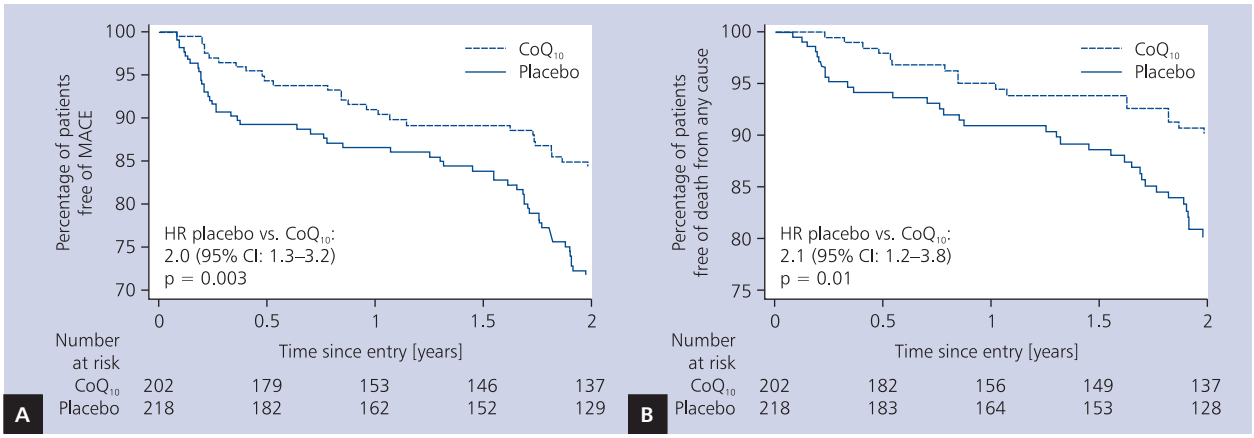

Figure 1. Kaplan-Meier estimates of the time to the primary end-point major adverse cardiovascular events (MACE) (**A**) and the secondary outcome death (**B**) in the placebo group (solid line) and the coenzyme Q_{10} (CoQ_{10}) group (dashed line). The primary end-point was composite MACE of hospital stay for worsening heart failure, cardiovascular death, mechanical support, or urgent cardiac transplantation; CI — confidence interval; HR — hazard ratio; this data was first presented at the European Society of Cardiology Heart Failure Congress in Lisbon in 2013 by Q-SYMBIO triallists

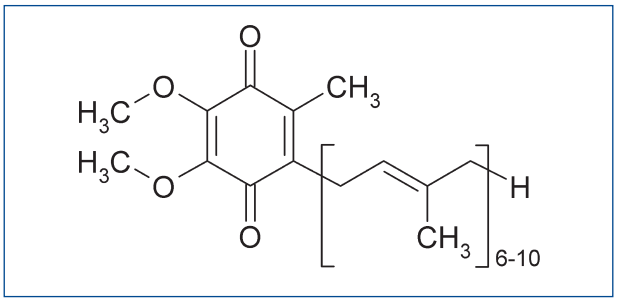

Figure 2. Coenzyme Q_{10} (CoQ_{10}), a 1,4-benzoquinone with an isoprenoid side chain. CoQ homologues, containing repeat numbers of isoprenoid units in the sidechain, occur with both CoQ_9 and CoQ_{10} present in human plasma with CoQ_{10} dominant

THE ROLE OF COENZYME Q_{10} IN BIOLOGICAL SYSTEMS

CoQ_{10} (Fig. 2), a benzoquinone with an isoprenoid side chain, was first isolated from beef heart mitochondria by Frederick Crane of Wisconsin, USA, in 1957 [7]. CoQ_{10} is present in the body in both a reduced (ubiquinol, $CoQ_{10}H_2$) and an oxidised (ubiquinone, CoQ_{10}) form. CoQ_{10} is lipophilic and transported in lipoprotein particles in the circulation. It is not surprising therefore that plasma CoQ_{10} correlates with plasma cholesterol and low density lipoprotein (LDL)-cholesterol [8–15]. CoQ_{10} is synthesised endogenously, and is also obtained from the diet, with meat products being the largest source in the normal diet [16].

CoQ_{10} is an essential cofactor in mitochondrial oxidative phosphorylation, and is vitally important for adenosine triphosphate (ATP) production (Fig. 3). In this role, CoQ_{10} acts as a mobile electron carrier, transferring electrons from complex 1 (NADH coenzyme Q reductase) to complex 3 (cytochrome bc_1 complex), or from complex 2 (succinate dehydrogenase) to complex 3. The reduced form of CoQ_{10} can act as an antioxidant directly protecting biological membranes against oxidation [17] as well as by inhibiting the peroxidation of lipoprotein lipids in the circulation [18]. Indeed, supplementation with exogenous CoQ_{10} has been shown to lead to an increase in the $CoQ_{10}H_2$ content of LDL, and a decrease of their peroxidisability [19]. As an antioxidant, $CoQ_{10}H_2$ may also have a role in recycling alpha-tocopherol, which may also have favourable implications for the pathogenesis of vascular disease [20].

COENZYME Q_{10} AND CARDIAC FUNCTION

Given the vital importance of CoQ_{10} in mitochondrial electron transport and ATP synthesis, it is not surprising that the myocardium has the highest concentration of CoQ_{10} compared to other tissues [16] and its depletion has been postulated to lead to 'energy starvation' of the myocardium and have a pathogenic role in the aetiology of CHF. Indeed, myocardial depletion of CoQ_{10} has been demonstrated in HF and the severity of the deficiency has been found to correlate with the severity of symptoms, with patients in NYHA class IV having significantly lower CoQ_{10} in endo-myocardial biopsy samples than those in NYHA class I [21].

There are also some findings that suggest that oxidative stress is increased in patients with CHF, is inversely correlated with left ventricular ejection fraction (LVEF) [22], and may predict clinical outcomes [22]. Coenzyme Q_{10} may also have a role in stabilising myocardial calcium-dependent ion channels and in preventing the consumption of metabolites essential for ATP synthesis [23].

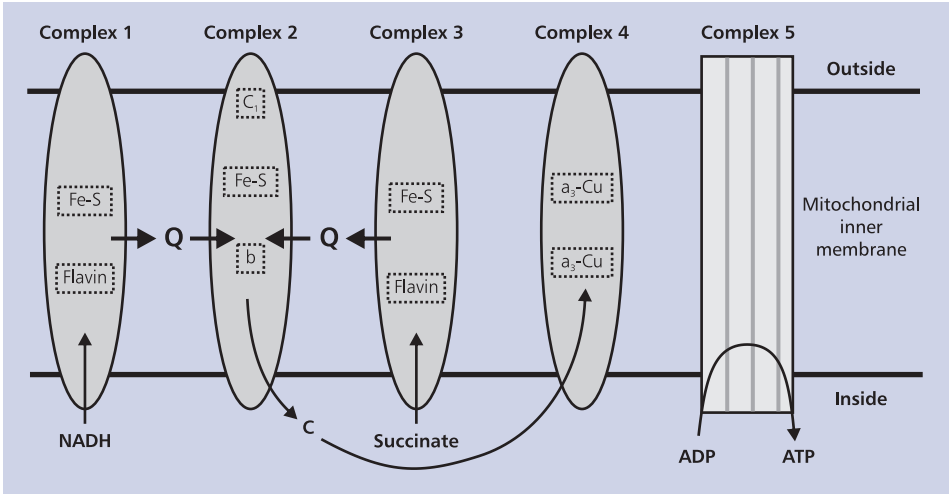

Figure 3. The mitochondrial electron transport chain; NADH — nicotinamide adenine dinucleotide; Q — coenzyme Q_{10}; C — cytochrome C; Fe-S — iron-sulfur clusters; C_1 — cytochrome C_1; b — cytochrome b; a_3-Cu — copper associated with cyctochrome a_3, ADP — adenosine diphosphate; ATP — adenosine triphosphate; arrows indicate the flow of electrons through the pathway; reproduced with permission from the Australasian Asssociation of Clinical Biochemists

COENZYME Q_{10} AND HEART FAILURE

An interesting observation is that total cholesterol is related to survival in CHF [24, 25]. In the study of Rauchhaus et al. [24], serum total cholesterol was independently associated with total mortality in a CHF cohort, with increasing total serum cholesterol predicting survival (HR 0.64, 95% CI 0.48–0.86), independent of the aetiology of CHF, age, LVEF and exercise capacity [24]. Although this seems somewhat counter-intuitive, postulated mechanisms for this association were that cholesterol may be limiting lipo-polysaccharide-induced production of cytokines, and that high cholesterol may provide a greater 'metabolic reserve' to deal with the CHF syndrome. The authors did not, however, make reference to CoQ_{10}, which is known to correlate with plasma total and LDL-cholesterol concentration [8–15] and which could be postulated to explain the worse outcomes seen in CHF patients with low cholesterol. Cardiac cachexia (lean tissue wasting associated with HF) was not considered to be a contributory mechanism in this group of patients, given that lipid levels were no different between patients with and without cachexia and that survival was independent of the presence of cachexia [24].

In a recent observational study, our group showed that CoQ_{10} level, but not statin therapy (known to lower CoQ_{10} in HF [6]), was an independent predictor of total mortality in a cohort of 236 subjects with HF [26]. We were unable to confirm that cholesterol was associated with survival in this cohort [26], although our patients were older and were followed for longer than the cohort of Rauchhaus et al. [24].

The important role played by CoQ_{10} in myocardial bio-energetics and cardiac function set the scene for numerous intervention studies and led to the conception of the Q-SYMBIO study [1, 27].

INTERVENTION STUDIES WITH COENZYME Q_{10} IN HEART FAILURE

Over the past few decades, several uncontrolled observational studies have been reported in the CHF population. They measured symptoms, ejection fraction, left ventricular size, and quality of life measurements before and after treatment with CoQ_{10}. Although they show dramatic improvements, severe study design flaws have limited their applicability [28–35].

There are, however, several small, randomised, blinded trials comparing CoQ_{10} with placebo dating back many decades. Some studies have shown that supplementation of CoQ_{10} over a relatively short time can improve systolic function and reduce ventricular size, whereas others showed no advantage over placebo. It may be contended that these neutral trials lack adequate power to detect an advantage or, conversely, that positive trials may give an exaggerated effect size because of small sample sizes. It is also possible that certain patients respond to CoQ_{10} supplementation and others do not, depending on the severity or aetiology of CHF. Results of these smaller trials have subsequently been pooled, in an attempt in increase power and provide insight into its true effectiveness.

Meta-analyses of CoQ_{10} supplementation in CHF have been undertaken [3, 36, 37]. Soja and Mortensen [36] reviewed eight double-blind placebo-controlled studies [38–45] and reported significant improvements in stroke volume, ejection fraction, cardiac output, cardiac index, and end-diastolic volume index, as a consequence of CoQ_{10} supplementation.

In another meta-analysis, Sander et al. [3] reviewed 12 studies, ten that evaluated ejection fraction [38, 40–42, 45–50] and two that evaluated cardiac output [44, 46] with CoQ_{10} doses ranging from 60 to 200 mg/day and treatment

Table 1. Trials evaluating coenzyme Q_{10} in heart failure in meta-analysis of Sander et al. [3]

	Age	Dose used	Treatment duration	Aetiology of chronic HF	NYHA class	Other HF medications
Crossover trials						
Hofman-Bang, 1995; (n = 69) [45]	61 (10)	100 mg QD	3 months (no washout)	Ischaemic and non-ischaemic (idiopathic, hypertensive, valvular, other)	II–IV (76% class II)	75% digoxin, 96% diuretics, 60% ACEI, no BB
Langsjoen, 1985; (n = 19) [47]	63	33.3 mg TID	3 months (no washout)	Idiopathic	III–IV	100% digoxin, 94% diuretics; no ACEI or BB
Morisco, 1994; (n = 6) [40]	29 (6.7)	50 mg TID	1 month (no washout)	4 CAD and 2 idiopathic	II–IV	Nitro derivatives; no ACEI or BB
Poggesi, 1991; (n = 18) [42]	67 (2.3)	50 mg BID	2 months	13 idiopathic, 7 ischaemic (18 completed the study)	II–III	Digoxin, diuretics, ACEI
Serra, 1991; (n = 20) [44]	59 (6.6)	60 mg QD	1 month (no washout)	13 CAD, 7 hypertensive	II–III	Digoxin, diuretics, nitrates
Watson, 1999; (n = 27) [48]	55 (11)	33 mg TID	3 months	77% idiopathic, 23% ischaemic	Mean 41 months duration, EF < 35%	80% digoxin, 93% diuretics 83% nitrates or hydralazine, 100% ACEI, no BB
Parallel trials						
Keogh, 2003; (n = 35) [49]	62 (8)	50 mg TID	3 months	Ischaemic, valvular, idiopathic	II–III; EF < 40%	71% digoxin, 91% diuretics, 22% nitrates or hydralazine; 100% ACEI, no BB
Khatta, 2000; (n = 46) [50]	64	200 mg/day	6 months	59% ischaemic	III–IV (91% class III); EF < 40%	96% diuretics, 100% digoxin, 100% ACEI or other vasodilators, 78% BB
Munkholm, 1995; (n = 22) [46]	57	100 mg BD	3 months	Ischaemic or dilated	II–III; EF < 45%	55% digoxin, 86% diuretics, 95% ACEI, no BB
Judy, 1986; (n = 10) [38]	66	100 mg/day	6 months	Various aetiologies	IV	Unknown
Permanetter, 1992; (n = 25) [41]	52	100 mg/day	3 months	Idiopathic	I–III (60% class III)	92% digoxin, 64% diuretics, 44% nitrates or nifedipine

ACEI — angiotensin-converting enzyme inhibitor; BB — beta-blockers; BD — twice daily; CAD — coronary artery disease; EF — ejection fraction; HF — heart failure; NYHA — New York Heart Association; QD — once daily; TID — three times daily

periods ranging from one to six months (Table 1). Overall, a 3.7% (95% CI 1.59–5.77) net improvement in the ejection fraction was found, and cardiac output was increased on average of 0.28 L/min (95% CI 0.03–0.53) [3]. Although cardiac index and stroke volume were not significantly affected by themselves, only a few studies with these parameters were included in these analyses and it is possible that the analysis was underpowered.

On subgroup analysis in this meta-analysis, it was postulated that CoQ_{10} may act through reduction in afterload. In support of this hypothesis, studies that included angiotensin converting enzyme inhibitors (ACEI) showed no increase in ejection fraction, whereas those without ACEI showed a 6.7% increase. This therefore suggests that CoQ_{10} therapy may be best targeted at patients who are intolerant of ACEI.

Unfortunately, beta-blockers were only used in one trial evaluated in this analysis [50]; therefore, subgroup analysis could not be performed to determine if concomitant beta-blocker or, for that matter, angiotensin II receptor blocker, or aldosterone-receptor antagonist therapy, would also negate the benefits of CoQ_{10}.

Given that patients with more severe CHF (NYHA classes III and IV) have lower plasma and myocardial levels of CoQ_{10} than those with less severe HF (NYHA classes I and II), it was considered that those with the most severe HF (NYHA class IV) would benefit the most from CoQ_{10}, although this was

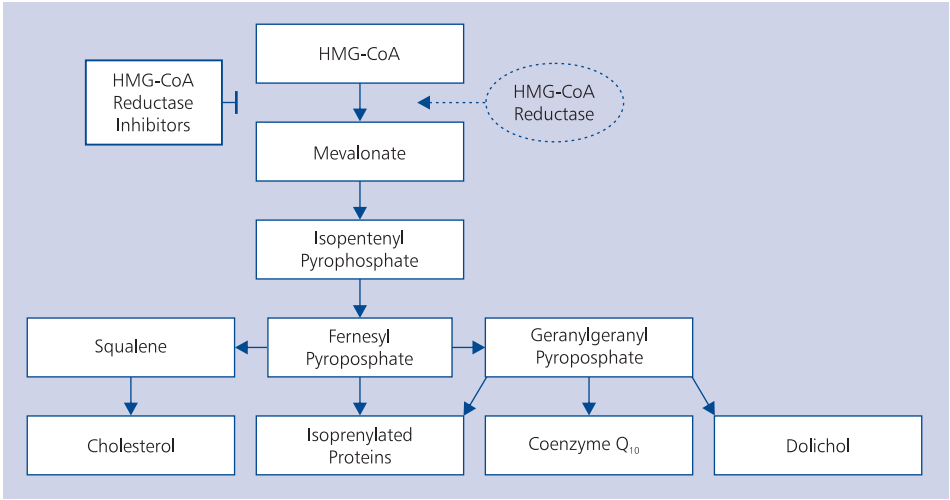

Figure 4. The mevalonate pathway. Inhibition of hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase by statins leads to depletion in products of the pathway including cholesterol and coenzyme Q_{10}; reproduced with permission from the Australasian Asssociation of Clinical Biochemists

not supported by sub-group analysis. It could be postulated that compared to more advanced HF, in which myocytes may be more severely compromised, less compromised hearts may possess more salvageable cardiac myocytes that are able to respond to CoQ_{10}. It is also worth noting that in all the intervention trials undertaken to date, those achieving higher plasma CoQ_{10} levels showed better clinical outcomes [27]. It has further been suggested that there may be a case for the measurement of plasma CoQ_{10} levels, in order to identify those subjects at increased risk of mortality and who might benefit from CoQ_{10} intervention [26]. It should also be noted that clinical trials that evaluated CoQ_{10}-containing multicomponent supplements in patients with HF were not included in this analysis.

Despite the improvements seen in these surrogate end-points, at the time of this meta-analysis there was a relative paucity of data for CoQ_{10} on hard end-points in CHF such as mortality, thus establishing the rationale for a randomised controlled trial such as Q-SYMBIO, with end-points including mortality.

A Cochrane review addressed randomised controlled trials that studied the beneficial and harmful effects of CoQ_{10} in HF [5]. Seven studies were identified, although most did not report on major outcomes and also had small population sizes. Meta-analysis was only possible for a few physiological measures and there was substantial heterogeneity between studies [5]. No overall effect on mortality was observed and it was concluded that no change in practice is warranted at this time given that more high quality and larger studies need to be conducted [5].

The Cochrane review thus served to highlight the methodological deficiencies of previously undertaken studies and to give further impetus to the rationale for the establishment of a randomised controlled trial such as Q-SYMBIO [1].

WHAT ARE THE IMPLICATIONS FOR STATIN THERAPY?

This also brings into perspective the role of statins and whether they may confer benefit or not in patients with CHF, given the likely underlying ischaemic aetiology in many patients [51]. Although they may be expected to confer benefit through cholesterol reduction, they also lower CoQ_{10} [6], given that they work through the common mevalonate pathway (Fig. 4). However, the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA) investigators failed to show a reduction in major vascular events in older patients with systolic HF [52].

Similarly, in the GISSI-HF study (which included CHF patients with both ischaemic and non-ischaemic aetiologies), there was also no reduction in vascular adverse outcomes with rosuvastatin therapy [53].

A plausible explanation for this may be the reduction in CoQ_{10}, as our group has shown to occur in patients with non-ischaemic HF [54]. We showed that 40 mg atorvastatin led to a 33% reduction in CoQ_{10} levels in non-ischaemic HF subjects, though this did not compromise improvements in endothelial function [54]. There was also a significant association ($r = -0.585$; $p = 0.011$) between CoQ_{10} reductions and improvement in endothelial function with forearm plethysmography, suggesting that the improvement in endothelial function with atorvastatin therapy is mediated through 'non-lipid pleiotropic' pathways. This study postulated a role of CoQ_{10} as a potential surrogate marker for improvement in endothelial function in resistance vessels, and it was also hypothesised that further benefits may accrue with concomitant CoQ_{10} supplementation.

The CORONA investigators subsequently measured serum CoQ_{10} in a pre-specified subset of 1,191 patients with ischaemic systolic HF and related this to clinical outcomes. Pa-

tients with lower CoQ_{10} concentrations were older and had more advanced HF. Mortality was significantly higher among patients in the lowest compared to the highest CoQ_{10} tertile in a univariate analysis (HR 1.50; 95% CI 1.04–2.6; p = 0.03), but not in a multivariable analysis. CoQ_{10} was not found to be an independent prognostic variable in HF [55], in contrast with the findings of our previous similar study [26].

Given these observations, and the complex interplay of cholesterol, statin therapy and clinical outcomes in HF, future trials incorporating a CoQ_{10} supplementation arm together with statin may be postulated to confer improved clinical outcomes that CORONA did not show [52].

The conflicting findings from these observational studies also gave further impetus to the establishment of a good randomised controlled clinical trial.

WHAT ABOUT THE ROLE OF COENZYME Q_{10} FOR CARDIAC FUNCTION IN OTHER SETTINGS?

Supplementation of CoQ_{10} and also selenium in a cohort of community-dwelling elderly people reduced the progression of cardiac wall tension, as measured by the cardiac biomarker NT-proBNP, and CV mortality, mainly in participants whose baseline plasma NT-proBNP ranged from the second to the fourth quintiles of the peptide [56]. This could be interpreted as indicating that the therapeutic response may be more pronounced in participants who are in the early stages of development of cardiac dysfunction and could provide a basis to initiate larger randomised trials evaluating the effect of CoQ_{10} and selenium on patients with HF.

COMMENTARY

Q-SYMBIO concluded that CoQ_{10} supplementation improves symptoms and reduces mortality and major adverse CV events in patients with CHF [1]. It is remarkable however that there was a long gestation of the study from the point of inception [27] to full publication [1]. As the authors indicated, CoQ_{10} is a non-patentable substance, with low budget and it was difficult to achieve competitive recruitment against pharmaceutical trials using licensed drugs [1]. This may at least partly explain why the study was not completed according to the original enrollment plan. Medication use is well documented, although it is difficult to be sure that individual patients were on optimal medical therapy and there may be differences in practice between countries. Baseline characteristics, including duration of CHF, were however well matched between the two treatment groups. NT-proBNP concentrations were more than halved in both study groups at 106 weeks compared to baseline, suggesting that the most severely affected patients had died.

CoQ_{10} deficiency has been implicated in several clinical disorders; in some, such as CHF, there is a biologically plausible rationale why supplementation therapy may confer a clinical benefit. The evidence base in support of a therapeutic role for CoQ_{10} in CHF however is still evolving. Although a landmark study, Q-SYMBIO is still a relatively small trial by pharmaceutical standards. In order to influence clinical behaviour on a more significant scale, it should ideally be replicated independently. It is hoped that its recent publication [1] will stimulate further interest and impetus to undertake such intervention trials.

Conflict of interest: *none declared*

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