CLINICAL RESEARCH　　　　　　　　　　　　　　　　　　　　　　　**Heart Failure**

Coenzyme Q_{10}

An Independent Predictor of Mortality in Chronic Heart Failure

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Objectives　　The aim of this study was to investigate the relationship between plasma coenzyme Q_{10} (CoQ_{10}) and survival in patients with chronic heart failure (CHF).

Background　　Patients with CHF have low plasma concentrations of CoQ_{10}, an essential cofactor for mitochondrial electron transport and myocardial energy supply. Additionally, low plasma total cholesterol (TC) concentrations have been associated with higher mortality in heart failure. Plasma CoQ_{10} is closely associated with low-density lipoprotein cholesterol (LDL-C), which might contribute to this association. Therefore we tested the hypothesis that plasma CoQ_{10} is a predictor of total mortality in CHF and could explain this association.

Methods　　Plasma samples from 236 patients admitted to the hospital with CHF, with a median (range) duration of follow-up of 2.69 (0.12 to 5.75) years, were assayed for LDL-C, TC, and total CoQ_{10}.

Results　　Median age at admission was 77 years. Median (range) CoQ_{10} concentration was 0.68 (0.18 to 1.75) μmol/l. The optimal CoQ_{10} concentration for prediction of mortality (established with receiver-operator characteristic [ROC] curves) was 0.73 μmol/l. Multivariable analysis allowing for effects of standard predictors of survival—including age at admission, gender, previous myocardial infarction, N-terminal peptide of B-type natriuretic peptide, and estimated glomerular filtration rate (modification of diet in renal disease)—indicated CoQ_{10} was an independent predictor of survival, whether dichotomized at the ROC curve cut-point (hazard ratio [HR]: 2.0; 95% confidence interval [CI]: 1.2 to 3.3) or the median (HR: 1.6; 95% CI: 1.0 to 2.6).

Conclusions　　Plasma CoQ_{10} concentration was an independent predictor of mortality in this cohort. The CoQ_{10} deficiency might be detrimental to the long-term prognosis of CHF, and there is a rationale for controlled intervention studies with CoQ_{10}.　　(J Am Coll Cardiol 2008;52:1435–41) © 2008 by the American College of Cardiology Foundation

Coenzyme Q_{10} (CoQ_{10}) is a fat-soluble quinone found in all cells, essential for adenosine triphosphate generation via mitochondrial oxidative phosphorylation (1). Its depletion might exacerbate chronic heart failure (CHF) (2,3).

It has been demonstrated that total cholesterol (TC) is related to survival in CHF (4–7). Rauchhaus et al. (5) reported that lower serum TC was independently associated with total mortality in a CHF cohort independent of etiology, age, left ventricular ejection fraction, and exercise capacity. The mechanisms postulated were that cholesterol might limit lipopolysaccharide-induced production of cyto-kines, and thus high levels of cholesterol might confer a survival advantage (5). They also postulated that high cholesterol might provide "greater metabolic reserve" to deal with the CHF syndrome. The authors did not, however, refer to CoQ_{10}, which is known to correlate with TC concentration (8) and which might contribute to the worse outcomes seen in CHF patients with low cholesterol. Myocardial deficiency of CoQ_{10} has been demonstrated in heart failure, and the severity of the deficiency correlated with severity of symptoms. Patients in New York Heart Association (NYHA) functional class IV have significantly lower CoQ_{10} in endomyocardial biopsy samples than those in NYHA functional class I (3).

Although beneficial effects of CoQ_{10} supplementation in CHF have been reported (9–23) and intervention studies such as Q-SYMBIO have been initiated (24), CoQ_{10} levels have not been previously related to outcomes of heart failure in observational studies. Therefore, we tested the hypothesis

that CoQ$_{10}$ is associated with cholesterol and predicts mortality in patients with CHF.

Methods

This study was part of an ongoing cohort study of biomarkers in heart failure, with data collected systematically and prospectively. The CoQ$_{10}$ hypothesis was generated retrospectively.

Patients. Patients able to give informed consent were recruited during admission to Christchurch Hospital with symptomatic CHF satisfying Framingham (25) (2 major and 2 minor criteria present concurrently) and European Society of Cardiology (26) criteria, between July 2000 and December 2004. Plasma N-terminal peptide of B-type natriuretic peptide (NT-proBNP) was required to be over 50 pmol/l. Exclusion criteria included active myocarditis/pericarditis, life expectancy due to noncardiovascular disease of <24 months, severe hepatic or pulmonary disease (forced expiratory volume <1 l), renal impairment (plasma creatinine >250 μmol/l), transient heart failure from myocardial infarction (MI) treated with acute revascularization and a subsequent ejection fraction during the index hospital admission of >40%, severe valvular disease being considered for surgery, severe aortic stenosis (valve area <1 cm^2), heart failure secondary to mitral stenosis, under consideration for cardiac transplantation, and age <18 years. A total of 3,576 patients were screened, yielding 998 eligible patients, of which 236 qualifying patients were enrolled. Eighty-four patients were excluded from the consented population on the basis of the exclusion criteria, primarily due to a reduction in NT-proBNP between consent (during hospital stay) and blood sampling. Qualifying patients visited within 28 days of the index hospital admission for collection of blood plasma samples, which were stored at −80°C.

At admission, all patients were severely symptomatic with heart failure. However, at the time of blood collection (median of 48 days after the index hospital admission), 65% were in NYHA functional class II. The median ejection fraction was 37%.

This study received ethical approval from the Canterbury Ethics Committee, and written informed consent was obtained from all participants.

Follow-up. Patients were followed-up for a median of 2.69 (range 0.12 to 5.75) years. Patients were followed up at a minimum of 3 monthly intervals to document medications, adverse events, readmissions to hospital, and death. No

patients were lost to follow-up. The primary end point of this study was all-cause mortality.

Measurement of analytes. Plasma total CoQ$_{10}$ was measured with high-performance liquid chromatography with electrochemical detection, similarly to Tang et al. (2001) (27). The within- and between-run coefficients of variation for the CoQ$_{10}$ assay are approximately 3.3%. The TC was determined by an enzymatic colorimetric method (Aeroset analyser Model LN, Abbott Laboratories, Chicago, Illinois), with a coefficient of variation of 1.6%. Direct low-density lipoprotein cholesterol (LDL-C) was measured with Roche Diagnostics reagents (Indianapolis, Indiana), with a coefficient of variation of 1.2%. The NT-proBNP was measured by immunoassay, with a coefficient of variation of 13% (28). Glomerular filtration rate (GFR) was estimated by the modification of diet in renal disease (MDRD) study equation (29).

Statistical analysis. Statistics were computed with SPSS version 11.5 (SPSS, Inc., Chicago, Illinois); p < 0.05 was considered significant. Due to skewed distributions, nonparametric statistics were used, and values are expressed as medians and ranges or percentages, as indicated. Reported correlations are Spearman rank correlations (R). To compare different predictive values at a particular time point, areas under the curve for sensitivity and specificity were constructed (receiver-operator characteristic [ROC] curve) (MedCalc 1993 to 2005, MedCalc Software, Mariakerke, Belgium). The best cutoff value for survival status at a given time point was defined as that point closest to the (0,1) point (the minimum Euclidean distance). Cox proportional hazards analyses were used to assess prognostic associations. A base model containing standard predictors of survival was constructed, which included age, gender, history of previous MI, glomerular filtration rate, and NT-proBNP, with additional factors added on to the base model as described. The hazard ratio (HR) with 95% confidence interval (CI) and p values by the likelihood ratio test are presented. Kaplan-Meier cumulative survival plots from date of admission were constructed with dichotomous data obtained with the cut-point from the ROC curve. Significance values for Kaplan-Meier curves are the log-rank comparisons. Differences in demographic variables for patients surviving more than and <1 year were compared with the Mann-Whitney rank sum test or chi-square test (Pearson chi-square 2-sided asymptotic significance).

Results

Samples from 236 patients were analyzed. The median (range) follow-up time was 2.7 (0.1 to 5.8) years. A total of 76 events (deaths) occurred. Maximum storage time for samples was 5.4 years. The patient demographic data of the complete cohort and the survivors and nonsurvivors at 1 year are shown in Table 1.

There was a significant correlation between CoQ$_{10}$ and TC (R = 0.663, p < 0.001) and LDL-C (R = 0.573, p < 0.001)

Table 1	Clinical and Biochemical Characteristics of All Patients at Index Hospital Admission and of Survivors and Nonsurvivors at 12 Months			
		12 Months		
Variable	All Patients (n = 236)	Nonsurvivors (n = 29)	Survivors (n = 205)	p Value*
Age at admission (yrs)	77 (32–89)	79 (61–86)	77 (32–89)	0.05†
Male gender (%)	63	62	63	0.89‡
Weight (kg)	75 (45–159)	69 (45–96)	75 (47–159)	0.12†
Height (cm)	168 (145–193)	168 (150–183)	168 (145–193)	0.98†
BMI (kg/m^2)	26 (18–43)	25 (18–35)	26 (19–43)	0.07†
GFR (MDRD) (ml/min/1.73 m^2)	60 (17–123)	59 (23–120)	60 (17–123)	0.37†
NT-proBNP (pmol/l)	238 (15–1540)	257 (71–1094)	234 (15–1540)	0.42†
CoQ$_{10}$ (μmol/l)	0.68 (0.18–1.75)	0.56 (0.18–1.29)	0.69 (0.20–1.75)	0.04†
TC (mmol/l)	4.78 (2.10–11.43)	4.46 (2.88–6.26)	4.90 (2.10–11.43)	0.08†
LDL-C (mmol/l)	2.52 (0.68–7.31)	2.47 (1.38–3.76)	2.62 (0.68–7.31)	0.35†
CoQ$_{10}$/TC ratio (mmol/mol)	0.14 (0.05–0.38)	0.12 (0.05–0.23)	0.14 (0.05–0.38)	0.12†
CoQ$_{10}$/LDL-C ratio (mmol/mol)	0.26 (0.09–0.84)	0.24 (0.09–0.41)	0.27 (0.09–0.84)	0.14†
Previous MI (%)	48	59	46	0.20‡
Diabetes (%)	21	28	20	0.35‡
Renal disease (%)	28	28	27	0.98‡
Smoking (%)				
Current	4	7	4	
Past	55	52	55	0.73‡
Never	41	38	41	
Medications (%)				
ACE inhibitor at admission	53	55	53	0.80‡
ACE inhibitor at discharge	82	72	83	0.15‡
Beta-blocker at admission	39	41	39	0.81‡
Beta-blocker at discharge	63	62	63	0.89‡
Statin at admission	33	41	31	0.27‡
Statin at discharge	45	45	44	0.97‡

Values are expressed as median (range) or percentage. *p values are for comparison between survivors and nonsurvivors at each time point. †As determined with the Mann-Whitney rank sum test. ‡As determined with the chi-square test.

ACE = angiotensin-converting enzyme; BMI = body mass index; CoQ$_{10}$ = coenzyme Q$_{10}$; GRF (MDRD) = estimated glomerular filtration rate calculated with the modification of diet in renal disease formula; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; NT-proBNP = N-terminal peptide of B-type natriuretic peptide; TC = total cholesterol.

and inversely between CoQ$_{10}$ and NT-proBNP (R = −0.258, p < 0.001). There was also a weaker but significant negative correlation between TC and NT-proBNP (R = −0.190, p = 0.004).

The ROC curves were constructed for putative predictors of survival. Significant discrimination was observed for CoQ$_{10}$ (Fig. 1), the ratios of CoQ$_{10}$ to TC and CoQ$_{10}$ to LDL-C, and also NT-proBNP and GFR (MDRD). A comparison of patient demographic data for patients with CoQ$_{10}$ values higher and lower than the ROC curve optimal cut-point (0.73 μmol/l) (Fig. 1) is shown in Table 2. Neither TC nor LDL-C by themselves significantly differed from zero discrimination (diagonal on ROC curve), and hence no cutoff value for predicting survival could be determined. The ROC curve cut-points were also used in a multivariate analysis as outlined in the following text.

Kaplan-Meier curves for CoQ$_{10}$ (Fig. 2A), the CoQ$_{10}$ to TC ratio, and the CoQ$_{10}$ to LDL-C ratio—dichotomized for either the ROC curve cut-point or the median (data not shown)—showed significant differences in survival (p < 0.01), with lower CoQ$_{10}$ and CoQ$_{10}$ to lipid ratios predicting poorer survival. Additionally, a Kaplan-Meier curve for a 4-way split between CoQ$_{10}$
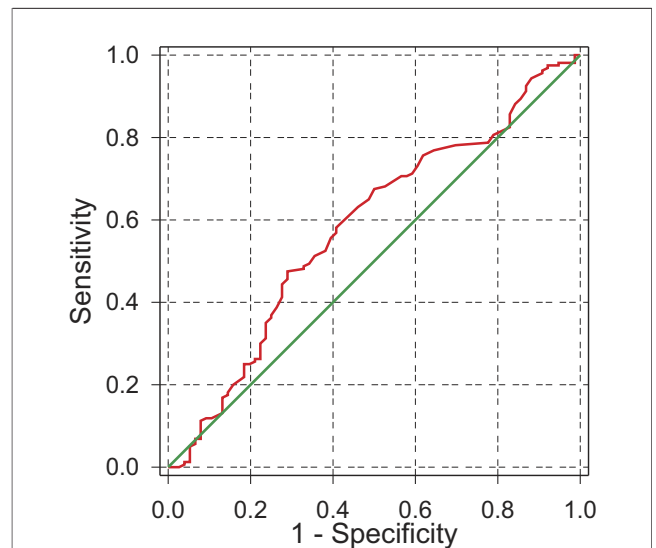

Figure 1   Receiver-Operator Characteristic Curve for CoQ$_{10}$

The receiver-operator characteristic curve for plasma coenzyme Q$_{10}$ (CoQ$_{10}$) (**red line**) as a predictor of total mortality, showing the optimal cut-point of 0.73 μmol/l. The **green line** represents the zero discrimination line.

Table 2	Clinical and Biochemical Characteristics of Patients With CoQ$_{10}$ Concentrations Above and Below the Mortality ROC Curve Cut-Point (0.73 μmol/l)		
Variable	**CoQ$_{10}$ Below ROC Curve Cut-Point (CoQ$_{10}$ 0.18–0.73 μmol/l) (n = 137)**	**CoQ$_{10}$ Above ROC Curve Cut-Point (CoQ$_{10}$ 0.73–1.75 μmol/l) (n = 98)**	**p Value**
Age at admission (yrs)	78	76	0.34*
Male gender (%)	64	63	0.90†
Died (%)	39	22	0.007†
Weight (kg)	75	76	0.65*
Height (cm)	168	169	0.88*
BMI (kg/m^2)	26	27	0.36*
GFR (MDRD) (ml/min/1.73 m^2)	59	61	0.04*
NT-proBNP (pmol/l)	258	194	0.004*
CoQ$_{10}$ (μmol/l)	0.53	0.92	<0.001*
TC (mmol/l)	4.30	5.45	<0.001*
LDL-C (mmol/l)	2.27	3.04	<0.001*
CoQ$_{10}$/TC ratio (mmol/mol)	0.12	0.17	<0.001*
CoQ$_{10}$/LDL-C ratio (mmol/mol)	0.23	0.31	<0.001*
Previous MI (%)	53	40	0.04†
Diabetes (%)	23	17	0.26†
Renal disease (%)	33	20	0.04†
Smoking (%)			
Current	3	6	
Past	58	50	0.28†
Never	39	44	
Medications (%)			
ACE inhibitor at admission	54	52	0.77†
ACE inhibitor at discharge	82	83	0.86†
Beta-blocker at admission	44	33	0.08†
Beta-blocker at discharge	71	53	0.005†
Statin at admission	38	26	0.05†
Statin at discharge	55	31	<0.001†

Values are expressed as median (range) or percentage. *As determined with the Mann-Whitney rank sum test. †As determined with the chi-square test.

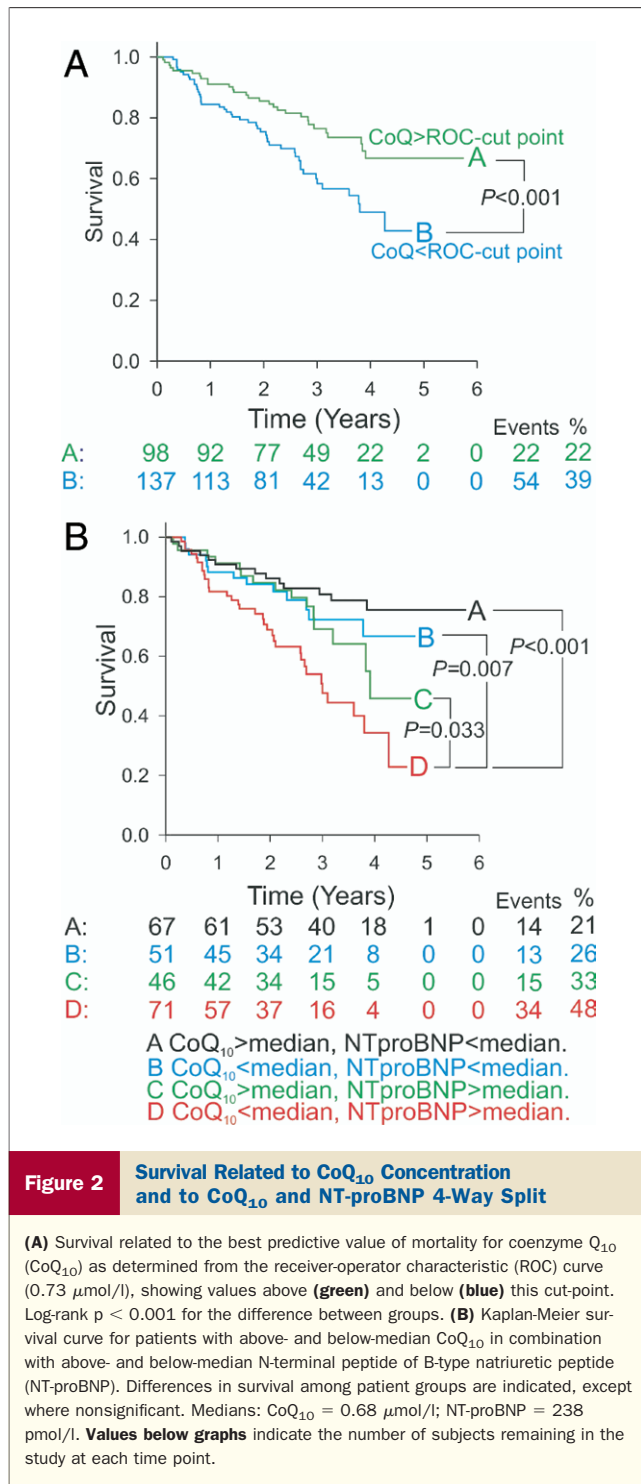ROC = receiver-operator characteristic; other abbreviations as in Table 1.

and NT-proBNP showed significantly better survival related to high CoQ$_{10}$ combined with low NT-proBNP levels compared with low CoQ$_{10}$ and high NT-proBNP levels (Fig. 2B). There is significantly better survival associated with high CoQ$_{10}$ plus high NT-proBNP than there is with low CoQ$_{10}$ together with high NT-proBNP. And there is significantly better survival associated with low CoQ$_{10}$ and low NT-proBNP than there is with low CoQ$_{10}$ and high NT-proBNP (Fig. 2B).

Multivariable analysis allowing for effects of standard predictors of survival, including age at admission, gender, previous MI, estimated GFR (MDRD), and NT-proBNP, showed that CoQ$_{10}$ was an independent predictor of survival, whether dichotomized at the ROC curve cut-point (HR: 1.99; 95% CI: 1.21 to 3.30, p = 0.007) or the median (0.68 μmol/l) (HR: 1.62; 95% CI: 1.01 to 2.59, p = 0.05) (Table 3). Total cholesterol was not a significant predictor of survival either added to the model as a continuous variable or dichotomized for the ROC curve cut-point of 5.2 mmol/l determined by Rauchhaus et al. (5) (Table 3).

The ratio of CoQ$_{10}$ to TC was a significant predictor of survival when added to the base model as a continuous variable (HR [for a 10-U change in the CoQ$_{10}$ to TC ratio]: 2.00; 95% CI: 1.03 to 3.85, p = 0.04) as well as when dichotomized for the median (median = 0.14 mmol/mol) (HR: 2.01; 95% CI: 1.23 to 3.31, p = 0.006). Similarly, the ratio of CoQ$_{10}$ to LDL-C was close to significant predictor when added to the base model as a continuous variable (HR: 12.50; 95% CI: 0.97 to 100.00, p = 0.05) as well as dichotomized for the median (median = 0.26 mmol/mol) (HR: 1.61; 95% CI: 1.00 to 2.59, p = 0.05). Neither LDL-C nor TC dichotomized at the median or statins at discharge were independent predictors of survival when added to the base model, either independently or together.

Discussion

We have found an independent association between lower CoQ$_{10}$ and increased risk of mortality in CHF. The strength of association between CoQ10 and mortality (HR: 1.99) was greater than that observed for NT-proBNP. The CoQ$_{10}$ predicted outcome independently of NT-proBNP,

Figure 2   **Survival Related to CoQ$_{10}$ Concentration and to CoQ$_{10}$ and NT-proBNP 4-Way Split**

(A) Survival related to the best predictive value of mortality for coenzyme Q$_{10}$ (CoQ$_{10}$) as determined from the receiver-operator characteristic (ROC) curve (0.73 μmol/l), showing values above **(green)** and below **(blue)** this cut-point. Log-rank p < 0.001 for the difference between groups. **(B)** Kaplan-Meier survival curve for patients with above- and below-median CoQ$_{10}$ in combination with above- and below-median N-terminal peptide of B-type natriuretic peptide (NT-proBNP). Differences in survival among patient groups are indicated, except where nonsignificant. Medians: CoQ$_{10}$ = 0.68 μmol/l; NT-proBNP = 238 pmol/l. **Values below graphs** indicate the number of subjects remaining in the study at each time point.

might be an important pathogenic mechanism associated with worse outcomes in CHF. Follow-up samples to determine whether CoQ$_{10}$ levels remain persistently depleted would provide interesting further information on the role of CoQ$_{10}$ in heart failure.

We were unable to confirm an independent association of plasma cholesterol with total mortality, as has been previously reported (4–7). This might be due to differences in the 2 study populations. Rauchhaus et al. (5) enrolled patients with CHF from a CHF and cardiomyopathy clinic with duration of CHF between 6 months and 20 years. The majority were in NYHA functional class III (5). Our cohort was less symptomatic at the time of sampling and had various etiologies. Our group was older (median age 77 years in our study vs. mean ages of 63.0 and 62.1 years in the derivation and validation studies of Rauchhaus et al. [5], respectively) and was followed-up for a longer duration. Our patients were recruited during admission to the hospital with symptomatic CHF, with the majority being discharged in NYHA functional class II. These differences might account for the failure to confirm plasma cholesterol as a predictor of mortality.

It has also been shown that the myocardium in patients with heart failure is deficient in CoQ$_{10}$ (3). Because plasma total CoQ$_{10}$ concentrations correlate with TC, the ratio of CoQ$_{10}$ to TC and/or LDL-C might be a better marker of CoQ$_{10}$ status and hence survival. However, our results with the CoQ$_{10}$ concentrations adjusted for lipids (TC or LDL-C) are similar to those with unadjusted CoQ$_{10}$ concentrations, suggesting that the use of adjusted values offers no advantage.

The low number of events in our study (n = 76) is a limitation, and it is possible that some of the borderline associations found were affected by this. The low number of events also limited the number of baseline variables that could be added to the multivariable models, and, therefore, we have concentrated our analyses on the most established and accepted predictors of survival.

The association of CoQ$_{10}$ and survival brings into question the role of statins in CHF. The role of statins in

Table 3   **Cox Proportional Hazards Model Analysis of Factors Predictive of Mortality for the Cohort**

Variable	Coefficient	HR	95% CI for HR	p Value
Age at admission (yrs)	0.059	1.06	1.02–1.10	0.001
Gender (male)	−0.243	1.28	0.78–2.09	0.34
Previous MI	−0.244	1.28	0.81–2.02	0.30
GFR (MDRD) (ml/min/1.73 m²)	−0.015	0.99	0.97–1.00	0.03
NT-proBNP*	−0.597	1.82	1.11–2.98	0.02
CoQ$_{10}$†	0.690	1.99	1.21–3.30	0.007
CoQ$_{10}$*	0.481	1.62	1.01–2.59	0.05
TC (mmol/l)	0.027	1.03	0.83–1.27	0.81
TC‡	0.004	1.00	0.60–1.67	0.99

*Dichotomized for median split. †Dichotomized for ROC curve optimal cut-point. ‡Dichotomized at 5.2 mmol/l, the ROC curve cut-point determined by Rauchhaus et al. (5).
CI = confidence interval; HR = hazard ratio; other abbreviations as in Tables 1 and 2.

suggesting that its longer-term contribution to function might be important regardless of the initial severity of the heart failure. The predictive power of CoQ$_{10}$ was significant when included in the model dichotomized according to either the median value or ROC curve optimal cut-point for survival. It is recognized that CoQ$_{10}$ deficiency occurs in CHF (3) and that this might compromise mitochondrial function. It is therefore plausible that CoQ$_{10}$ deficiency

CHF is controversial (30); however, statin use has been associated with lower risk of death in patients with CHF (7,31). CoQ$_{10}$ and cholesterol are both products of the mevalonate biosynthetic pathway, and statin therapy also lowers plasma total CoQ$_{10}$ (32). If statins do confer benefit in CHF patients, it might be through mechanisms other than cholesterol reduction, so called pleiotropic effects. In 1 small study (33), CoQ$_{10}$ reduction on statin therapy was associated with an improvement in endothelial function in CHF patients, suggesting that it might be a marker of pleiotropism. Larger and more long-term interventional studies with statins in CHF are required to assess the effect on clinical outcomes.

In our present study, patients with higher CoQ$_{10}$ (above the ROC curve cut-point) were less likely to be receiving statins (or beta-blocker drugs); however, statin therapy at discharge from the index admission was not an independent predictor of survival, and CoQ$_{10}$ remained an independent predictor of mortality in a multivariable model that included statin treatment. The CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure) investigators failed to show a reduction in major vascular events in older patients with systolic heart failure (34). It could be postulated that this was due to a reduction in CoQ$_{10}$ that offset any other beneficial effect of statin and warrants further investigation with a larger sample size than the current study.

Several clinical trials (10–17,19–22) have suggested benefits from CoQ$_{10}$ supplementation in CHF. Two meta-analyses of CoQ$_{10}$ supplementation in CHF have been conducted. Soja and Mortensen (9) used 8 double-blind placebo-controlled studies (10–17) and reported a significant improvement in stroke volume, ejection fraction, cardiac output, cardiac index, and end-diastolic volume index, as a consequence of CoQ$_{10}$ supplementation. Changes in systolic time intervals and total work capacity were not statistically significant (9). More recently, Sander et al. (18) used 11 studies—10 that evaluated ejection fraction (10,12–14,17,19–22), and 2 that evaluated cardiac output (16,23)—with CoQ$_{10}$ doses ranging from 60 to 200 mg/day and treatment periods ranging from 1 to 6 months. A 3.7% net improvement in the ejection fraction was found, and cardiac output was increased an average of 0.28 l/min (18). Recently an international multicenter intervention study, Q-SYMBIO, has been initiated (24). This is a randomized, double-blind, multicenter trial with focus on symptoms, biomarker status (B-type natriuretic peptide), and long-term outcomes (24).

No previous studies, however, have formally studied the relationship between CoQ$_{10}$ and outcomes in CHF in a longitudinal observational study such as ours. Our findings in a clearly defined, prospectively studied group that CoQ$_{10}$ depletion is associated with worse outcomes in CHF give further support to the rationale of the intervention studies that have already been initiated.

Conclusions

Plasma CoQ$_{10}$ is an independent predictor of mortality in CHF. CoQ$_{10}$ deficiency might be implicated in the long-term prognosis of CHF, and there is a rationale for further controlled intervention studies of CoQ$_{10}$ supplementation.

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