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The Effect of Coenzyme Q_{10} on Morbidity and Mortality in Chronic Heart Failure

Results From Q-SYMBIO: A Randomized Double-Blind Trial

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ABSTRACT

OBJECTIVES This randomized controlled multicenter trial evaluated coenzyme Q_{10} (CoQ_{10}) as adjunctive treatment in chronic heart failure (HF).

BACKGROUND CoQ_{10} is an essential cofactor for energy production and is also a powerful antioxidant. A low level of myocardial CoQ_{10} is related to the severity of HF. Previous randomized controlled trials of CoQ_{10} in HF were underpowered to address major clinical endpoints.

METHODS Patients with moderate to severe HF were randomly assigned in a 2-year prospective trial to either CoQ_{10} 100 mg 3 times daily or placebo, in addition to standard therapy. The primary short-term endpoints at 16 weeks were changes in New York Heart Association (NYHA) functional classification, 6-min walk test, and levels of N-terminal pro–B type natriuretic peptide. The primary long-term endpoint at 2 years was composite major adverse cardiovascular events as determined by a time to first event analysis.

RESULTS A total of 420 patients were enrolled. There were no significant changes in short-term endpoints. The primary long-term endpoint was reached by 15% of the patients in the CoQ_{10} group versus 26% in the placebo group (hazard ratio: 0.50; 95% confidence interval: 0.32 to 0.80; $p = 0.003$) by intention-to-treat analysis. The following secondary endpoints were significantly lower in the CoQ_{10} group compared with the placebo group: cardiovascular mortality (9% vs. 16%, $p = 0.026$), all-cause mortality (10% vs. 18%, $p = 0.018$), and incidence of hospital stays for HF ($p = 0.033$). In addition, a significant improvement of NYHA class was found in the CoQ_{10} group after 2 years ($p = 0.028$).

CONCLUSIONS Long-term CoQ_{10} treatment of patients with chronic HF is safe, improves symptoms, and reduces major adverse cardiovascular events. (Coenzyme Q10 as adjunctive treatment of chronic heart failure: a randomised, double-blind, multicentre trial with focus on SYMptoms, BIomarker status [Brain-Natriuretic Peptide (BNP)], and long-term Outcome [hospitalisations/mortality]; ISRCTN94506234) (J Am Coll Cardiol HF 2014;2:641–9) © 2014 by the American College of Cardiology Foundation.

Optimal therapy of heart failure (HF) is a considerable challenge. Standard treatments are administered to block rather than to enhance cellular processes (1), and some important requirements of the myocardium may not be covered. There are multiple causes of HF, but dysfunction of bioenergetics leading to energy starvation of the cardiac myocytes may be an important

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ABBREVIATIONS AND ACRONYMS

CI = confidence interval

CoQ_{10} = coenzyme Q_{10}

EF = ejection fraction

HF = heart failure

HR = hazard ratio

MACE = major adverse cardiovascular event(s)

6MWT = 6-min walk test

NT-proBNP = N-terminal pro-B-type natriuretic peptide

NYHA = New York Heart Association

RCT = randomized controlled trial

VAS = visual analogue scale

contributive mechanism (2,3). Coenzyme Q_{10} (CoQ_{10}) is a powerful lipid-soluble antioxidant (4), as well as a central redox component of the electron transport chain and the synthesis of adenosine triphosphate (5). A reduced myocardial tissue content of CoQ_{10} has been demonstrated in patients with HF, and it correlates with the severity of symptoms and the degree of left ventricular dysfunction (6). Low plasma CoQ_{10} has been shown to be an independent predictor of mortality in HF (7), but this was not replicated in another observational study (8). Published meta-analyses of randomized controlled trials (RCTs) with CoQ_{10} in HF have mostly indicated a positive effect on left ventricular ejection fraction (EF) with or without improvement of New York Heart Association (NYHA) functional class (9–11). The RTCs have been underpowered to address major clinical endpoints. In 2 systematic reviews, there was either a nonsignificant trend toward reduced mortality (12) or no effect on total mortality from CoQ_{10} (13).

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We report the results of Q-SYMBIO, a prospective, randomized, double-blind, placebo-controlled, multicenter trial of CoQ_{10} as adjunctive treatment of chronic HF focusing on changes in *SYM*ptoms, *BI*omarker status, and long-term *O*utcome.

METHODS

Patients were enrolled in 17 European, Asian, and Australian centers from 2003 to 2010. Q-SYMBIO was conducted according to good clinical practice guidelines.

In previous RCTs with CoQ_{10} in HF, the authors aimed for a serum level of CoQ_{10} of at least 2 μg/ml, by using a dosage of 100 to 200 mg/day to obtain a positive clinical effect. A dosage of CoQ_{10} 100 mg twice daily provided a better absorption and a higher serum level compared with 200 mg once daily, probably because of a saturation phenomenon with a delay of uptake in the small intestine (14). In Q-SYMBIO, we selected the CoQ10 dosage in the active treatment group to be 100 mg 3 times daily to ensure a significant increase in the serum level.

The study data from clinical record forms were sent by the investigators to the Data and Safety Monitoring Board, which blindly evaluated all possible adverse events in the 2 treatment arms. Clinical endpoints were adjudicated in a blinded fashion by the Clinical Endpoint Committee. All analyses were performed by the independent statistician after the study was terminated. The study was approved by the institutional review board and the regional ethics committee of each participating institution and by the appropriate national ethics committees and was conformed to the ethical guidelines of the Declaration of Helsinki. All patients provided written informed consent. The study was registered at the International Standard Randomised Controlled Trial Number (ISRCTN) registry (ISRCTN94506234).

OBJECTIVES

The study had a 2-phase objective. The aim of the short-term part (16 weeks) was a blinded evaluation of patients' symptoms (NYHA functional class) and functional status with visual analogue scale (VAS) for symptoms (Online Appendix 1), a 6-min walk test (6MWT), and echocardiography (left ventricular EF and cavity dimensions). Serum samples were obtained for determination of CoQ_{10} and N-terminal pro-B-type natriuretic peptide (NT-proBNP), a biomarker of HF (15). The aim of the long-term part (106 weeks) of the study was to test, on an intention-to-treat basis, whether CoQ_{10} could reduce cardiovascular morbidity and mortality in HF as a composite endpoint.

The primary short-term endpoints were NYHA functional class, 6MWT, and NT-proBNP. A secondary endpoint was scoring of symptoms on VAS: dyspnea, fatigue, and change of symptoms.

The primary long-term endpoint was composite major adverse cardiovascular events (MACE), consisting of unplanned hospital stay resulting from worsening HF, cardiovascular death, mechanical assist implantation, or urgent cardiac transplantation; a time to first event analysis was used. Secondary long-term endpoints were NYHA functional class, NT-proBNP, echocardiography, and mortality.

PATIENTS. Patients were eligible for enrollment if they had chronic HF in NYHA functional class III or IV. Patients were included with typical symptoms and signs of HF. A specific cut-point with respect to EF was not used. The trial enrollment criteria are listed in the Online Table 1.

STUDY DESIGN AND FOLLOW-UP. Patients meeting the inclusion criteria were further assessed for eligibility in the run-in period of 2 weeks on placebo capsules 3 times daily. The patients were evaluated at the start and end of the run-in period regarding NYHA functional classification, with VAS, 6MWT, and echocardiography. Serum samples were obtained for measurements of CoQ_{10} and NT-proBNP. Patients with stable standard HF therapy were randomized in parallel groups to either CoQ_{10} or identical placebo

capsules (Online Appendix 2). The randomization code was prepared by means of a random number generator software in blocks of 6 and was kept in sealed envelopes. Sequentially numbered coded drug packs were distributed, supervised by a central pharmacist to the local center with the instruction to assign new patients to the next available randomization number.

Clinical parameters were registered again after 16 weeks with VAS, 6MWT, and echocardiography, and serum samples for CoQ_{10} and NT-proBNP were repeated. An overview of the times of effect recordings up to 106 weeks is shown in the Online Table 2. All patients continued to receive the assigned treatment for the intended duration of the study. Patients were censored when they reached their first primary endpoint (MACE), and only the first event was included in this analysis. Patients were offered to continue the study medication blindly after a MACE (i.e., hospital stay for HF) for up to 2 years from randomization.

Patients undergoing implantation of a cardiac resynchronization device were censored at the time of implantation. Devices were not inserted for worsening HF but as a result of logistics in the centers after this therapy was introduced while our study was ongoing (16). Patients listed in status 2 for heart transplantation were censored at the admission for the procedure. This was not an endpoint but an elective procedure because of a matching donor arrival. Hospital stay for worsening of HF was defined as the occurrence of increasing symptoms and the need for intravenous treatment with diuretics. In addition, the necessity for using inotropic support and the use of intra-aortic balloon pumping were recorded.

In Q-SYMBIO, hospital stays within 30 days of randomization in either group were not counted as primary endpoints. In previous observational studies, improvements in HF symptoms were observed after approximately 4 weeks (up to 12 weeks) of supplementation with CoQ_{10} (14). From absorption trials, it was estimated that at least 2 weeks would be needed before the raised serum level could be translated into an increase in the mitochondrial content of CoQ_{10} (17). Based on this estimate, we found a blanking period of 30 days appropriate. Incorporation of an early quarantine has been applied in other RCTs of HF (16). All possible adverse effects were monitored from the start of the study.

The randomization code was unavailable to investigators, participants, or statisticians at any time during the study until all data material had been collected, all blood samples had been analyzed, and statistical analysis had been performed. The Q-SYMBIO study was closed in the fall of 2012 by the Steering Committee before the planned number of 550 patients was reached, as a result of a low recruitment rate. The DSMB was not involved in the decision to stop the trial, and the code was broken after the final statistical analysis was done and the database had been locked.

DETERMINATION OF SERUM COENZYME Q_{10} AND N-TERMINAL PRO-B-TYPE NATRIURETIC PEPTIDE. A sample of 25 ml of venous blood was drawn for measurement of serum CoQ_{10} and NT-proBNP while the patients were resting and before they had breakfast and medications. Serum was isolated from blood samples by centrifugation at 3.000 g and thereafter stored at −20° C or at −80° C (for storage >6 months). Samples of serum were investigated for levels of CoQ_{10} by using high-performance liquid chromatography with ultraviolet detection (18) and NT-proBNP using the Elecsys 2010 immunoassay method (Roche Diagnostics, Mannheim, Germany) (19).

STATISTICAL ANALYSIS. The results of the power calculations in the protocol are presented in the Online Table 3. All pre-specified analyses of responses and endpoints were conducted according to the intention-to-treat principle. Descriptive analyses of baseline data were reported as frequencies. Percentages for categorical data and for continuous data were reported as mean ± SD for normally distributed data and median and lower upper quartile for non-normal data. All responses at weeks 16 and 106 recorded from the health status questionnaires and blood samples were analyzed as individual changes from baseline. The significance of treatment on continuous responses was analyzed by a linear model with each investigational center treated as a random intercept effect. The treatment effects were analyzed and adjusted for pre-defined confounders such as age, sex, NYHA functional class, inclusion diagnosis (HF from ischemic heart disease or dilated cardiomyopathy), and center. A chi-square test for independence with exact p values was calculated for the evaluation of the treatment effect on categorical responses. Cumulative incidence curves for the risk of MACE, hospital stay for HF, total cardiovascular mortality, and all-cause mortality were constructed by the Kaplan-Meier method and were analyzed by the Cox proportional hazards regression model stratified according to center. After the intention-to-treat analysis had been carried out, an additional sensitivity analysis was performed with a worst-case scenario for the primary endpoint by assuming MACE events in patients in the intervention group who were censored because they were lost to follow-up, whereas the

corresponding patients taking placebo were assumed to be event free. The hazard ratio (HR) was adjusted in subanalyses on MACE stratified by the presence of a series of risk factors at baseline; tests of treatment-by-factor interactions were performed. The rates for adverse effects were compared between treatment groups by means of a chi-square test for independence reported with exact p values.

For the primary efficacy variables in the short-term phase, the study would achieve its pre-specified objective if the difference between the groups in all 3 endpoints had a p value ≤0.05. For the primary endpoint in the long-term phase, the study would achieve its pre-specified objective if the difference between the groups had a p value <0.05. For secondary endpoints, p values <0.05 were used to assess statistical significance. All data were analyzed with the statistical analysis program Stata/SE 11·2 for Windows (StataCorp LP, College Station, Texas).

TABLE 1 Baseline Characteristics of the Patients

Characteristic	Current HF Therapy + CoQ_{10} (N = 202)	Current HF Therapy + Placebo (N = 218)
Age, yrs	62.3 ± 12	62.3 ± 11
Male/female ratio	154/48	151/67
Weight, kg	77.1 ± 17	77.9 ± 18
BMI, kg/m^2	28 ± 5	28 ± 6
Heart rate, beats/min	80 ± 16	82 ± 14
Systolic blood pressure, mm Hg	125 ± 18	122 ± 16
Diastolic blood pressure, mm Hg	78 ± 11	77 ± 11
Sinus rhythm	148 (73)	161 (74)
Atrial fibrillation	33 (16)	41 (19)
Rhythm, other (pace)	21 (10)	16 (7)
Ischemic heart disease	137 (68)	156 (72)
Dilated cardiomyopathy	54 (27)	59 (27)
Valvular heart disease	11 (5)	3 (1)
Duration of HF, months	38 ± 47	35 ± 36
NYHA functional class II	6 (3)	8 (4)
NYHA functional class III	178 (88)	189 (87)
NYHA functional class IV	18 (9)	21 (10)
Left ventricular EF, %	31 ± 10 (10-65)	31 ± 10 (10-70)
Left ventricular EDD, mm	66 ± 8	64 ± 9
Left ventricular ESD	55 ± 11	54 ± 11
6MWT (m)	287 ± 98 (25-525)	286 ± 92 (90-490)
Serum CoQ_{10}, μg/ml*	1.14 ± 0.08	0.91 ± 0.06
NT-proBNP, pg/ml*†	1,883 ± 271 (50-799)	1,692 ± 229 (50-735)
Use of medications		
ACE inhibitors/ARBs	178 (90)	195 (90)
Beta-blockers	141 (72)	164 (76)
Digoxin	90 (46)	97 (45)
Diuretics	155 (79)	176 (81)
Aldosterone antagonists	66 (34)	74 (34)
Statin derivatives	74 (38)	77 (35)
Anticoagulation	49 (25)	54 (25)
Diabetes treatment	44 (22)	51 (24)
Device therapy,		
Cardiac resynchronization device	2	5
Implanted cardioverter defibrillator	3	4

Values are mean ± SD, n (%), mean ± SD (range), mean ± SD (median), or n. *Values are mean ± SE. †To convert values for NT-proBNP to picomoles per liter, divide by 8.457.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BMI = body mass index; CoQ_{10} = coenzyme Q_{10}; EDD = end-diastolic diameter; ESD = end-systolic diameter; EF = ejection fraction; HF = heart failure; NT-proBNP = N-terminal pro–B-type natriuretic peptide; NYHA = New York Heart Association; 6MWT = 6-min walk test.

RESULTS

A total of 420 patients were randomly assigned to active treatment with CoQ_{10} (N = 202) or placebo (N = 218), (Online Appendix 2). There were 36 withdrawals (i.e., 22 patients in the CoQ_{10} group and 14 patients in the placebo group) (consort flow diagram, Online Figure 1). An analysis of the reasons for the withdrawals did not show any significant between-group difference (p = 0.118). Withdrawals were not removed from the intention-to-treat analysis. By the end of the study, the survival status of all patients was known, except for 4 patients in each treatment group who were classified as lost to follow-up. A total of 87 patients had reached the primary endpoint (MACE), and 60 patients had died.

BASELINE CHARACTERISTICS OF THE STUDY POPULATION. The 2 groups were similar with respect to a range of baseline characteristics established after the run-in period at week 2 (**Table 1**). Mean duration of HF was around 3 years in both groups, and baseline EF of mean 31% and 6MWT distances were equal between groups. The standard treatments of HF were balanced between the study groups at baseline. Of these patients, 90% received angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and 75% received beta-blockers with use of evidence-based dosages according to the guidelines. Modifications of dosages were infrequent throughout the study period, and it is unlikely that the minor changes should have affected differences in endpoints.

Two of 4 patients treated for <30 days with CoQ_{10} (protocol deviation, consort flow diagram) (Online Figure 1) had unplanned hospital stays for HF within 30 days after randomization. There were no fatal events in any of the treatment groups in the blanking period.

EFFECT ON THE SPECIFIED ENDPOINTS AT WEEK 16. There were improvements in NYHA functional class, VAS score, and 6MWT in both treatment groups at week 16, and differences between groups were not statistically significant. There were no significant differences in heart rate, blood pressure, and echocardiographic measurements (Online Table 4). The level of serum CoQ_{10} at week 16 increased significantly to about 3 times the baseline value in the CoQ_{10}-treated group. The between-group changes in

serum NT-proBNP from baseline to week 16 were not significantly different. However, there was a trend with a mean reduction of 384 pg/ml (20%) of NT-proBNP in the CoQ_{10} group and a proportional rise of 199 pg/ml (12%) of NT-proBNP in the placebo group (Online Table 5).

EFFECT ON THE SPECIFIED PRIMARY ENDPOINT AT WEEK 106. At week 106, there were significantly fewer MACE in the CoQ_{10} group (N = 30, 15%) than in the placebo group (N = 57, 26%), findings corresponding to a 43% relative reduction (p = 0.005, Fisher-exact test) (Table 2). From a Cox regression analysis stratified by center, the HR for CoQ_{10} versus placebo was 0.50; 95% confidence interval (CI): 0.32 to 0.80; p = 0.003 (Figure 1A).

Four patients were lost to follow-up in each treatment group. A regulatory approach to a sensitivity analysis could be that the 4 patients in the CoQ_{10} arm are counted as deaths, and the 4 patients in the placebo arm are counted as survivors. If the 2 hospital stays <30 days are included in the sensitivity analysis of the primary endpoint and the 4 patients lost to follow-up in the CoQ_{10} group are counted as deaths and the 4 patients in the placebo group are counted as survivors, the result remains in favor of CoQ_{10} treatment (HR [CoQ_{10} vs. placebo]: 0.64; 95% CI: 0.42 to 0.98; p = 0.038).

EFFECT ON THE SPECIFIED SECONDARY ENDPOINTS AT WEEK 106. At week 106, the CoQ_{10} group showed a greater proportion of patients with improved NYHA functional classification (N = 86, 58%) compared with the placebo group (N = 68, 45%), (p = 0.028), comprising an improvement of at least 1 grade in NYHA functional class. There were no significant between-group differences in the echocardiographic measurements. Serum NT-proBNP was reduced by a mean of 1,137 pg/ml (60%) in the CoQ_{10} group and by a mean of 881 pg/ml (52%) in the placebo group compared with baseline, which was not significantly different between groups (Online Tables 5 and 6).

Cardiovascular deaths. The total number of cardiovascular deaths within the study period of 106 weeks was lower in the CoQ_{10} group (N = 18, 9%) compared with the placebo group (N = 34, 16%), corresponding to a 43% relative reduction (p = 0.039, Fisher-exact test). From a Cox regression analysis stratified by center, the HR (CoQ_{10} vs. placebo) was 0.51; 95% CI: 0.28 to 0.92; p = 0.026 (Online Table 7, Online Figure 2A).

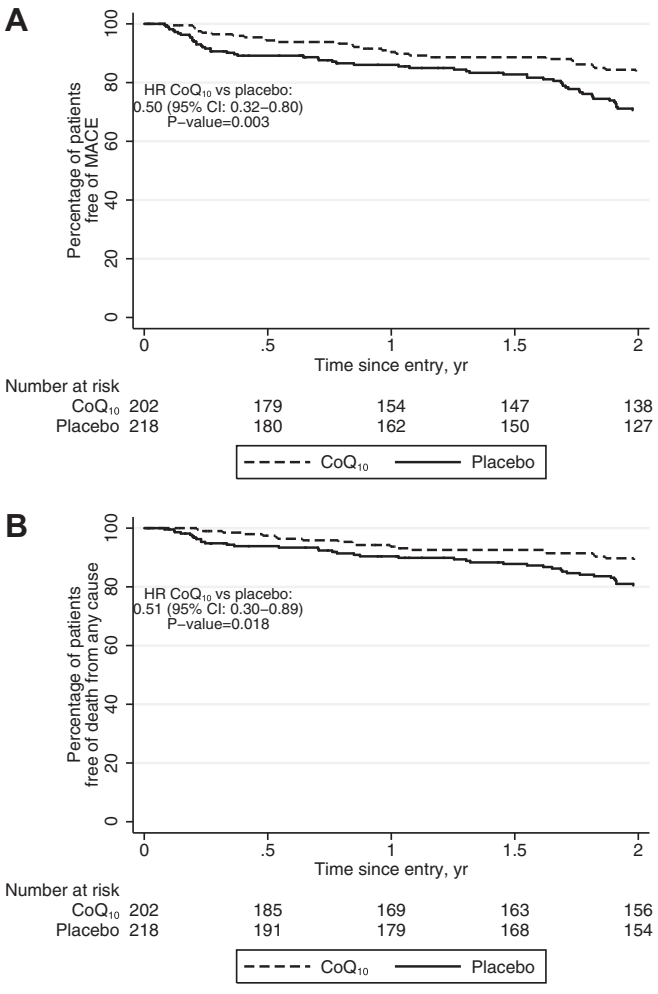

FIGURE 1 Kaplan-Meier Estimates of the Time to Primary and Secondary Endpoints

Kaplan-Meier estimates of the time to the primary endpoint 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 endpoint was composite MACE of hospital stay for worsening heart failure, cardiovascular death, mechanical support, or urgent cardiac transplantation. A specified secondary outcome was death from any cause. CI = confidence interval; HR = hazard ratio.

TABLE 2 Major Adverse Cardiovascular Events

Endpoint	CoQ_{10} (n = 202)	Placebo (n = 218)	Total (N = 420)
Death from MI	2	3	5
Death from HF	1	10	11
Sudden cardiac death	9	13	22
Hospital stay for worsening HF	12	24	36
Hospital stay for acute HF	3	5	8
Hospital stay for acute HF + IABP	2	2	4
LVAD	1	0	1
Total	30* (15%)	57 (26%)	87

Values are n or n (%). *p = 0.005.

IABP = intra-aortic balloon pumping; LVAD = left ventricular assist device; MI = myocardial infarction; other abbreviations as in Table 1.

Hospital stays for heart failure. The number of hospital stays for HF (counted as MACE) was lower in the CoQ_{10} group (N = 17, 8%) versus the placebo group (N = 31, 14%); HR (CoQ_{10} vs. placebo): 0.51; 95% CI: 0.27 to 0.95; p = 0.033 (Online Figure 2B).

Death from any cause. Within the study period of 106 weeks, there were 21 deaths (10%) from all causes in the CoQ_{10} group compared with 39 deaths (18%) in the placebo group, corresponding to a 42% relative reduction (p = 0.036, Fisher-exact test) (Online Table 8). From a Cox regression analysis stratified by center, the HR (CoQ_{10} vs. placebo) was 0.51; 95% CI: 0.30 to 0.89; p = 0.018 (**Figure 1B**). Retrospectively, all-cause mortality was lower in the CoQ_{10} group also at week 16, with HR: 0.18; 95% CI: 0.04 to 0.87; p = 0.032.

Adverse events. The number of adverse events tended to be lower in the CoQ_{10} group compared with the placebo group, 26 (13%) versus 41 (19%), respectively, p = 0.110, (Fisher-exact test) (**Table 3**).

Subgroup analyses. HRs were adjusted in a series of subgroup analyses on MACE (**Figure 2**). No significant subgroup interactions were observed. There were trends with favorable effects of treatment with CoQ_{10} in the following groups: elderly patients, male patients, patients in NYHA functional class III, patients with dilated cardiomyopathy, patients with NT-proBNP ≥300 pg/ml, and patients with left ventricular EF of ≥30% (p = 0.065). In addition, the benefits of CoQ_{10} were in addition to those afforded by beta-blockers and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers.

TABLE 3 Adverse Events

Event	CoQ_{10} (n = 202)	Placebo (n = 218)	Total (N = 420)
Peripheral arterial vascular events	2	2	4
Deep venous thrombosis	1	0	1
Cerebral stroke	1	6	7
Probable or definitive MI	3	2	5
CABG	1	2	3
PCI	3	3	6
Arrhythmia	3	4	7
Chest pain	0	3	3
Gastrointestinal disturbances	2	8	10
Allergy	1	3	4
Infection	3	2	5
Malignancy	1	1	2
Non-CV or unknown causes of deaths	3	2	5
Other adverse events	2	3	5
Total	26* (13%)	41 (19%)	67

Values are n or n (%). *p = 0.110.

CABG = coronary artery bypass graft; CV = cardiovascular; PCI = percutaneous coronary intervention; other abbreviation as in Tables 1 and 2.

DISCUSSION

Results from RCTs with CoQ_{10} in HF have accumulated since the late 1980s. Although encouraging, the studies have been underpowered to address major clinical endpoints.

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 mortality in HF.

Despite considerable improvements in pharmacological HF therapy, the supplementation with CoQ_{10} significantly reduced MACE and cardiovascular death by 43% and all-cause mortality by 42% in our study. Furthermore, CoQ_{10} supplementation improved the patients' symptoms according to the NYHA functional classification after 2 years.

The combination of the selected dosage and formulation of CoQ_{10} in Q-SYMBIO may have given the therapeutic threshold in serum and tissue of CoQ_{10} (17) required for efficacy to achieve the positive result in MACE. In addition to a higher dosage of CoQ_{10}, the CoQ_{10} formulation used has shown good bioavailability in controlled studies (20,21) (Online Appendix 2).

We found an insignificant reduction in NT-proBNP in the CoQ_{10} group at 16 weeks. After 106 weeks, NT-proBNP levels were more than halved in both study groups compared with baseline; this finding may reflect that the most symptomatic patients with the highest NT-proBNP levels have died. Monitoring with NT-proBNP may be an important tool to ensure clinical stability in outpatients with HF (15).

In meta-analyses of RCTs with CoQ_{10}, small, significant improvements were found in left ventricular EF (9-11). Despite improvements of the long-term endpoints in Q-SYMBIO, we found insignificant positive changes in EF in both treatment groups. The absolute figures of improved EF have been small in RCTs with CoQ_{10}, as well as in trials with angiotensin-converting enzyme inhibitors or beta-blockers (22,23). We did not exclude patients from our study with HF and preserved EF, and 7% of the patients had EF ≥45%. In general, patients are selected with decreased EF in HF trials; however, physical signs of HF may provide important prognostic information above and beyond echocardiographic parameters (24).

The changes of other parameters obtained from the RCTs with CoQ_{10} (e.g. improvement in exercise capacity) have been modest, as in the Scandinavian cross-over study with CoQ_{10} 100 mg daily versus placebo (25). Nonetheless, the improvement of exercise capacity during CoQ_{10} therapy has been in the

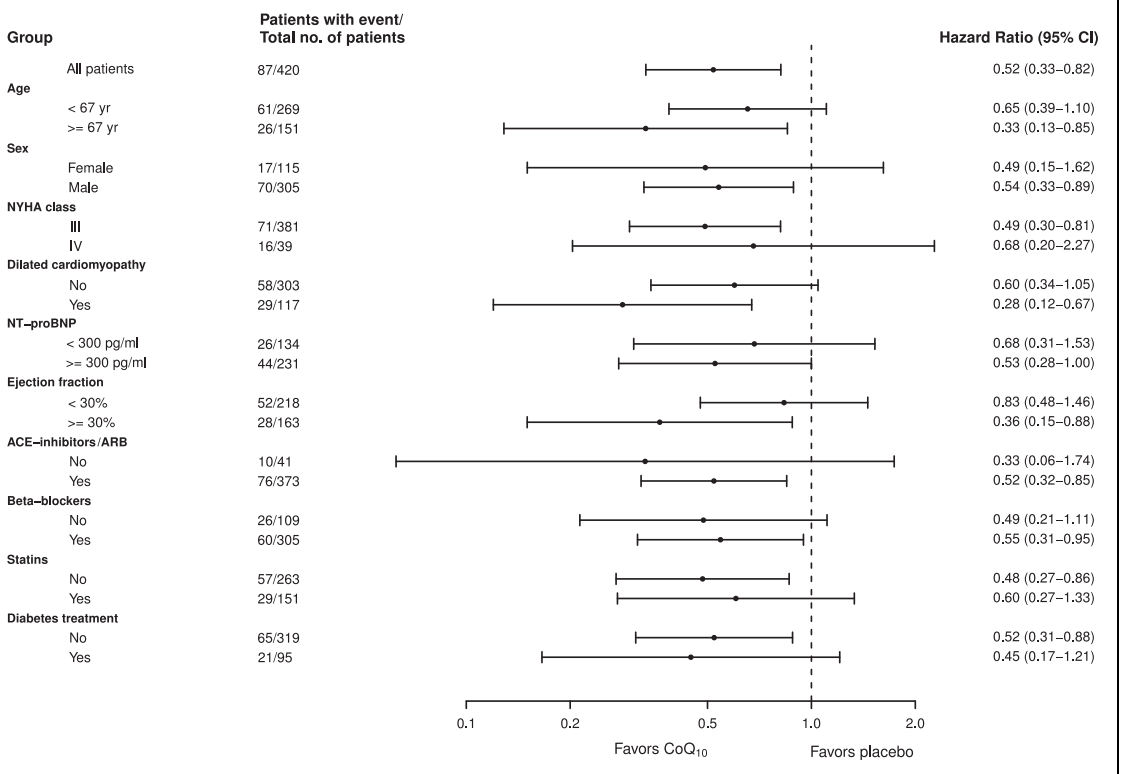

FIGURE 2 Results of Subgroup Analyses

Shown are the adjusted HR for the primary endpoint within specific subgroups. The **dotted line** denotes HR; **horizontal lines** represent 95% CI. HR indicates the relative risk in the coenzyme Q_{10} (CoQ_{10}) group versus the placebo group within each stratum. To convert values for NT-proBNP to picomoles per liter, divide by 8.457. ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; other abbreviations as in Figure 1.

same order of magnitude as that found in previous studies with angiotensin-converting enzyme inhibitors (26). In the largest 1-year study from Italy (1993), the dosage of CoQ_{10} was 50 mg 2 to 3 times daily according to weight versus placebo. Significantly fewer patients in this study were readmitted for worsening HF in the CoQ_{10} group, and fewer patients in the CoQ_{10} group died (N = 16) compared with the placebo group (N = 21), but the difference was not statistically significant (27).

The biological mechanisms behind the improvement of symptoms and survival from CoQ_{10} in HF may be multiple (1,28,29). The velocity of the oxidative phosphorylation in the respiratory chain strongly depends on the CoQ_{10} concentration of the inner mitochondrial membrane (5), and small changes of the availability of CoQ_{10} may lead to significant changes in the respiratory rate.

CoQ_{10} treatment may impede the vicious metabolic cycle in HF (30), via a favorable alteration in redox signaling in the mitochondria that leads to increased energy production in the failing heart. In addition, CoQ_{10} therapy may lead to increased stabilization of the mitochondrial permeability transition pore and may shield the myocardium against apoptotic cell loss (28). Furthermore, it has been shown that CoQ_{10} may improve endothelial function (31), and it may protect the myocardium against ischemia (17). The high level of reactive oxygen species resulting from oxidative stress in HF increases the demand of antioxidants (32). This may lead to compromised function of CoQ_{10} in the respiratory chain and may ultimately explain the low levels seen in myocardial tissue from patients with HF (6).

Hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) block the mevalonate pathway and the synthesis of both cholesterol and CoQ_{10} (33,34). Additional CoQ_{10} depletion via statins in patients with HF and pre-existing CoQ_{10} deficiency may be a critical issue and may at least theoretically have contributed to neutral outcomes of RTCs with statins in HF (6).

The endogenous synthesis of CoQ_{10} in the body declines with age, and there may be a rationale for supplementation in the elderly patients (35). In a 5-year randomized double-blind placebo-controlled study of healthy elderly people, supplementation with a combination of CoQ_{10} and selenium reduced cardiovascular mortality significantly (36).

Many patients with HF are malnourished as a result of defects in substrate utilization and energy supply (37,38). Because the current medications for HF do not substitute for essential micronutrients, the possible deficiencies of these factors remain and contribute to symptoms and reduced survival in HF (29). Several dysfunctions may be present, and more research is required for further elucidation of the molecular causes of HF.

STUDY LIMITATIONS. CoQ_{10} is a nonpatentable substance, and with Q-SYMBIO having a low budget, the competition with other HF trials using licensed pharmaceuticals was difficult. This explains why the study was not completed according to the original enrollment plan and why the predefined estimate of the study population of 550 patients was not reached.

About 20% of the patients in both treatment groups at baseline were stabilized on standard therapy without diuretics. Therefore, we cannot exclude that more patients were in NYHA functional class II than specified in **Table 1**. The possible higher proportion of patients with milder symptoms may explain the death rate after 2 years that was lower than expected.

CONCLUSIONS

Our results demonstrate that treatment with CoQ_{10} in addition to standard therapy for patients with moderate to severe HF is safe, well tolerated, and associated with a reduction in symptoms and MACE.

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For the visual analogue scale for symptoms and study medication information as well as supplemental figures and tables, please see the online version of this article.