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Effect of coenzyme Q_{10} in Europeans with chronic heart failure: A sub-group analysis of the Q-SYMBIO randomized double-blind trial

Running title: Effect of coenzyme Q10 in Europeans with chronic heart failure

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Abstract

Background: Geographical differences in patient characteristics, management and outcomes in heart failure (HF) trials are well recognized. The aim of this study was to assess the consistency of the treatment effect of coenzyme Q_{10} (CoQ_{10}) in the European sub-population of Q-SYMBIO, a randomized double-blind multinational trial of treatment with CoQ_{10}, in addition to standard therapy in chronic HF.

Methods: Patients with moderate to severe HF were randomized to CoQ_{10} 300 mg daily or placebo in addition to standard therapy. At 3 months the primary short-term endpoints were changes in New York Heart Association (NYHA) functional classification, 6-min walk test, and levels of N-terminal pro–B type natriuretic peptide (NT-proBNP). At 2 years the primary long-term endpoint was major adverse cardiovascular events (MACE).

Results: There were no significant changes in short-term endpoints. The primary long-term endpoint of MACE was reached by significantly fewer patients in the CoQ_{10} group (n = 10, 9%) compared to the placebo group (n = 33, 27%, p = 0.001). The following secondary endpoints were significantly improved in the CoQ_{10} group compared with the placebo group: all-cause and cardiovascular mortality, NYHA classification and ejection fraction. In the European sub-population, when compared to the whole group, there was greater adherence to guideline directed

therapy and similar results for short- and long-term endpoints. A new finding revealed a significant improvement in ejection fraction.

Conclusions: The therapeutic efficacy of CoQ_{10} demonstrated in the Q-SYMBIO study was confirmed in the European sub-population in terms of safely reducing MACE, all-cause mortality, cardiovascular mortality, hospitalization and improvement of symptoms.

Key words: chronic heart failure, coenzyme CoQ_{10}, ubiquinone, randomized controlled trial, major adverse cardiovascular events, mortality, hospitalization

Introduction

Heart failure (HF) is a progressive worsening of cardiac function, due to a variety of causes including ischemic heart disease, hypertension, cardiomyopathy and diabetes. Despite considerable advances in treatment options, HF continues to be associated with a high symptomatic burden, frequent hospitalizations and a poor long-term prognosis with 50% of HF patients dying within 5 years of diagnosis [1].

Coenzyme Q_{10} (CoQ_{10}) is an essential component in the production of cellular energy (ATP) in mitochondria. In addition, CoQ_{10} has strong anti-oxidative properties that protects against cellular damage from free radicals including reactive oxygen species [2–4]. CoQ_{10} is primarily synthesized endogenously and in sufficient amounts during normal physiological conditions. However, endogenous production of CoQ_{10} declines with age and an actual deficiency is observed in a number of pathophysiological conditions including HF [5–7]. The biochemical rationale of CoQ_{10} supplementation in HF patients is to correct a documented deficit in heart tissue CoQ_{10} that may lead to failure in mitochondrial bioenergetics and a compromised cellular antioxidant capacity of the myocardium [8–11].

The Q-SYMBIO study, a multinational prospective, randomized, double-blind trial, demonstrated that treatment with CoQ_{10}, in addition to standard therapy for patients with chronic HF, improved symptoms and reduced adverse cardiovascular events and mortality [12]. In Q-SYMBIO, patients with HF were enrolled from European and non-European (mainly Asian) centers.

Geographic differences in patient characteristics and management have the potential to affect the outcome of clinical trials. These differences have recently been analyzed and described in large HF trials [13–15]. For example, the Angiotensin–Neprilysin Inhibition versus Enalapril in

Heart Failure (PARADIGM) trial included patients from five regions including European and Asian countries, and notable regional differences were found in baseline characteristics and background HF therapy. Furthermore, differences in event-rates of heart failure outcomes were found, however the benefit of sacubitril/valsartan was consistent across regions [16].

The aim of the present study was to assess the consistency of the treatment effect of CoQ_{10} in a European sub-population (n = 231) of the total population of Q-SYMBIO (n = 420).

Methods

The efficacy of CoQ_{10} in a European sub-population (n = 231) of a Q-SYMBIO trial (n = 420) by post-hoc analysis of baseline characteristics for short-term (3 month) and long-term (2 year) endpoints were investigated. Patients with moderate to severe HF were enrolled from 14 centers in six European countries (Poland, Denmark, Sweden, Hungary, Austria and Slovakia) and were randomized in parallel groups to either CoQ_{10} 300 mg (Ubiquinone, Pharma Nord ApS) daily (n = 108) or placebo (n = 123) in addition to standard HF therapy.

The short-term primary endpoints were changes in New York Heart Association (NYHA) functional class, 6-min walk test (6MWT), and N-terminal pro–B-type natriuretic peptide (NT-proBNP). The secondary short-term endpoint was the scoring of symptoms (dyspnea, fatigue, and change in symptoms) by patients on visual analogue scale (VAS).

The primary long-term endpoint was a composite of major adverse cardiovascular events (MACE) defined as unplanned hospitalization due to worsening of HF, cardiovascular death, urgent cardiac transplantation or mechanical support using time to first event analysis. Secondary long-term endpoints were mortality, changes in NYHA functional class, NT-proBNP and echocardiography (left ventricular ejection fraction [EF] and cavity dimensions).

Samples of serum were shipped to the core Biochemical Laboratory in Ancona, Italy and assayed for levels of CoQ_{10} by using high-performance liquid chromatography with ultraviolet detection [17] and NT-proBNP using the Elecsys 2010 immunoassay method (Roche Diagnostics, Mannheim, Germany) [18].

Statistical analysis

Descriptive analyses of baseline data were reported as frequencies. Percentages for categorical data and for continuous data were reported as mean ± standard deviation or mean ± standard error for normally distributed data and median and lower upper quartile for non-normal

data. The significance of treatment on continuous responses was analyzed by a linear model with each investigation center was treated as a random intercept effect. The treatment effects were analyzed and adjusted for pre-defined confounders. A chi-square test for independence with exact p values was calculated using the Fisher exact test 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 the center. The rates for adverse effects were compared between treatment groups by means of a chi-square test for independence. For the short-term primary endpoints, the pre-specified objective was reached if the difference between the groups in all three endpoints had a p value < 0.05. For the primary long-term endpoint MACE, the pre-specified objective was reached 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).

Results

Baseline characteristics

The two treatment groups of the European sub-population were similar regarding baseline characteristics except male gender, CoQ10 (83%) vs. Placebo (71%) ($p= 0.03$) and systolic blood pressure: CoQ_{10} (127 mmHg) vs. Placebo (121 mmHg) ($p= 0.03$; Table 1). At the beginning of the study, an average of 90% of patients were classified as NYHA class III, 6% as NYHA class II and 6% as NYHA class IV and with an EF of 33%. The two treatment groups were balanced for medication usage with an average of 92% patients receiving angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (ARBs), 88% receiving beta-blockers, 32% digoxin, 37% anticoagulants, 55% aldosterone antagonists, 57% statin derivatives and 26% diabetic medication (Table 1).

Changes in serum CoQ_{10} levels

Changes in biochemical status were examined at short term (3 months) and long-term follow-up (2 years). After 3 months, serum CoQ_{10} significantly increased 3-fold in the CoQ_{10} group ($p < 0.001$) from 0.95 ± 0.08 μg/mL (mean ± SE) at baseline to 3.42 ± 0.21 μg/mL and was maintained during the study period with a level of 3.55 ± 0.34 μg/mL ($p < 0.001$) after 2 years. In

the placebo group, there was a non-significant decrease in mean serum CoQ_{10} from 0.90 ± 0.07 μg/mL at baseline to 0.76 ± 0.04 μg/mL after 2 years (Table 2).

Effect on short-term endpoints

At 3 months there was a borderline significant reduction in serum NT-proBNP (p= 0.052) in the CoQ_{10} group compared to baseline but not in the placebo group (Table 2). There were no changes from baseline in the specified short-term endpoints NYHA functional class, VAS score, 6MWT or heart rate in either treatment group or between groups (Table 3).

Effect on long-term endpoints

The long-term primary endpoint MACE was reached by significantly fewer patients in the CoQ_{10} group (n = 10, 9%) compared to the placebo group (n = 33, 27%, p = 0.001; Table 4). A significant risk reduction in MACE with CoQ_{10} compared to placebo was found from a Cox proportional hazards regression analysis stratified by center (hazard ratio [HR] 0.23; 95% confidence interval [CI] 0.11–0.51; p < 0.001; Fig. 1).

A significantly greater proportion of patients in the CoQ_{10} group improved by at least one grade in NYHA functional classification after two years (n = 39, 48%) compared to the placebo group (n = 19, 25%, p = 0.003; Table 3). In the CoQ_{10} group there was a significant improvement of 6% in EF compared to baseline (p = 0.021) but there was no significant change in the placebo group (p = 0.234; Table 3). In the CoQ_{10} group, compared to baseline, serum NT-proBNP was reduced by a mean of 702 pg/mL (28%) in the CoQ_{10} group and a reduction of 276 pg/mL (12%) in the placebo group. Neither of these values were significantly different from baseline nor were there differences between the two groups (Table 2). For heart rate and blood pressure there were no significant changes from baseline with treatment in either group nor were there any between-group differences (Table 3).

All-cause mortality was lower in the CoQ_{10} group, 10 (9%) patients vs. 24 (20%) patients in the placebo group, corresponding to a relative reduction of 53% (p = 0.040). Using a Cox proportional hazards regression analysis stratified by center revealed a significant reduction in all-cause mortality with CoQ_{10} compared to placebo (HR 0.37; 95% CI 0.16–0.82; p = 0.014; Fig. 2). The total number of cardiovascular deaths, was also lower in the CoQ_{10} group compared to the placebo group, 9 (8%) vs. 21 (17%) corresponding to a relative reduction of 51% (p = 0.052). From a Cox regression analysis stratified by center, the HR (CoQ_{10} vs. Placebo) was 0.36 (95% CI 0.15–

0.85; p = 0.020). Three (3%) patients were hospitalized due to worsening HF in the CoQ_{10} group vs. 16 (13%) patients in the placebo group (p = 0.007). The risk of unplanned hospitalization due to worsening HF counted as MACE was significantly lower in the CoQ_{10} group with a HR of 0.07 (95% CI 0.01–0.36; p = 0.001) using a Cox proportional hazards regression analysis stratified by center.

Adverse effects

There were no differences in the total number of adverse events in the CoQ_{10} group, 17 (16%) vs. 28 (23%) in the placebo group (p = 0.188).

Comparison of the European population with the total population

Baseline patient characteristics and management. In comparison with the whole population of Q-SYMBIO, the Europeans were slightly older (mean 65 vs. 62 years), heavier (84.3 vs 77.5 kg) with a lower heart rate (73 vs. 81 bpm), and a higher prevalence of atrial fibrillation (26% vs 18%) (Table 5). The majority of both populations were classified as NYHA class III (89% and 87%). Almost half as many of the European patients were classified as NYHA IV compared to the total population (5% vs. 9%). The lower percentage of patients with end-stage HF in the European population was in accordance with a greater average performance in 6MWT (325 m vs. 287 m) and a slightly higher mean EF (33% vs. 31%). The Europeans were more frequently treated with beta-blockers (88% vs. 73%), statins (57% vs. 36%) and anticoagulants (37% vs. 25%). Patients treated with device-based therapy in Q-SYMBIO were all European.

Event rate and treatment effects. The serum CoQ_{10} levels and overall event rates in the CoQ_{10} treated group of the European sub-population were similar or better than in the total population (Table 6). In the European sub-population, there was a significant improvement of 6% in EF compared to baseline (p = 0.021) in the CoQ_{10} group but no significant change in the placebo group (p = 0.234; Table 3). Whereas in the total population there were no significant between-group differences or changes from baseline in any of the echocardiographic measurements [12].

Discussion

Summary

The beneficial effect of CoQ_{10} in the landmark Q-SYMBIO study of 420 international patients was reflected in the more racially homogeneous, more intensively treated subgroup of 231

European patients in terms of a significant improvement in NYHA class and a significant risk reduction for the primary composite MACE endpoint and reductions in the secondary endpoints of all-cause mortality, cardiovascular mortality and hospitalization for HF. The improvements in major clinical endpoints were supported by a significant increase in EF in the European population which had not been found in the larger cohort [12]. It was concluded that the therapeutic efficacy of CoQ_{10} demonstrated in the original Q-SYMBIO study was confirmed and even enhanced in the European sub-population.

Despite a careful selection of patients and an apparently homogenous population in clinical studies there are inherent hidden factors in HF trials that may affect outcomes. These factors include ethnicity, medical preferences of physicians, financing of medical care and drug availability [13–15, 19]. This study aimed to investigate if the therapeutic efficacy of CoQ_{10} found in a total international population of Q-SYMBIO (n = 420) also applied to a more homogeneous European sub-population (n = 231). Compared to the total population of Q-SYMBIO, the European sub-population was slightly older, with a lower heart rate, a higher EF and a higher percentage with atrial fibrillation. Similar differences in baseline characteristics have recently been found in trials of chronic HF (PARADIGM-HF, EMPHASIS-HF) and acute HF (ASCEND-HF, ASTRONAUT) with patients enrolled from 5–6 global regions including Asia and Europe. The European sub-population of Q-SYMBIO showed a higher adherence to guideline recommended medical and device therapies when compared to the entire study population. The Europeans were more frequently prescribed beta-blockers, statins and anticoagulants and less frequently digoxin. Furthermore, all patients receiving device-based therapy in Q-SYMBIO were European.

A sub-optimal use of guideline-directed medical therapy in Asian countries compared to Western countries has been described previously in registries for HF and recent large-scale HF trials [14, 20, 21]. Global differences in adherence to guideline-directed therapy in PARADIGM-HF and ASTRONAUT correspond to differences found in Q-SYMBIO including a higher rate in the prescription of beta-blockers, anticoagulation and a lower rate of digoxin in European populations compared to Asian-Pacific populations [16, 20]. A lower use of lipid-lowering agents such as statins in Asian countries is also well known [22]. Similarly, to Q-SYMBIO, analyses of PARADIGM-HF, ASTRONAUT and ASCEND-HF demonstrated a markedly lower use of device-based therapy in Asian-Pacific regions compared to other regions, probably reflecting economic differences [16, 20, 21]. The more frequent prescription of anti-coagulants reflects the higher occurrence of atrial fibrillation in the European sub-population of Q-SYMBIO. However, not all

differences in medication can be explained by differences in baseline characteristics. Differences in medication and device therapy may be related to medical practice patterns, resources in medical care and perceptions of drug tolerability in Asian populations [21].

The findings in this analysis showing no major differences in outcomes in the European sub-population despite differences in medical therapy and baseline characteristics in accordance with PARADIGM-HF and EMPHASIS. In contrast, regional differences in outcome that have been found in acute HF trials ASTRONAUT and ASCEND-HF and may be a result of differences in the management and duration of hospitalization for acute HF patients having a greater impact on outcome [14].

The serum level of CoQ_{10} in the CoQ_{10} treated European sub-population remained constant and above 3 μg/mL throughout the study period (Tables 2, 6). In contrast, the serum level of CoQ_{10} in CoQ_{10} treated patients in the total population decreased from 3.01 ± 0.17 μg/mL at 3 months to 2.01 ± 0.20 μg/mL at 2 years (Table 6) [12]. This could indicate a problem with compliance in the non-European patient population towards the end of the study period. The higher serum levels of CoQ_{10} of the European HF patients during the full study period may have contributed to the slightly increased CoQ_{10} efficacy (increased EF; Table 3) compared with the efficacy found in the total population [12], despite the fact that the European cohort was better medicated and smaller sample size.

Current drug therapy for HF predominately targets the secondary consequences of the failing heart by blocking overactivated neurohormonal pathways. While this therapy provides some relief of symptoms, improves prognosis and prevents some degree of cardiac remodeling, it does not target the basic energy depletion of the failing myocardium [24]. Significantly decreased tissue levels of CoQ_{10} have been found in patients with failing hearts such as dilated cardiomyopathy, restrictive cardiomyopathy and toxic myocardial disease [9]. In patients with HF of mixed etiology, a deficiency of CoQ_{10} in serum and tissue is more pronounced in the severest stages of HF. After oral supplementation with CoQ_{10} of selected patients with cardiomyopathy undergoing repeat biopsies after 5 months of treatment, tissue deficiency was reduced significantly and this was accompanied by an improvement in clinical and hemodynamic parameters [9, 10, 25]. The therapeutic efficacy of CoQ_{10} is primarily ascribed to its important role as electron carrier in the electron transport chain and strong anti-oxidative properties thus increasing bioenergetics and preventing oxidative damage of the failing myocardium [26, 27]. Other beneficial actions of CoQ_{10} include stabilization of cell membranes and the mitochondrial membrane transition pore thus

protecting the myocardium from apoptotic events [28]. Further evidence suggests that endothelial function is improved [29, 30] and cardiac contractility increased by CoQ_{10} [31, 32]. In concert, these actions by CoQ_{10} may halt the vicious cycle of HF and protect the myocardium from further deterioration and perhaps facilitate a potential for myocardial recovery [33].

Limitations of the study

In comparing the European subgroup with the main Q-SYMBIO group it was not possible to ascribe differences between European vs. non-European to ethnic or geographic differences. The main Q-SYMBIO group of 420 included 231 patients from Europe, 178 patients from Asia and 11 patients from Australia. Thus, it was not possible in this subgroup analysis to elucidate ethnic differences but rather to study and confirm the efficacy of CoQ_{10} in a sub-group where standard therapy was more closely applied. The present study was not powered to assess between-population differences. Measurements of EF have a varying intra- and interobserver variance from 3–7% depending on how trained the observer is, nevertheless, an absolute improvement of 6% in EF is likely to be genuine and clinically relevant.

Conclusions

It was concluded that in the European subgroup of the Q-SYMBIO study the evidence of therapeutic efficacy of CoQ_{10} found in the original study was confirmed, despite higher adherence to guideline directed therapy than that of the whole group. In addition, CoQ_{10} therapy was associated with an increase in EF in the European population which had not been found in the larger cohort. This subgroup analysis provides confirmatory evidence for the conclusion of the original study that the treatment of patients with moderate to severe HF with CoQ_{10} in addition to standard therapy is safe, well tolerated and is associated with a reduction in symptoms, MACE and with improved survival.

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Conflict of interest: None declared

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Table 1. Baseline characteristics of patients.

Baseline characteristics of the patients	**Standard HF therapy + CoQ_{10} (47%, n = 108)**	**Standard HF therapy + placebo (53%, n = 123)**
Age, yrs	65.7 ± 10	64.0 ± 12
Male gender*	90 (83%)	87 (71%)
Weight [kg]	83.7 ± 18	84.8 ± 18
BMI [kg/m^2]	29 ± 5	29 ± 7
Heart rate [bpm]	72 ± 12	75 ± 12
Systolic BP [mmHg]*	127 ± 21	121 ± 19
Diastolic BP [mmHg]	77 ± 11	74 ± 11
Sinus rhythm	67 (62%)	77(63%)
Atrial fibrillation	27 (25%)	32 (26%)
Rhythm, other (pace)	14 (13%)	14 (11%)
Ischemic heart disease	68 (63%)	84 (68%)
Dilated cardiomyopathy	35 (32%)	38 (31%)
Valvular heart disease	5 (5%)	1 (1%)
Duration of HF [months]	42 ± 59	39 ± 41
NYHA class II [%]	6 (6%)	7 (6%)
NYHA class III [%]	97 (90%)	109 (89%)
NYHA class IV [%]	5 (5%)	7 (6%)
Left ventricular EF [%], [range]	33 ± 12 [10–65]	33 ± 12 [10–70]
Left ventricular EDD [mm]	64 ± 10	62 ± 11
Left ventricular ESD [mm]	51 ± 12	50 ± 13
6MWT [m], [range]	331 ± 91 [25–525]	321 ± 90 [90–490]
Serum CoQ_{10} [µg/mL]§	0.95 ± 0.08	0.90 ± 0.07
NT-proBNP [pg/mL] §†	2470 ± 369, p50: 1208	2335 ± 398, p50: 1174
Use of medications:		
ACEI/ARBs	99 (92%)	112 (91%)
Beta-blockers	94 (87%)	110 (89%)
Digoxin	35 (32%)	39 (32%)
Diuretics	90 (83%)	104 (85%)
Aldosterone antagonists	59 (55%)	66 (54%)
Statins	62 (57%)	69 (56%)
Anticoagulants	38 (35%)	48 (39%)
Diabetes medication	27 (25%)	32 (26 %)
Device therapy		

Cardiac resynchronization device	2	5
Implanted cardioverter defibrillator	3	4

Values are mean ± standard deviation, number (percentage), mean ± standard deviation [range], mean ± standard deviation (median, p50), or number. §Values are mean ± standard error. †To convert values for NT-proBNP to picomoles per liter, divide by 8.457, *p= 0.03. ACEI/ARB — angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; BMI — body mass index; BP — blood pressure CoQ_{10} = coenzyme Q10; 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

Table 2. Biochemical assessments at baseline at 3 months and two years.

Variable	**CoQ_{10} (mean ± SE) 3 months: n = 80 2 years: n = 40**	**Placebo (mean ± SE) 3 months: n= 88 2 years: n = 45**
Serum CoQ10 [µg/mL]:		
Baseline	0.95 ± 0.078	0.90 ± 0.073
3 months	3.42 ± 0.209*	0.82 ± 0.064
2 years	3.55 ± 0.343*	0.76 ± 0.044
Serum NT-proBNP [pg/mL]†		
Baseline	2470 ± 369	2335 ± 398
3 months	2144 ± 370§	2343 ± 418
2 years	1768 ± 375	2059 ± 390

*p < 0.001 vs. baseline, §p = 0.052 vs. baseline, †To convert values for NT-proBNP to picomoles per liter, divide by 8.457. CoQ_{10} — coenzyme Q_{10}; NT-proBNP — N-terminal pro–B-type natriuretic peptide

Table 3. Clinical and echocardiographic assessment changes from baseline.

Change in values from baseline (Δ)	**3 months**		**2 years**	
	CoQ_{10} (n = 98)	**Placebo (n = 109)**	**CoQ_{10} (n = 81)**	**Placebo (n = 77)**
NYHA classification:				
Improvement	27 (28%)	26 (245)	39 (48%)*	19 (25%)
Unchanged	68 (69%)	82 (75%)	42 (52%)	58 (71%)

Deterioration	3 (3%)	1 (1%)	1 (1%)	3 (4%)
VAS score (% ± SEM):				
Dyspnea	–9.6 ± 2.4	–6.4 ± 2.3	NA	NA
Fatigue	–8.7 ± 2.6	–8.7 ± 2.1	NA	NA
General symptoms change	–7 ± 8.5	–7 ± 8.6	NA	NA
6MWT [m]	+25 ± 60	+20 ± 71	+19 ± 75	+2 ± 102
Heart rate [bpm]	0 (72 ±15)	0 (74 ±14)	0 (72 ±13)	–1 (73 ±14)
Systolic BP [mmHg]	0 (127 ±23)	0 (121 ±18)	0 (127 ±21)	–3 (124 ±20)
Diastolic BP [mmHg]	–3 (74 ±12)	–1 (75 ±12)	0 (74 ±10)	0 (75 ±11)
Left ventricular EF [%]	+3 (36 ±13)	+1 (34 ±12)	+6 (39 ±12)**	+2 (35 ±14)
Left ventricular EDD [mm]	–2 (62 ±10)	0 (62 ±10)	–1 (61 ±9)	–1 (61 ±11)
Left ventricular ESD [mm]	–2 (49 ±11)	-2 (48 ±12)	–2 (47 ±13)	0 (48 ± 15)

Values given are ± standard deviation unless otherwise stated. *p = 0.003, **p = 0.021 for CoQ_{10} vs. placebo at 2 years, BP — blood pressure; CoQ_{10} — coenzyme Q_{10}; EDD — end-diastolic diameter; EF — ejection fraction; ESD — end-systolic diameter; 6MWT — 6-min walk test; NYHA — New York Heart Association; VAS — Visual Analogue Scale

Table 4. Major adverse cardiovascular events at 2 years.

Endpoint	**CoQ_{10} (n = 108)**	**Placebo (n = 123)**
Death due to MI	2	3
Death due to HF	1	6
Sudden cardiac death	4	8
Hospitalization due to acute HF and PE	0	1
Hospitalization due to worsening HF	3	15
Total	**10 (9%)***	**33 (27%)**

*p = 0.001. CoQ_{10} — coenzyme Q_{10}; HF — heart failure; MI — myocardial infarction; PE — pulmonary embolism

Table 5. Comparison of baseline characteristics in European and total population.

Characteristic	**European population (n = 231)**	**Total population (n = 420)**	**P**
Age [years]	64.8 ± 11	62.2 ± 12	0.0073
Male sex	77%	73%	0.2051

Weight [kg]	84.3 ± 17.8	77.5 ± 17	< 0.0001
BMI	28.9 ± 6	28 ± 6	0.0495
Heart rate [bpm]	73 ± 12	81 ± 15	< 0.0001
Systolic BP [mmHg]	124 ± 20	123 ± 17	0.8054
Diastolic BP [mmHg]	75 ± 11	78 ± 11	< 0.0001
Sinus rhythm	62%	74%	0.0032
Atrial fibrillation	26%	18%	0.0193
Rhythm, other (pace)	12%	9%	0.1376
Ischemic heart disease	66%	70%	0.3327
Dilated cardiomyopathy	32%	27%	0.1525
Valvular heart disease	3%	3%	1.0000
Duration of HF [months]	41 ± 50	37 ± 41	0.2711
NYHA class II,	6%	3%	0.0769
NYHA class III	89%	87%	
NYHA class IV	5%	9%	
Left ventricular EF [%],	33 ± 12 [10–70]	31 ± 10 [10–70]	0.0130
Left ventricular EDD [mm]	63 ± 11	65 ± 9	0.0157
Left ventricular ESD [mm]	51 ± 13	54 ± 11	0.0001
6MWT [m], [range]	325 ± 91 [25–525]	287 ± 98 [25–525]	< 0.0001
Serum CoQ_{10} [μg/mL]	0.92 ± 0.07	0.92 ± 0.05	0.2106
NT-proBNP† [pg/mL]	2399 ± 272, p50: 1196	1783 ± 276, p50: 782	0.0509
Use of therapy			
ACEI/ARBs	91%	89%	0.476
Beta-blockers	88%	73%	< 0.0001
Digoxin	32%	45%	0.0015
Diuretics	84%	79%	0.1383
Aldosterone antagonists	54%	56%	0.9341
Statin derivatives	57%	36%	< 0.0001
Anticoagulation	37%	25%	0.0008
Diabetes treatment	26%	23%	0.4409

Values are mean or number. †To convert values for NT-proBNP to picomoles per liter, divide by 8.457. ACE/ARB — angiotensin converting enzyme inhibitor/angiotensin receptor blocker; BMI — body-mass index; BP — blood pressure; 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

Table 6. Comparison of serum coenzyme Q_{10} (CoQ_{10}) and overall event rates and risk reduction at 2 years in the European and total population.

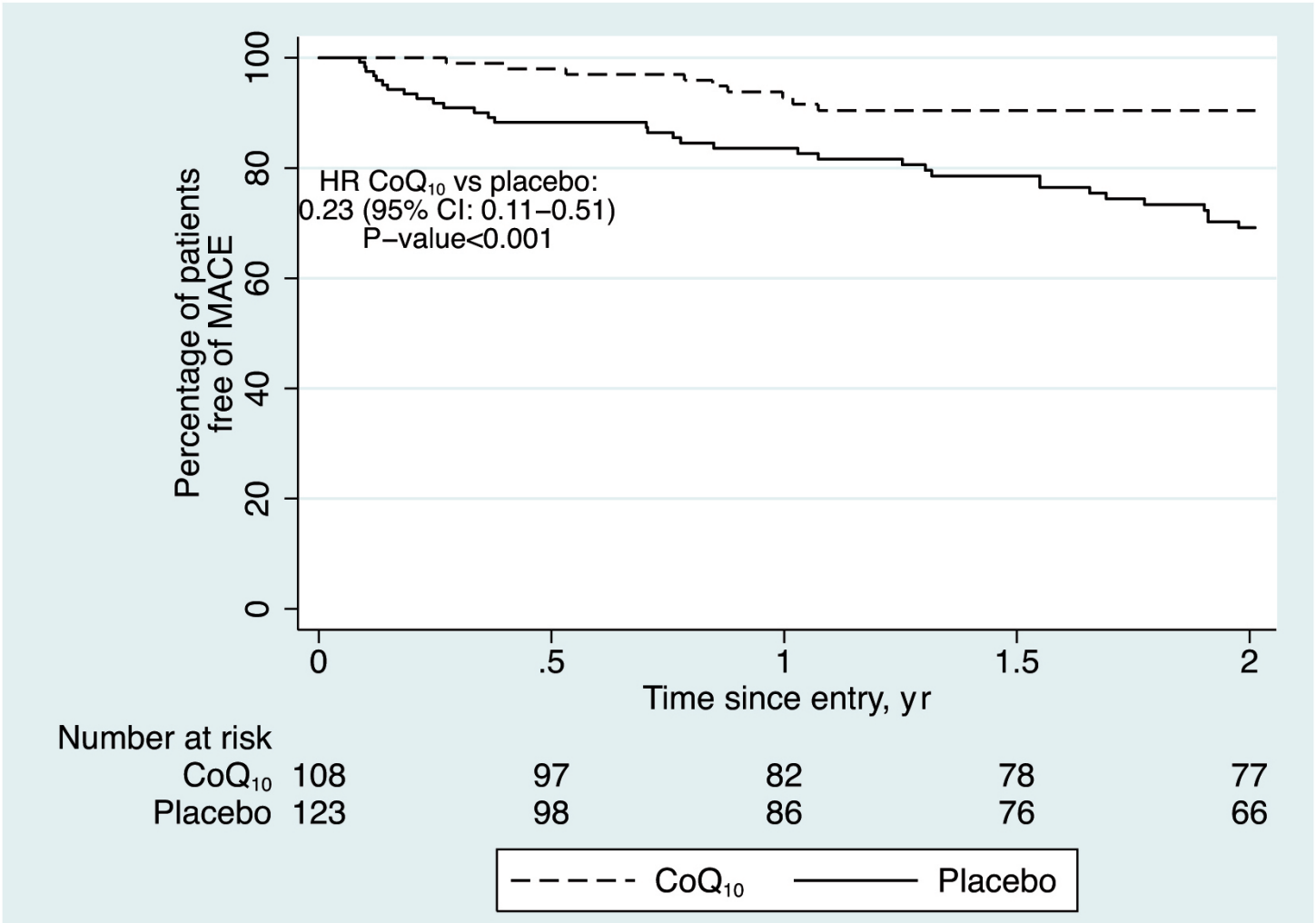
Endpoint	European sub-population				Total population			
	CoQ_{10} (n = 108)	**Placebo (n = 123)**	**RRR**	**P**	**CoQ_{10} (n = 202)**	**Placebo (n = 218)**	**RRR**	**P**
CoQ_{10}-S [μg/mL]	3.55	0.76		0.0001	2.01	0.81		0.0001
MACE	9%	27%	65%	0.001	15%	26%	43%	0.005
Death from any cause	9%	20%	53%	0.040	10%	18%	42%	0.036
Cardiovascular death	8%	17%	51%	0.052	9%	16%	43%	0.039
Hospitalization for HF	3%	13	79%	0.007	8%	14%	41%	0.067

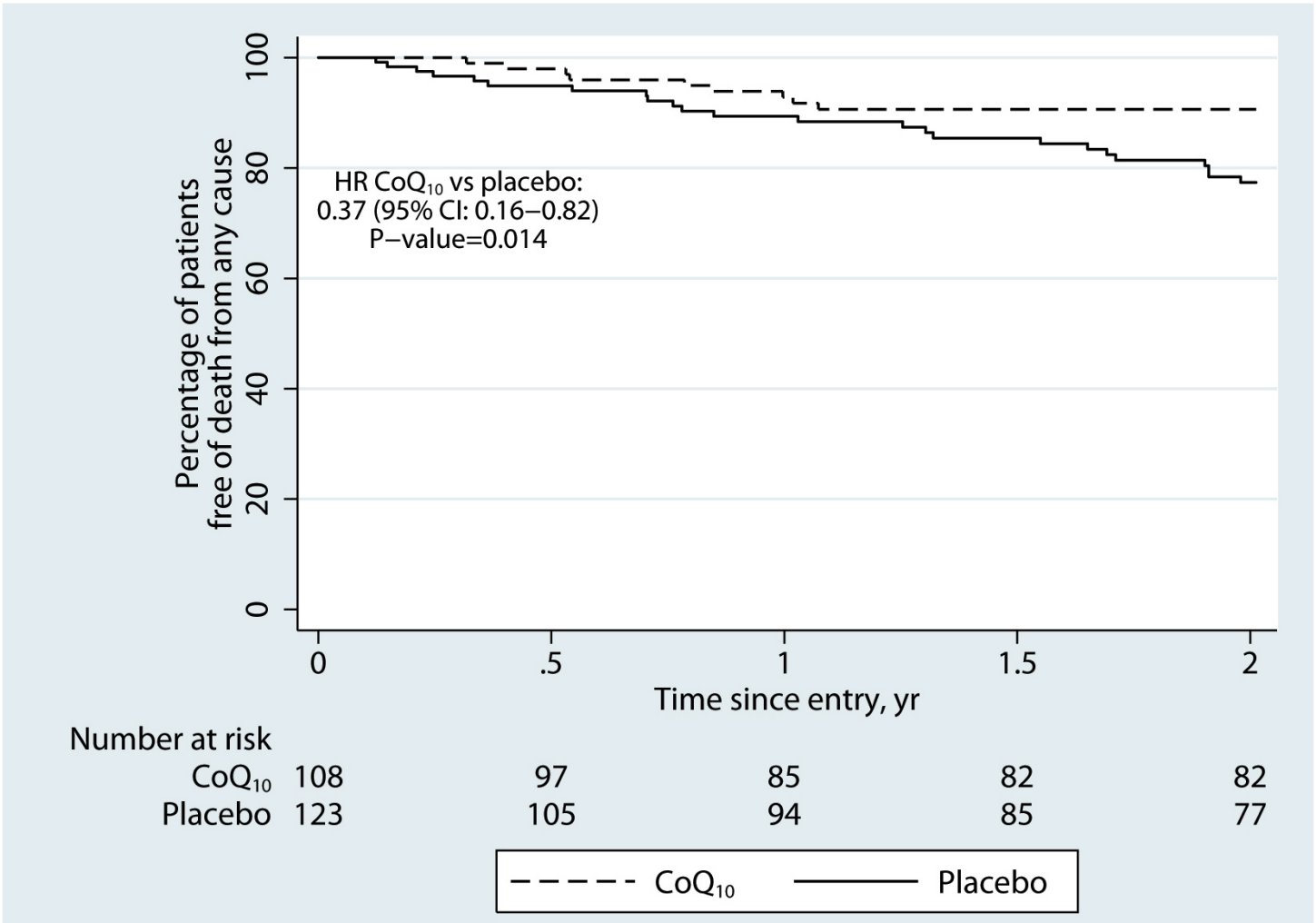
HF — heart failure; MACE — major adverse cardiovascular events

FIGURES LEGENDS

Figure 1. Estimates of the time to primary endpoint of major adverse cardiovascular events (MACE) 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; CI — confidence interval; HR — hazard ratio.

Figure 2. Estimates of the secondary outcome death from any cause in the placebo group (solid line) and the coenzyme Q_{10} (CoQ_{10}) group (dashed line); CI — confidence interval; HR — hazard ratio.


Percentage of patients free of MACE
0
20
40
60
80
100
HR CoQ10 vs placebo:
0.23 (95% CI: 0.11–0.51)
P–value<0.001
0
.5
1
1.5
2
Time since entry, yr
Number at risk
CoQ10 108 97 82 78 77
Placebo 123 98 86 76 66
CoQ10
Placebo


Percentage of patients free of death from any cause
0
20
40
60
80
100
HR CoQ10 vs placebo:
0.37 (95% CI: 0.16–0.82)
P–value=0.014
0
.5
1
1.5
2
Time since entry, yr
Number at risk
CoQ10 108 97 85 82 82
Placebo 123 105 94 85 77
CoQ10
Placebo