The effect of coenzyme Q10 on morbidity and mortality in chronic heart failure

Results from the Q-SYMBIO study

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Introduction

Dysfunction of bioenergetics and energy starvation of the myocardium may be a dominant feature of heart failure (HF).

The myocardial tissue level of the essential redox component of the respiratory chain coenzyme Q10 (CoQ_{10}) has been found inversely related to the severity of HF. CoQ_{10} fulfills various criteria of a supporting adjunct in HF based on previous controlled trials, however these have been underpowered to address survival.

We investigated in a double-blind trial the effects of CoQ_{10} on patients symptoms, functional capacity, biomarker status and the long-term outcome.

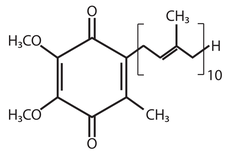

Figure 1: Structure of CoQ_{10} in the oxidized form

Methods

Patients with chronic HF who were receiving current pharmacologic therapy were randomly assigned in parallel groups to either CoQ_{10} 100 mg three times daily or placebo.

Inclusion criteria
Patients aged > 17 years with HF in NYHA classes III-IV.
Predominantly HF with reduced EF% (HF-REF).
Patients with preserved EF% (HF-PEF) were also included.
Ability to participate in a 6-min. walk test.

Exclusion criteria
MI, PCI, cardiac surgery or stroke within the past 6 weeks.
Planned surgery or resynchronization therapy (CRT).
Inotrope dependent, LVAD patients, status-1 listed for transplant.
HF due to hypertrophic or restrictive cardiomyopathy.
HF due to congenital heart disease, acute myocarditis.
Severe non-cardiac disease with life expectancy < 1 year.

Primary short term endpoints
NYHA classification, 6 min. walk test (6MWT), s-NT-proBNP.

Secondary short term endpoints
Symptoms on visual analogue scale (VAS).
Other: heart rate; blood pressure; echocardiography; s-CoQ_{10}.

Primary long-term endpoint
Composite MACE (major adverse cardiovascular events) using a time to first event analysis incl. unplanned hospitalisation due to worsening of HF, cardiovascular death, urgent cardiac transplantation and mechanical support.

Secondary long term endpoints
NYHA classification, NT-proBNP, echocardiography.

Results

A total of 420 patients were randomly assigned to active treatment with CoQ_{10} (n=202) or control with matched placebo (n=218) with a follow-up time of 2 years. The groups were similar with respect to a range of baseline characteristics (Table1).

Characteristics	Optimal HF-therapy + CoQ_{10} N= 202	Optimal HF-therapy + placebo N= 218
Age (mean ± SD)	62,3 ± 12	62,3 ± 11
Male/female ratio	154/48	151/67
Weight (kg, mean ± SD)	77,1 ± 17	77,9 ± 18
Heart rate (mean ± SD)	80 ± 16	82 ± 14
BMI (mean ± SD)	28 ± 5	28 ± 6
Sinus rhythm n (%)	148 (73)	161(74)
Atrial fibrillation n (%)	33 (16)	41 (19)
Rhythm, other (pace) n (%)	21 (10)	16 (7)
Ischemic heart disease n (%)	137 (68)	156 (72)
Dilated cardiomyopathy n (%)	54 (27)	59 (27)
Valvular heart disease n (%)	11 (5) *	3 (1)
Duration of HF (months, mean ± SD)	38 ± 47	35 ± 36
NYHA class II n (%)	6 (3)	8 (4)
NYHA class III n (%)	178 (88)	189 (87)
NYHA class IV n (%)	18 (9)	21 (10)
Left ventricular EF % (mean ± SD)	31 ± 10, RNG 10-65	31 ± 10, RNG 10-70
Left ventricular EDD (mm ± SD)	66 ± 8	64 ± 9
Left ventricular ESD (mm ± SD)	55 ± 11	54 ± 11
6-min. walk distance (m)	287 ± 98, RNG 25-525	286 ± 92, RNG 90-490
Serum CoQ10 (µg/ml, mean ± SE)	1,14 ± 0,08 *	0.91 ± 0,06
NT-proBNP (pg/ml, mean ± SE)	1883 ± 271	1692 ± 229
ACE-I / ARB n (%)	178 (90)	195 (90)
Beta-blockers n (%)	141 (72)	164 (76)
Digoxin n (%)	90 (46)	97 (45)
Diuretics n (%)	155 (79)	176 (81)
Aldosterone antagonists n (%)	66 (34)	74 (34)
Statin derivatives n (%)	74 (38)	77 (35)
Anticoagulation n (%)	49 (25)	54 (25)
Diabetes treatment n (%)	44 (22)	51 (24)

Table 1: Baseline characteristics of patients enrolled, (P<0.05).*

After 3 months
The clinical results were neutral with improvements of NYHA classification in both treatment arms, 44% vs. 39% in the CoQ_{10} group vs. placebo group, respectively.
Serum CoQ_{10} showed a threefold increase in the active treated group to 3,01 ± 0,17 µg/ml (P<0.0001).
There was a trend in subgroup analysis with NT-proBNP reduction in the CoQ_{10} group (P=0.057) which was significant in patients with dilated cardiomyopathy (P=0.035).

After 2 years
The CoQ_{10} group showed a greater proportion with improved NYHA classification (58%) than the placebo group (45%), P=0.047.
The CoQ_{10} group had fewer adverse events than the placebo group (P=0.073).
NT-proBNP levels were more than halved in both groups reflecting an improved prognosis of the surviving patients.
Δ NTproBNP (mean levels): ÷ 1135 pg/ml and ÷ 881 pg/ml, CoQ_{10} and placebo, respectively when compared to baseline (n.s.).

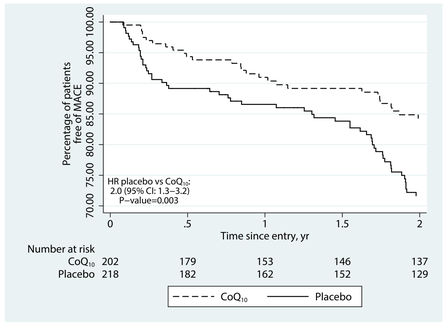

Figure 2: Freedom from major adverse cardiovascular events (MACE).

Endpoint	CoQ_{10} N=202	Placebo N=218	Total N=420
Death due to MI	2	3	5
Death due to HF	1	8	9
Sudden cardiac death	8	12	20
Hospitalisation due to worsening HF	12	24	36
Hospitalisation due to acute HF	3	5	8
Hospitalisation due to acute HF + IABP	2	2	4
LVAD	1	0	1
Other CV death (pulmonary embolism)	0	1	1
Total	29 * (14%)	55 (25%)	84

Table 2: Major adverse cardiovascular events.

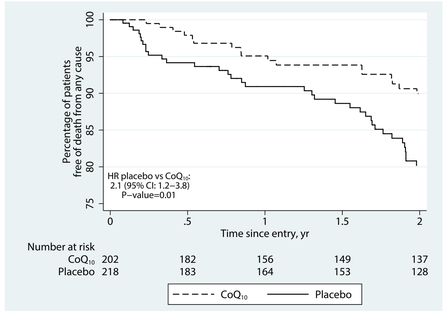

Figure 3: Freedom from death from any cause.

Cause of death	CoQ_{10} N=202	Placebo N= 218	Total N=420
Death due to MI	2	3	5
Death due to HF	2	13	15
Sudden cardiac death	11	15	26
LVAD	1	0	1
Urgent cardiac transplantation	1	0	1
Other CV death (pulmonary embolism)	0	1	1
Cerebrovascular death	0	3	3
Other non-cardiovascular deaths	1	1	2
Total	18 * (9%)	36 (17 %)	54

Table 3: Cause of death.

Major Adverse Cardiovascular Events (MACE)
There were fewer MACE in the CoQ_{10} group (14%) than in the placebo group (25%) * P=0.007 (Table 2).
From a Cox regression analysis stratified by Center the HR placebo vs. CoQ_{10} was 2.0 (95% CI: 1.3-3.2; P=0.003) by intention to treat analysis (Figure 2).

Cardiovascular death
The total number of cardiovascular deaths, was lower in the CoQ_{10} group compared to the placebo group, 17 (8%) vs. 32 (15%); HR placebo vs. CoQ_{10} 2.1 (95% CI: 1.1-3.8; P=0.02). There were 2 deaths vs.13 deaths of HF in the CoQ_{10} group and placebo group, respectively.
The incidence of hospitalisation for HF counted as primary endpoint was lower in the CoQ_{10} group 17 patients (8%) vs. 31 patients in the placebo group (14%); HR 1.8 (95% CI: 1.0-3.4); P=0.05.

Death from any cause
There were 18 deaths from all causes in the CoQ_{10} group (9%) which was less than the 36 deaths in the placebo group (17%) * P=0.028 (Table 3); HR placebo vs. CoQ_{10} 2.1 (95% CI: 1.2-3.8); P=0.01 (Figure 3).

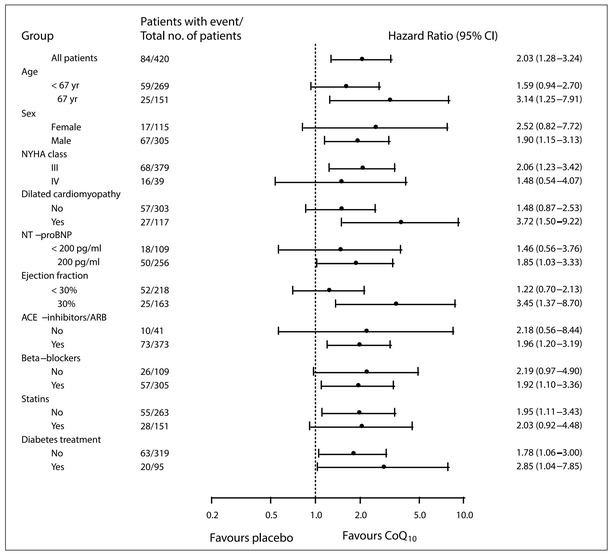

Figure 4: Subgroup analyses.

Sub-group analyses showed that favourable effects of CoQ_{10} were most pronounced in: elderly patients; NYHA class III; dilated cardiomyopathy; LV-EF > 30% and NTproBNP > 200 pg/ml.
The benefits were in addition to those afforded by beta-blockers and ACE-inhibitors or ARB´s.
Statin therapy did not increase the effect of CoQ_{10} (Figure 4).

Conclusions

CoQ_{10} supplementation in patients with chronic HF receiving optimal drug therapy:
is safe, improves symptoms, reduces mortality and adverse cardiovascular events.
CoQ_{10} should be considered as adjunctive therapy of patients with chronic HF.