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Coenzyme Q-10 in the treatment of patients with chronic heart failure and reduced left ventricular ejection fraction: systematic review and meta-analysis

Aim	The aim of the study was evaluation of the effect of the coenzyme Q10 (Q10) treatment on all-cause and cardiovascular mortality of patients with chronic heart failure (CHF). Q-10 increases the electron transfer in the mitochondrial respiratory chain and exerts anti-inflammatory and antioxidant effects. These effects improve the endothelial function and reduce afterload, which facilitates the heart pumping function. Patients with reduced left ventricular (LV) ejection fraction (EF) (CHFrEF) have low Q10.
Material and methods	Criteria of inclusion in the meta-analysis: 1) placebo-controlled studies; 2) enrollment of at least 100 patients; 3) publications after 2010, which implies an optimal basic therapy for CHF; 4) duration of at least 6 months; 5) reported cardiovascular and/or all-cause mortality; 6) using sufficient doses of Q10 (>100 mg/day). The search was performed in CENTRAL, MEDLINE, Embase, Web of Science, E-library, and ClinicalTrials.gov databases. All-cause mortality was the primary efficacy endpoint in this systematic review and the meta-analysis. The secondary endpoint was cardiovascular mortality. Meta-analysis was performed according to the Mantel-Haenszel methods. The Cochrane criterion (I^2) was used for evaluation of statistical heterogeneity. The random effects model was used at $I^2 \geq 50\%$, whereas the fixed effects model was used at $I^2 < 50$.
Results	Analysis of studies published from 01.01.2011 to 01.12.2021 identified 357 publications, 23 of which corresponded to the study topic, but only 6 (providing results of four randomized clinical trials, RCT) completely met the predefined criteria. The final analysis included results of managing 1139 patients (586 received Q10 and 553 received placebo). Risk of all-cause death was analyzed by data of four RCTs (1139 patients). The decrease in the risk associated with the Q10 treatment was 36% (OR=0.64, 95% CI 0.48–0.87, p=0.004). The heterogeneity of studies was low (Chi^2=0.84; p=0.84; I^2=0%). Risk of cardiovascular mortality was analyzed by data of two RCTs (863 patients). The decrease in the risk associated with the Q10 treatment was significant, 55% (OR=0.45, 95% CI: 0.32–0.64, p=0.00001). In this case, the data heterogeneity was also low (Chi^2=0.41; p=0.52; I^2=0%).
Conclusion	The meta-analysis confirmed the beneficial effect of coenzyme Q10 on the prognosis of patients with CHFrEF receiving the recommended basic therapy.

Keywords	Coenzyme Q10; CHF with reduced EF; prognosis; meta-analysis
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Chronic heart failure (CHF), since representing the outcome of all cardiovascular diseases, determines the prognosis for the vast majority of cardiac patients. Published guidelines for the diagnosis and treatment of CHF offer a new treatment algorithm for patients with chronic heart failure with reduced (≤40%) ejection fraction (HFrEF) based on the fastest possible use of quadruple therapy. The following drug classes were shown to improve prognosis for patients with chronic HFrEF: angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor-neprilysin inhibitors (ARNIs) and beta-blockers (BBs), mineralocorticoid receptor antagonists (MRAs), and sodium-glucose co-transporter 2 (SGLT2) [1, 2]. Diuretics should be used for fluid retention. All the above drug classes, classed as recommendations I (to be used), act on important neurohormonal mechanisms of CHF progression rather than the main trigger mechanism of the disease. Triple neurohormonal blockade (ACE inhibitor/ARNI plus BB, and MRA) has been historically considered as complementary to standard CHF treatment, which included cardiac glycosides with positive inotropic

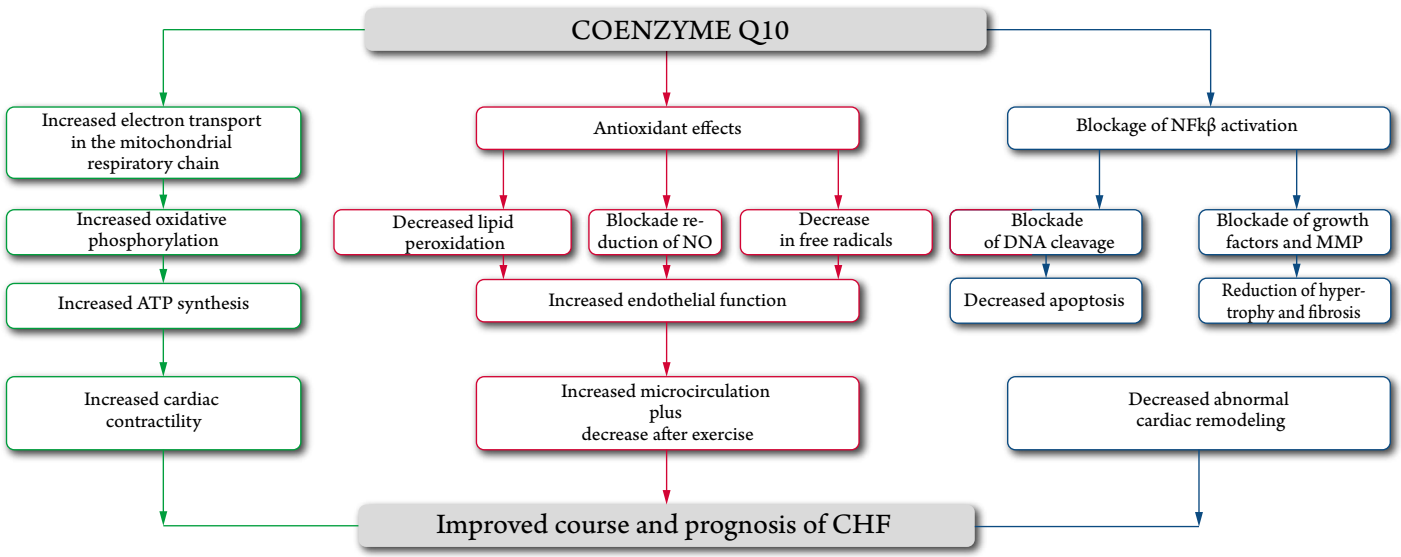
properties and a combination of diuretics. CHF is defined in the 2002 Guidelines by the Society of Heart Failure Specialists (OSSN), along with the Russian Society of Cardiology (RSC) and the Russian Scientific Medical Society of Internists (RSMSI), as "... a syndrome that result from the impaired ability of the heart to fill and/or empty...» [3]. Patients with chronic HFrEF have impaired pump (contractile) function of the heart, which triggers neurohormonal mechanisms of compensation and, later, the disease progression in the case of continuous neurohormonal imbalance. In other words, the main classes of drugs recommended for the treatment of chronic HFrEF in 2021 do not affect the main trigger mechanism of the disease. The role of digoxin positions in atrial fibrillation (class IIa – should be considered) and, especially, in sinus rhythm (class IIb – may be considered) are largely underestimated. At the same time, the recent article «Does the positive effect of digoxin differ from SGLT2 in patients with chronic HFrEF?» demonstrated almost the same effect on the risk of death and hospitalization of cardiac glycosides and SGLT2 with class of evidence IA in the treatment of chronic HFrEF [4]. The use of other drugs that improve the pumping function of the heart is not recommended. Although a randomized clinical trial (RCT) GALACTIC-HF (2020) has shown that the myosin activator omecamtiv reduces the risk of death and exacerbation of CHF, especially in patients with reduced LVEF (<30%) and sinus rhythm, this drug has yet to be approved [5].

In CHF, a lack of energy supplied to the myocardium is mainly due to mitochondrial dysfunction [6], which occurs as a result of transcriptional changes in key enzymes involved in these metabolic pathways [7, 8]. Pharmacological effects on mitochondrial metabolism represent a novel treatment approach to reducing energy deficiency in HF [9]. Since cardiotropic treatments for CHF are a neglected area of research, the present study analyzes the possibility of using endogenous enzymes such as ubiquinone (coenzyme Q10, first isolated from mitochondria in 1957) to improve the metabolic properties of the myocardium [10]. Peter Mitchell's description of chemiosmotic phosphorylation involving coenzyme Q10 led to his being awarded the Nobel Prize in Chemistry in 1978 [11]. Since the mid-1960s, many attempts have been made to use coenzyme Q10 in cardiology.

Mechanism of action and potential role of coenzyme Q10 in CHF

A much-cited review of the issue under the eloquent title «Heart in CHF – motor without fuel» provided a detailed rationale for the role of mitochondrial dysfunction in cardiac contractile dysfunction in patients with symptomatic CHF [12]. The role of endogenous coenzyme Q10 (which guarantees its safe use) in maintaining mitochondrial function and improving myocardial function is well established [13]. Ubiquinone increases electron transport in the respiratory mitochondrial chain, which is accompanied by the activation of oxidative phosphorylation and synthesis of adenosine triphosphate (ATP) (Figure 1) [14]. Its anti-inflammatory and antioxidant effects are additional potentially important mechanisms for improving vascular endothelial function and reducing post-load, which facilitates cardiac pumping [15]. At

Figure 1. Potential mechanisms of action of coenzyme Q10



MMP – matrix metalloproteinases; ATP – adenosine triphosphate; NFκB – nuclear factor kappa-light-chain-enhancer of activated B cells.

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the same time, the blockade of free radical formation is likely to decrease the toxic load on cardiomyocytes, block the DNA destruction, and reduces the activity of apoptosis or programmed cardiomyocyte death [16, 17]. Ubiquinone is also able to slow down the development of myocardial fibrosis and cardiac remodeling by influencing the expression of the nuclear transcription factor NF-kB [18, 19].

Coenzyme Q10 deficiency in CHF

There is a strict concurrency between mitochondrial activity and oxidative stress on the one hand, and coenzyme Q10 deficiency on the other, in patients with CHF, and especially chronic HFrEF. [20].

As shown in Figure 2A, patients with severe chronic HFrEF functional class (FC) III–IV had lower plasma levels of ubiquinone compared to those with chronic HFrEF FC I–II (green bars 0.62 μg/mL vs. 0.75 μg/mL, p<0.05). There were much greater differences in the coenzyme Q10 levels in the myocardium (Figure 2A, red bars). The levels of ubiquinone in the myocardium decreased statistically significantly in patients with chronic HFrEF as the disease progressed from FC I to FC II and then to FC III [21]. Differences between patients with chronic HFrEF FC III–IV and FC I–II were highly significant (0.0280.036 μg/mL vs. 0.036 μg/mL, p<0.001).

Figure 2B shows the correlation between the levels of coenzyme Q10 and the prognosis of patients with chronic HFrEF. If ubiquinone levels were less than median (0.73 μg/mL), mortality was significantly higher (39% vs. 22%, p<0.001). Additional analysis included a combination of ubiquinone and N-terminal pro-brain natriuretic peptide (NT-proBNP). The 2.69-year mortality was minimal (21%) with sufficient (> 0.68 μg/mL) levels of Q10 and low (<235 mmol/L) levels of NT-proBNP [22]. Mortality increased to 26% when ubiquinone levels decreased below the median and to 33% with a higher concentration of NT-proBNP than median to achieve a maximum (48%) with a simultaneous decrease in Q10 and an increase in NT-proBNP. Figure 2B shows the subanalysis of mortality in chronic HFrEF depending on the plasma levels of coenzyme Q10 in the subjects of the CORONA RCT (analysis planned in the trial protocol). The 32.8-month mortality was 9.6% in patients with the highest levels of ubiquinone (higher tertile=1.1 μg/mL). It was much higher (14.7%) in patients with chronic HFrEF and the lowest tertile of coenzyme Q10 levels (0.49 μg/mL) [23]. While the risk of death in chronic HFrEF with low ubiquinone increased 1.5-fold (p=0.03) in the univariate analysis,

Figure 2A. Levels of coenzyme Q10 in plasma and myocardium of patients with chronic HFrEF depending on the functional class [17]

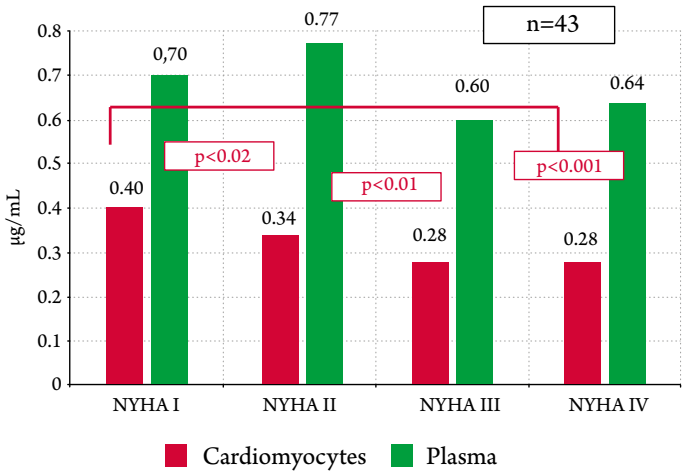
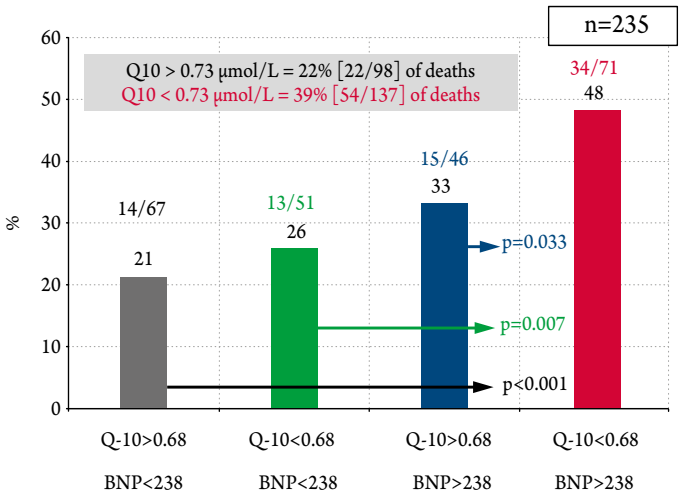
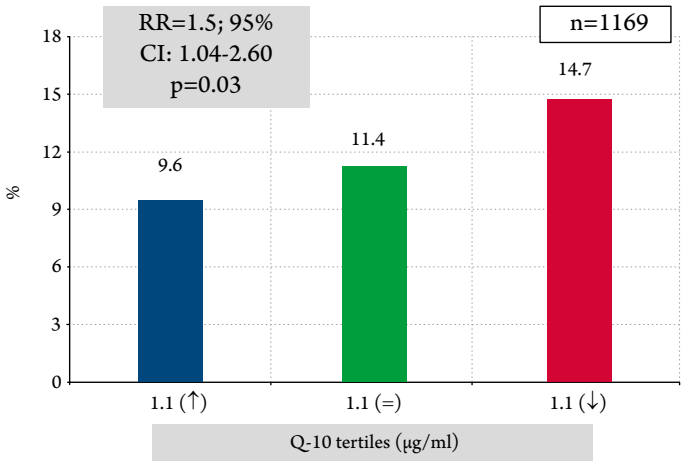


Figure 2B. Correlation of the levels of coenzyme Q10 and brain natriuretic peptide with mortality of patients with chronic HFrEF [18]



BNP – brain natriuretic peptide.

Figure 2C. Analysis of the risk of death in patients with chronic HFrEF depending on the plasma levels of coenzyme Q10 [19]



RR – relative risk; CI – confidence interval.

this indicator lost its independent effect on the prognosis in the multivariate analysis, being inferior to the NT-proBNP levels. The results obtained in three completely different trials showed good repeatability. For example, in the trial with simultaneous myocardial biopsy the median plasma level of ubiquinone was 0.68 μg/mL, 0.73 μg/mL and 0.68 μg/mL in the different survival analyses of the chronic HFrEF, respectively, and 0.74 μg/mL in the subanalysis in the CORONA RCT. The use of coenzyme Q10 in the treatment of patients with CHF was prompted by the presented data.

Trials assessing clinical efficacy of coenzyme Q10 in CHF

Since 1967, many trials have been conducted, having different selection criteria for patients with CHF, objectives, endpoints, duration of follow-up, ubiquinone doses used, and, consequently, types of result analyses. Here, we will try to briefly summarize the analysis of the effects of coenzyme Q10 on the prognosis of patients with chronic HFrEF. The first serious attempts to assess the effects of coenzyme Q10 on systolic function of the heart in CHF were made in a 2006 meta-analysis that included 11 trials (n=297) conducted from 1967 to 2005 [24]. Although ten of those trials (60–200 mg/day of ubiquinone) showed a significant increase in LVEF of 3.68% (95% CI: 1.59–5.77; p<0.00001), the included trials had high observed heterogeneity (I2=86%). Moreover, the increase in LVEF was large and statistically significant in patients not receiving ACE inhibitors (+6.74%; 4 trials), but not significant in addition to ACE inhibitor therapy (+1.51%; 6 trials) [24]. Due to the heterogeneity of the trials and variable effects depending on the concomitant therapy, not all barriers to the approval of ubiquinone as an appropriate treatment for chronic HFrEF were eliminated.

The second relevant meta-analysis, published in 2014 by the Cochrane Laboratory, included 7 trials, including 4 trials from the previous meta-analysis [25]. The results demonstrated a significant increase in the plasma levels of coenzyme Q10 (3 trials; n=112), the absence of significant changes in LVEF (2 trials, n=60), and changes in exercise tolerance (2 trials; n=85). The authors also concluded that, due to the absence of reliable information in most trials, it was impossible to reliably judge the effects of coenzyme Q10 on the prognosis of patients with CHF. A multicenter, double-blind, placebo-controlled, randomized study KUDESNIK (Use of Qudesan to Treat Patients with Cardiac Failure: Efficacy and Safety in Combination with Standard Therapy) was conducted in the Russian Federation to test the hypothesis of the positive effect of coenzyme Q10 on the course of CHF [26]. In the treatment group, a water-soluble coenzyme Q10 (3% drops) was used [27]. Studies conducted in the Department of Pharmacology (the Faculty of Basic Medicine of Moscow State University) under the supervision of Professor Medvedeva O. S. showed that the bioavailability of the solubilized coenzyme Q10 (Qudesan) is 2.5 times higher than the bioavailability of the lipid-soluble coenzyme Q10 [28]. The dose of Qudesan 90 mg/day corresponded to 225 mg of the lipid-soluble form of the drug, which is higher than previously used doses [28, 29]. During the use of Qudesan for 6 months (n=101), compared with placebo (n=47, randomization 2:1), the levels of coenzyme Q10 significantly increased from 1.43 μg/mL to 2.62 μg/mL (p<0.001). This was accompanied by a significant decrease in CHF FC (p=0.033), clinical improvement according to the Symptomatic Hospital and Outpatient Clinical Score (SHOCS; p=0.036), as well as a longer 6-minute walking distance (p=0.044), as compared to placebo. LVEF increased by 3.1% (p=0.001; vs. control p=0.038). Statistically significant differences of changes in the levels of brain natriuretic peptide were identified during treatment: – 33 pg/mL in the Qudesan group versus +34 mg/mL in the placebo group (p=0.032). Quality of life (p<0.001) and ability of self-care (p=0.003), assessed according to the Kansas City Cardiomyopathy Questionnaire, also improved. Water-soluble coenzyme Q10 may be taken into consideration as a possible addition to the CHF therapy due to its significant improvements to the effects of standard therapy.

Assessment of the possible effects of Q10 on the prognosis of patients with CHF

Two long-term RCTs of the use of coenzyme Q10 to treat chronic HFrEF were complete in 2013 and allowed discussing for the first time the ability of the drug to affect the prognosis. In the first study conducted in Sweden, coenzyme Q10200 mg/day, used in combination with dietary supplement containing selenium (n=221) compared with placebo (n=222), significantly reduced the risk of cardiovascular mortality from 12.6% to 5.9% (p=0.015) over a period of 5.2 years [30]. At the same time, there was also a significant decrease in the levels of NT-proBNP (p=0.014) representing an improvement in the CHF course. All-cause mortality decreased statistically insignificantly from 16.2% to 12.8% (p=0.29). Follow-up results published two years later confirmed a significant decrease in the risk of cardiovascular mortality in the ubiquinone/selenium

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group (46 of 221 versus the control – 86 of 222; hazard ratio (HR)=0.52, 95% CI: 0.36–0.74, p=0.0004) [31]. Interestingly, the risk of cardiovascular death was observed in any severity of CHF (from FC I to FC III). The observed decrease in the risk of all-cause mortality was also statistically significant (98 of 221 in the treatment group versus 120 of 222 in the control group, p=0.041). The other trial (Q-SYMBIO) assessed the efficacy of a high dose (300 mg/day) of coenzyme Q10 (n=202) versus placebo (n=218) on the composite endpoint (cardiovascular mortality plus hospitalization for exacerbated CHF; the need for mechanical circulatory support or heart transplantation) [32]. After 106 weeks of treatment, the risk of achieving the primary endpoint of the study was 43% (30 (15%) of 202 events in the ubiquinone group versus 57 (26%) of 218 events in the placebo group, p=0.005). Secondary endpoints were cardiovascular and all-cause mortality. The total number of cardiovascular deaths decreased significantly by 43% (p=0.039) from 16% (34 of 218 cases in the placebo group) to 9% (18 of 202 cases in the treatment group). According to the findings of this study, a total of 14 patients were to be treated with coenzyme Q10 for 2 years to prevent one cardiovascular death in CHF patients. The 42% decreased risk of all-cause mortality was statistically significant (p=0.036) from 18% (39 of 218 deaths in the control group) to 10% (21 of 202 deaths in the coenzyme Q10 group). The number of adverse reactions (13%) was similar to the placebo group (19%) (p=0.110). The trial was criticized for its long-term enrollment (total duration of the RCT was 8 years) and the significant positive effect from a moderate number of patients and endpoints of interest, which may have produced over-optimistic results [32]. Moreover, there were doubts about careful monitoring of patients in different geographical areas. An individual subanalysis of patients from the European site only, where the trial was fully consistent with Good Clinical Practice (GCP), was performed to partially address these criticisms [33]. European patients (n=231) were older (64.8 years vs. 62.2 years, p=0.007), more likely to have atrial fibrillation (26% vs. 18%, p=0.019), as well as more likely to take BBs (88% vs. 73%, p<0.001), statins (57% vs. 36%, p<0.001), and anticoagulants (37% vs. 25%, p=0.001). The risk of achieving the primary endpoint in this group decreased by 77% (HR=0.23; 95% CI 0.11–0.51; p<0.001) or from 27% (33 of 123 cases) in the placebo group to 9% (10 of 108 cases) in the coenzyme Q10 group. The relative risk of all-cause death decreased from 20% (24 of 123) to 9% (10 of 108) or 53% (p=0.04). In other words, the results were fully consistent with the main analysis. Following the completion of these two absolutely positive trials, critical comments mainly concerned the potential role of coenzyme Q10 in the treatment of CHF, positive effects on the prognosis and availability, a minimal risk of adverse reactions, and its low cost [34, 35]. An editorial commenting on the Q-SYMBIO trial was concluded with an equivoque paraphrasing Albert Camus: «CHF patients expend tremendous energy merely to be normal» [36]. Of course, there were also comments about the need to conduct another larger RCT. The principal investigator in Q-SYMBIO, Professor Mortensen, believes that conducting another study is both extremely unlikely, due to the lack of funding for off-patent drugs, and not entirely ethical, given the well-established significant efficacy of coenzyme Q10 [37]. However, the results of the above trials were not taken into consideration in the 2016 and 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. In 2017, a new meta-analysis was published, including 14 RCTs (n=2,149), of which 7 trials (n=1,827) evaluated all-cause mortality following treatment with ubiquinone in patients with chronic HFrEF [38]. The results demonstrated a significant reduction in the death risk by 31% (95% CI: 0.50–0.95; p=0.02; I2=0%). Moreover, while a significant increase in exercise tolerance was identified, changes in LVEF and CHF FC did not show statistically significant differences. There was no publication bias for the mortality rate p=0.387 (Egger's test). Although the authors confirmed that the exclusion of any of those trials did not affect the findings, this meta-analysis can be criticized like any other. Besides the above mentioned relatively large trials (Swedish trial and Q-SYMBIO), another one, completed in 2015, was carried out during the current standard therapy of CHF [31, 32, 39]. Due to the other four trials being performed before 2000, neither the doses of ubiquinone nor the basic therapy of CHF was consistent with the current guidelines. 2021 saw the publication of another meta-analysis of the use of coenzyme Q10. Performed by the Cochrane Laboratory, this study included 1,573 patients of 11 trials (6 of which were included in the 2017 meta-analysis and 5 new trials) [40]. However, the authors' conclusion that «…coenzyme Q10 may reduce mortality (by 42%) and risk of hospitalization for CHF based on medium quality data» was based on the data of only one RCT Q-SYMBIO. In two trials (n=1,061), the relative risk (RR) of hospitalizations for exacerbated CHF decreased statistically significantly 38% (RR=0.62, 95% CI: 0.49–0.78). Thus, 10 patients with chronic HFrEF were to be treated with ubiquinone to prevent one hospitalization. According to the meta-

analysis, the increase in LVEF was +1.77% compared to placebo, which was statistically significant (+1.8% in the KUDESNIK trial). The increase in exercise tolerance was not statistically significant, nor was the decrease in the risk of adverse events, although the changes favored coenzyme Q10 [41]. The authors of the meta-analysis emphasized that the data were heterogeneous.

New meta-analysis of the effects of coenzyme Q10 on the prognosis of patients with chronic HFrEF

Despite the positive results of RCTs (Q-SYMBIO) and the results of the previous meta-analyses, we attempted to conduct another meta-analysis meeting the following criteria: 1) placebo-controlled trials; 2) inclusion of at least 100 patients; 3) published after 2010, implying optimal background therapy of CHF; 4) duration of at least 6 months; 5) reporting of cardiovascular and/or all-cause mortality; 6) use of adequate doses of coenzyme Q10 (> 100 mg/day). The meta-analysis fully complied with the international rules and PRISMA Guidelines [42], the latest recommendations of the Cochrane Laboratory [43], and the Russian guidelines for meta-analyses [44]. The search was performed in the CENTRAL, MEDLINE, Embase, Web of Science, E-library, and ClinicalTrials.gov databases. All-cause death was the primary endpoint of efficacy; the secondary endpoint was cardiovascular death. A single investigator conducted the systematic search and selection of papers. Odds ratio (OR) was used as a measure of effect. The meta-analysis was performed using the Mantel-Haenszel method and RevMan software. Statistical heterogeneity, assessed using the Cochrane test (I2), was considered significant with I2 ≥ 50%, on which basis the meta-analysis used a random effects model. Heterogeneity was also estimated using the χ^2 test with a statistical significance of $p<0.1$. When statistical heterogeneity did not achieve 50%, a fixed-effect model was used for meta-analysis. The methodological quality of the included RCTs was assessed using the Cochrane tool [41]. From an analysis of the CENTRAL, MEDLINE, Embase, Web of Science, E-library, and ClinicalTrials.gov databases carried out between 01/01/2011 and 12/01/2021, 357 publications were found, of which 23 corresponded to the issue of interest, but only 6 (describing the results of four RCTs) fully met the criteria. Table 1summarizes the trials and assessments of the methodological quality of the included RCTs.

As a result, treatment outcomes of 1,139 patients (586 in the coenzyme Q10 group and 553 in the placebo group) were included in the final analysis, whose baseline characteristics are provided in Table 2. As shown in the table, the groups were fully balanced and represented typical patients with chronic HFrEF (LVEF ≈33.5%, NT-proBNP ≈ 1003 pg/mL) of various severity. CHF FC I, FC II, FC III, and FC IV were diagnosed in 21%, 22%, 53%, and 4% of the subjects, respectively. Background therapy, such as the use of triple neurohormonal blockade, was mainly consistent with the guidelines.

Figure 3 presents the results of the meta-analysis (4 RCTs, 1,139 patients), confirming a statistically significant reduction of the risk of all-cause death in patients with chronic HFrEF during the optimal neurohormonal blockade and the use of coenzyme Q10. The risk decreased by 36% (OR=0.64; 95% CI 0.48–0.87; p=0.004). The heterogeneity of the trials was low (χ^2=0.84; p=0.84; I2=0%), confirming the validity of the meta-analysis results. In order to prevent one death, twelve patients should be treated for mean of 35 months.

Figure 4 presents the results of the meta-analysis of the effects of coenzyme Q10 on the risk of cardiovascular death in patients with chronic HFrEF (2 RCTs, 863 patients). The risk decreased by 55% (OR=0.45, 95% CI: 0.32–0.64, p=0.00001). The heterogeneity of data was low (χ^2=0.41; p=0.52; I2=0%). In patients with chronic HFrEF, nine patients should be treated with ubiquinone for 35 months to prevent one cardiovascular death. A funnel plot analysis was carried out to eliminate the bias of the papers included in the meta-analysis (Figure 5).

The presented data (symmetry of the findings of individual RCTs) confirm the correctness of the meta-analysis and the lack of bias of the published data [45, 46]. In one of the trials included in the meta-analysis, coenzyme Q10 was used in combination with selenium [30, 31]. According to the BIOSTAT-HF study, low levels of selenium were combined with decreased LVEF, increased mortality, and deteriorated mitochondrial function in patients with chronic HFrEF [47]. According to the researchers, concomitant selenium use can have a positive effect on the course and prognosis of CHF [48]. Given the impossibility of isolating the effect of each component of the combination therapy (coenzyme Q10200 mg/day plus selenium), we carried out an additional sensitivity analysis of the model without this study (Figure 6).

At the same time, the risk of all-cause death (3 RCTs, 696 patients) statistically significantly decreased by 41% (OR=0.59, 95% CI: 0.36–0.97; p=0.04). The heterogeneity of the trials remained low (χ^2=0.84; p=0.84; I2=0%), confirming the validity of the conclusions of the main meta-analysis. Similarly, there was a significant reduction in the risk of cardiovascular

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Table 1. Trials of using coenzyme Q10 in patients with chronic HFrEF included in the meta-analysis

Trial	N (Q10)/ N (placebo)	Coenzyme Q10, mg/day	Offset resulting during the randomization process	Offset due to deviations from the scheduled interventions	Offset due to lacking data on outcomes	Bias in measuring the result	Bias in selecting the reported result
Alehagen et al., 2013, Alehagen et al., 2015	221/222	200	+	+	?	+	+
КУДЕСНИК, Мареев В.Ю. и др., 2016	101/47	225	+	+	?	–	?
Q-SYMBIO Mortensen et al., 2014, 2018	202/218	300	+	+	+	+	+
Zhao et al., 2015	62/66	2 mg/kg	?	?	+	+	?

Table 2. Baseline characteristics of patients included in the meta-analysis

Parameters	Coenzyme Q10, n = 586	Placebo, n = 553
Four RCTs, duration, months (Q10 vs. placebo)	62 (221 vs 222); 6 (101 vs 47); 24 (202 vs 218); 12 (62 vs 66)	
Age, years	68 ± 7.4*	68.5 ± 7.1
Mean FC	2.40 ± 0.88	2.42 ± 0.91
LVEF, %	33.6 ± 5.0	33.3 ± 5.2
NT-proBNP, pg/mL	1017 ± 258	988 ± 221
RAAS blockers	*405 (69.1 %)*	*391 (70.7 %)*
BBs	*365 (62.3 %)*	*352 (63.6 %)*
MRAs	*157 (26.8 %)*	*142 (25.7 %)*

* Data scatter was calculated based on the mean values of each RCT.

RCT – randomized clinical trial; FC – functional class; LVEF – left ventricular ejection fraction; NT-proBNP – N-terminal pro-brain natriuretic peptide (B-type); RAAS – renin-angiotensin-aldosterone system; BB – beta-blocker; MRA – mineralocorticoid receptor antagonist.

death (1 RCT, 420 patients) by 47% (RR=0.53, 95% CI: 0.29–0.97; p=0.04). A sensitivity analysis, in which RR was used instead of OR to assess the efficacy, also showed a decreased in the risk of all-cause (RR=0.77, 95% CI: 0.64–0.92, p=0.003) and cardiovascular death (RR=0.55, 95% CI: 0.42–0.71). The decreased risk of all-cause and cardiovascular death remained after the exclusion of the trial, in which selenium was used (RR=0.57, 95% CI: 0.33–0.98 and RR=0.63, 95% CI: 0.41–0.98).

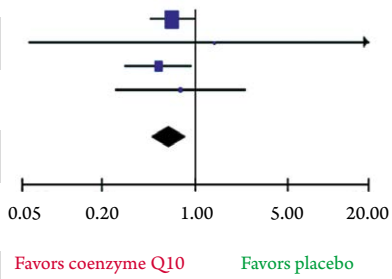
Thus, our meta-analysis confirmed the positive effects of coenzyme Q10 on the prognosis of patients with chronic HFrEF during the recommended background therapy.

Conclusion

Are there grounds for including coenzyme Q10-based therapies in the Clinical Guidelines for the diagnosis and treatment of CHF? Despite the clear data, the large RCT (Q-SYMBIO), and repeated positive meta-analyses, including our meta-analyses, the clinical

Figure 3. Meta-analysis of the effects of coenzyme Q10 on the risk (odds ratio) of all-cause mortality in patients with chronic HFrEF

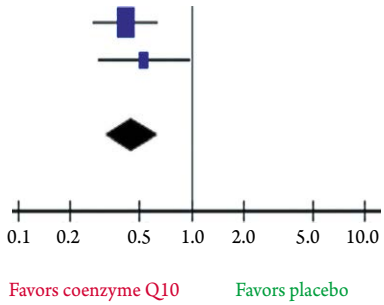
RCT	Coenzyme Q10 Cases	Coenzyme Q10 n	Placebo Cases	Placebo n	Weight	Odds ratio Mantel-Haenszel, 95 % CI	Odds ratio Fixed effect, 95 % CI
Alehagen et al.	98	221	120	222	61.7%	0.68 (0.47-0.98)	
Kudesnik	1	101	0	47	0.6%	1.42 (0.06-35.46)	
Q-SYMBIO	21	202	39	218	31.1%	0.53 (0.30-0.94)	
Zhao et al.	6	62	8	66	6.5%	0.78 (0.25-2.38)	
Total, 95 % CI		586		553	100%	0.64 (0.48-0.87)	
Total of cases	126		167				



Heterogeneity: $\chi^2 = 0,84$; df = 3 (p = 0.84); I2 = 0%.
Significance of overall effect: Z = 2.89 (p = 0.004). RCT – randomized clinical trial; CI – confidence interval.

Figure 4. Meta-analysis of the effects of coenzyme Q10 on the risk (odds ratio) of cardiovascular mortality in patients with chronic HFrEF

RCT	Coenzyme Q10 Cases	Coenzyme Q10 n	Placebo Cases	Placebo n	Weight	Odds ratio Mantel-Haenszel, 95 % CI	Odds ratio Fixed effect, 95 % CI
Alehagen et al.	46	221	86	222	69.5%	0,42 (0.27-0.63)	
Q-SYMBIO	18	202	34	218	30.5%	0,53 (0.29-0.97)	
Total, 95 % CI		423		440	100%	0.45 (0.32-0.64)	
Total of cases	64		120				



Heterogeneity: $\chi^2 = 0,84$; df = 3 (p = 0.84); I2 = 0%.
Significance of overall effect: Z = 2.89 (p = 0.004). RCT – randomized clinical trial; CI – confidence interval.

guidelines typically omit coenzyme Q10 as an effective treatment for CHF. While the 2018 OSSN-RSC-RSMSI guidelines state that "… the use of coenzyme Q10 300 mg/day (equivalent to 120 mg of Qudesan) can be used to further reduce the risk of death or decompensation in patients with CHF and systolic dysfunction receiving the optimal treatment (IIb, B)» [3], the 2020 Clinical Guidelines approved by the Ministry of Health of the Russian Federation do not mention this treatment. According to the Guidelines for the evaluation of evidential reliability and the credibility of the recommendations developed by the Center for Expertise and Control of Medical Care Quality, there are criteria for assessing the efficacy of treatment of a particular pathology [49]. Here, levels of evidence are treated as essential. The most reliable evidence level

Figure 5. Funnel scatter plot of the findings of trials included in the meta-analyses on the use of coenzyme Q10 in patients with chronic HFrEF

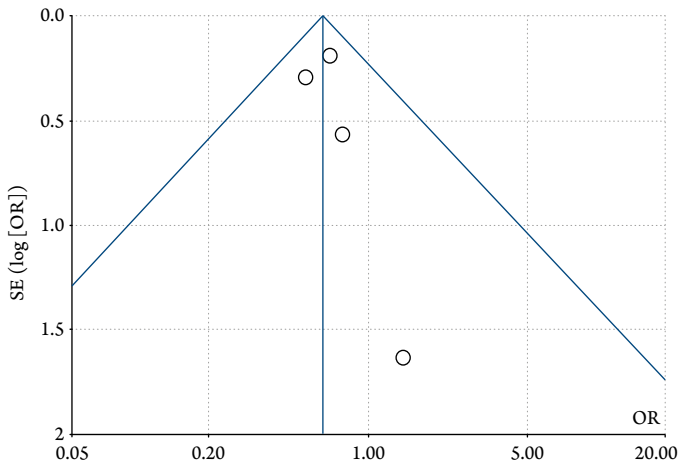
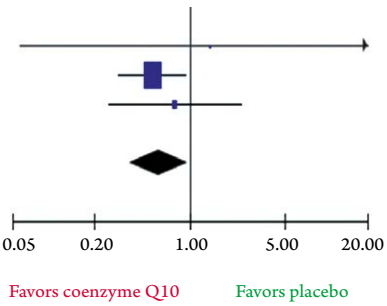


Figure 6. Additional sensitivity analysis of the effects of coenzyme Q10 (without other dietary supplements) on the odds ratio of all-cause mortality in patients with chronic HFrEF

RCT	Coenzyme Q10 Cases	Coenzyme Q10 n	Placebo Cases	Placebo n	Weight	Odds ratio Mantel-Haenszel, 95 % CI	Odds ratio Fixed effect, 95 % CI
Alehagen et al.	98	221	120	222	0.0%	0.68 (0.47-0.98)	
Kudesnik	1	101	0	47	1.6%	1.42 (0.06-35.46)	
Q-SYMBIO	21	202	39	218	81.4%	0.53 (0.30-0.94)	
Zhao et al.	6	62	8	66	17.0%	0.78 (0.25-2.38)	
Total, 95 % CI		365		331	100%	0.59 (0.36-0.97)	
Total of cases	28		47				



Heterogeneity: $\chi 2 = 0,64$; df = 2 (p = 0.73); I2 = 0 %.
Significance of overall effect: Z = 2.09 (p = 0.04). RCT – randomized clinical trial; CI – confidence interval.

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is «systematic reviews of RCTs using meta-analysis», while the next level is «Individual RCTs and systematic reviews of trials other than RCTs using meta-analysis». The available data presented in this article correspond to at least evidential level 2 for the use of coenzyme Q10 in the treatment of CHF. The second criterion used for the evaluation of the treatment results is grades of recommendation. The highest recommendation grade A implies simultaneous fulfillment of three conditions: 1) all outcomes of interest are significant; 2) all trials are of high or satisfactory methodological quality; 3) conclusions concerning the outcomes of interest are consistent. The available findings on the use of coenzyme Q10 in the treatment of chronic HFrEF are quite close to this definition. However, given the small number of patients in the Q-SYMBIO RCT and presence of methodological errors in the other trials included in the meta-analyses, the lower recommendation grade B will be more appropriate for the treatment under discussion. Given the high safety of coenzyme Q10, it can be recommended to include the drug in the Clinical guidelines for the diagnosis and treatment of CHF to improve the prognosis of patients with chronic HFrEF who receive optimal therapy (level of evidence 2, grade of recommendation B). Ideally, a large RCT should be conducted to verify the results obtained in small RCTs to conclusively determine the role of coenzyme Q10 in the treatment of patients with CHF. However, since coenzyme Q10 products are not patented, manufacturers are unlikely to conduct larger trials. Thus, coenzyme Q10 is one among a number of potential treatments requiring further study, but one that is of less interest to pharmacological companies. Trials supported by governments and/or respective ministries of health can address this and similar problems. In several countries, such trials have been conducted both before (e.g., study of colchicine in CAD [50] or telemetry of implanted devices) and during the COVID-19 pandemic period (RECOVERY and SOLIDARITY trials [51]).

No conflict of interest is reported.

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