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Coenzyme Q_{10} in targeted supportive therapy of heart failure – a comprehensive review and proposal of an algorithm for clinical practice

Koenzým Q_{10} v cielenej podpornej terapii srdcového zlyhávania – komplexný prehľad a návrh postupu v klinickej praxi

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Abstract. Heart failure (HF) progresses typically as a chronic disease with reduced quality of life and high mortality despite modern therapeutic options. One explanation is that current treatment strategies are not directly aimed at improving the bioenergetics of the failing myocardium. Therapy with some nutraceuticals (e.g. coenzyme Q_{10} – CoQ_{10}) increases energy generation in the mitochondria of remaining viable cardiomyocytes. Several clinical studies and meta-analyses have confirmed the improvement of myocardial function and quality of life as well as a decrease in mortality and hospitalization for HF with the proper use of CoQ_{10}. The quality and bioavailability of the remedy (optimally soluble in water and fat, alternatively in oil emulsion with decrystallized CoQ_{10}), dosage form (soft gel capsules), taking with food (with a small amount of fat), adequate dose (on average 200-300 mg per day with a plasma concentration of at least 3 μg/ml) and duration of treatment (at least several months) are crucial. The acceptance of CoQ_{10} in the next official guidelines for the management of HF and its registration among approved drugs (such as in Hungary or Japan) would certainly contribute to a wider and more affordable use of this safe and effective nutraceutical. The aim of the article is to provide a comprehensive review on the benefit of both forms of CoQ_{10} (ubiquinone and ubiquinol) for patients with HF and to propose an algorithm for its therapeutic use in clinical practice. Fig. 3, Tab. 1, Ref. 100, on-line full text (Free, PDF) www.cardiologyletters.sk

Keywords: heart failure – coenzyme Q_{10}, CoQ_{10}, ubiquinone – ubiquinol – nutraceuticals

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Abstrakt. Srdcové zlyhávanie (SZ) prebieha typicky ako chronické ochorenie so zníženou kvalitou života a vysokou mortalitou napriek moderným terapeutickým možnostiam. Jedným z vysvetlení je, že súčasné liečebné postupy nie sú priamo zamerané na zlepšenie bioenergetiky

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zlyhávajúceho myokardu. Terapia niektorými nutraceutikami (napríklad koenzýmom Q_{10} – CoQ_{10}) zvyšuje tvorbu energie v mitochondriách zostávajúcich viabilných kardiomyocytov. Viaceré klinické štúdie a metaanalýzy potvrdili zlepšenie funkcie myokardu a kvality života, ako aj pokles mortality a hospitalizácií pre SZ pri správnom užívaní CoQ_{10}. Rozhodujúca je kvalita a biologická dostupnosť prípravku (optimálne s rozpustnosťou vo vode i tuku, prípadne v olejovej emulzii s dekryštalizovaným CoQ_{10}), lieková forma (kapsule z mäkkého gélu), užívanie s jedlom (s malým množstvom tuku), adekvátna dávka (priemerne 200 – 300 mg denne s dosiahnutím plazmatickej koncentrácie aspoň 3 μg/ml) a dĺžka liečby (minimálne niekoľko mesiacov). Zaradenie CoQ_{10} do budúcich oficiálnych odporúčaní pre manažment SZ a jeho registrácia medzi schválené lieky (ako napríklad v Maďarsku alebo Japonsku) by určite prispeli k širšiemu a cenovo dostupnejšiemu využitiu tohto bezpečného a efektívneho nutraceutika. Cieľom článku je priniesť komplexný prehľad o prínose oboch foriem CoQ_{10} (ubichinónu aj ubichinolu) pre pacientov so SZ a navrhnúť postup pre jeho terapeutické použitie v klinickej praxi. Obr. 3, Tab. 1, Lit. 100, on-line full text (Free, PDF) www.cardiologyletters.sk

Kľúčové slová: srdcové zlyhávanie – koenzým Q_{10} – CoQ_{10} – ubichinón – ubichinol – nutraceutiká

Heart failure (HF) progress typically as a chronic disease with reduced quality of life and unfavourable long-term prognosis. It affects about 2% of the adult population and more than half of the patients die approximately 5 years after the diagnosis (1). The number of hospitalizations for HF is increasing significantly in our country, from less than 10,000 in 2005 to more than 25,000 in 2017). This brings, in addition to the medical burden, also significant economic costs (2).

Current European and American guidelines for the treatment of HF with reduced left ventricular ejection fraction (EF) (HFrEF) emphasize the administration of renin-angiotensin-aldosterone system inhibitors, beta-blockers, mineralocorticoid receptor antagonists, and sodium-glucose cotransporter 2 inhibitors (SGLT2i) (1, 3). We define them as guideline-directed medical therapy. Optimal therapy represents the use of all of these drugs in the target or maximum tolerated dose. In patients with HF and mildly reduced left ventricular (LV) EF – HFmrEF – and also in patients with HF and preserved LVEF (HFpEF), only SGLT2i have a clearly proven benefit on cardiovascular mortality and hospitalizations for HF (4). Despite treatment advances, mortality in HF remains disproportionately high. Cardiovascular mortality was around 10% in patients with HFrEF after approximately one and a half years in the treatment arms of recent large studies with SGLT2i (along with other complex HF therapy) (5, 6). One of the possible explanations is that the currently recommended drugs do not significantly improve the energy metabolism of the failing myocardium (7, 8).

HF usually lasts for many years, with most cardiomyocytes being viable at the onset of the disease. However, a significant part of them is dysfunctional due to impaired metabolism and energy deficit. They are in the so-called vegetative state. Therapy with nutritional supplements – nutraceuticals (e.g. coenzyme Q_{10}) increases energy production in mitochondria and prevents premature death of cardiomyocytes, which leads to (at least partial) recovery of the hemodynamic function of the myocardium (9). The aim of the article is, after a brief description of bioenergetics in HF, to bring a more detailed view of coenzyme Q_{10} (CoQ_{10}), which is a potential therapeutic option for patients with HF (10-12).

Bioenergetics of the failing myocardium

From the pathophysiological point of view, HF is characterized by a lack of energy for mechanical contraction adequate to the metabolic needs of the tissues. The main source of energy is adenosine triphosphate (ATP), which is 90% produced in the respiratory chain of mitochondria mainly from fatty acids and glucose (13). Cardiomyocytes need ATP not only to ensure adequate blood circulation, but also for their growth, regeneration after damage and basic survival (14). Due to continuous

aerobic work, the myocardium contains more than 3500 mitochondria in each cell (15).

Cardiomyocytes in HF are characterized by a decrease in the number, as well as defects in the structure and function of mitochondria, which leads to an excessive production of destructive oxygen radicals and a deficit of ATP (16). The amount of ATP gradually decreases to values 30% lower than in a healthy heart (17). Increasing the supply of macronutrients (fatty acids, glucose or ketones) to the myocardium turns out to be worthless, since the mitochondria are unable to convert them into energy due to the lack of micronutrients (e.g. CoQ_{10}, selenium, amino acids, etc.) (18).

Lack of energy triggers a cycle of pathological reactions, the ultimate consequence of which is the depletion of ATP reserves and toxic damage to cells from excessive amounts of calcium. The result is necrosis of the cardiomyocytes, with their replacement by fibrotic tissue (19). Deficiency of micronutrients is therefore an important factor in the pathophysiology of the failing myocardium, and supplementation with nutraceuticals is a promising treatment strategy for HF (18).

Physiology of CoQ_{10}

CoQ_{10} is an organic, lipophilic and vitamin K-like substance. It is necessary for the synthesis of ATP in the respiratory chain and in the so-called Q-cycle of mitochondria (20). The content of CoQ_{10} in the human body is 500-1500 mg, with the highest concentration in the myocardium (114 μg/g tissue) (11). It occurs in all organs as part of cell membranes and also in lipoproteins with high or low density (LDL). 90% of the total amount of CoQ_{10} is in the reduced form (ubiquinol), about 10% is in the oxidized form (ubiquinone) and a minimal amount is in a radical molecule (semiubiquinone). Almost 80% of the CoQ_{10} in cells is found in the mitochondria (21, 22).

CoQ_{10} also acts as a strong antioxidant (ubiquinol), contributes to the protection of proteins and deoxyribonucleic acid, participates in the epigenetic regulation of genes for cell signaling and growth. It also ensures the "revitalization" of damaged vitamin C and E, with their repeated participation in the inhibition of lipid peroxidation (7, 23). Another important role of CoQ_{10} is the stabilization of membranes (regulation of the flow of calcium ions or the release of cytochrome c from mitochondria) with subsequent reduction of apoptosis of cardiomyocytes. It also improves the availability of nitric oxide and the function of the vascular endothelium, as well as reduces fibrotization and hypertrophy of the myocardium (24).

The human body obtains approximately 75% of CoQ_{10} through its own biosynthesis from mevalonic acid and tyrosine with the participation of trace elements, vitamin C and various group B vitamins (B_2, B_3, B_5, B_6, B_9 and B_{12}) (25). Cholesterol, heme A, and selenoproteins are also produced from mevalonic acid (26). About 25% of CoQ_{10} is taken in the diet (3-5 mg/day). Sources include pork or beef offal and meat, poultry and fish (salmon, tuna, sardines), nuts, soy, eggs, dairy products, fruits and vegetables (especially broccoli and spinach). Frying reduces its content in food by 15-30% (25).

Dietary intake and nutraceuticals become crucial for CoQ_{10} deficiency in HF due to its increased consumption and reduced synthesis. Endogenous production of CoQ_{10} is not decreased by using nutraceuticals, but it decreases with age (starting in the fourth decade of life). Similarly, the ability to convert ubiquinone to ubiquinol – the active form – decreases over the years (25). The use of certain drugs (statins, beta-blockers, etc.) also contributes to the deficit (23). CoQ_{10} thus becomes conditionally essential and is also referred to as „vitamin Q" (25). Supplementation of CoQ_{10} has been shown to lead not only to an increase in its concentration in plasma and cells, but also to the modification of mitochondrial metabolism and to increased ATP production (27-29).

To determine the plasma concentration of CoQ_{10}, the method of high-performance liquid chromatography is used, a value from 0.7±0.3 to 1.1±0.2 μmol/l or 0.8-1.2 mg/l is considered as normal (13, 23). The main carriers of CoQ_{10} in the circulation are lipoproteins: approximately 58% of CoQ_{10} is bound to LDL (22). Therefore, indexing of CoQ_{10} against LDL (normal value 0.33±0.1 μmol/mmol) or total cholesterol (normal range from 0.16±0.05 to 0.24±0.07 μmol/mmol) is also used (24). However, the plasma value does not accurately reflect the CoQ_{10} concentration in the tissues (22). In the myocardium, a value of 0.4 μg/g dry weight is considered physiological (30, 31).

Background for the treatment of HF with CoQ_{10}

In a group of 43 patients with HF of various etiologies, a significant correlation was found between the decrease in CoQ_{10} concentration in biopsy samples of the myocardium and severity of HF according to the NYHA (New York Heart Association) classification. Patients in NYHA classes III and IV had significantly lower CoQ_{10} content compared to patients in NYHA classes I and II. Likewise, their blood CoQ_{10} levels were significantly lower. In five patients, control examinations were performed after taking CoQ_{10} (100 mg daily for 2-8 months). Supplementation resulted in a more than two-fold increase in the blood level (from 0.66±0.2 to 1.5±0.78 µg/ml, p=ns) and a significant increase in the intramyocardial concentration (from 0.27±0.04 to 0.38±0.06 µg/mg dry weight, p<0.02) (**Figure 1**) (31).

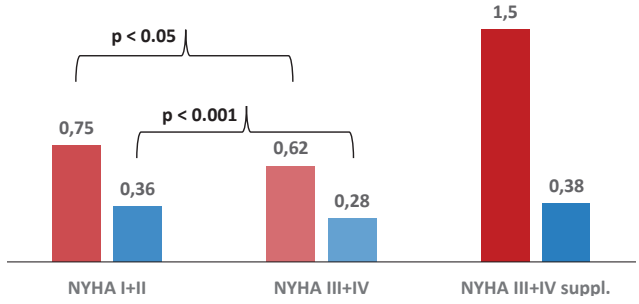

Figure 1 CoQ_{10} deficiency in plasma (red; µg/ml) and myocardium (blue; µg/mg dry weight)* in relation to HF severity according to the NYHA classification and changes after supplementation (100 mg/day for 2-8 months; according to 31)**

CoQ_{10} – coenzyme Q_{10}, HF – heart failure, NYHA – New York Heart Association, suppl. – supplementation.

*average values; **for changes in plasma after supplementation p = ns, for changes in myocardium p<0.02

There was also a detected difference in the amount of CoQ_{10} (as well as carnitine and taurine) in myocardial samples after treatment with a combined nutritional preparation before cardiac surgical revascularization. Within about 30 days, a dose of 150 mg resulted in an increase in myocardial CoQ_{10} concentration compared to placebo (138±40 vs 57±23 nmol/g tissue, p<0.001) (32).

CoQ_{10} is an important prognostic marker in patients with HF of various etiologies. In a cohort of 236 patients from New Zealand, a plasma value less than 0.73 µmol/l was an independent predictor of all-cause mortality (p=0.007). After indexing to total cholesterol or LDL, the cut-off value was lower than 0.14 mmol/mol (p=0.006) or 0.26 mmol/mol (p=0.05), respectively. The plasma concentration of CoQ_{10} is inversely correlated with the level of the N-terminal fragment of B-type natriuretic peptide (NT-proBNP). In this cohort, CoQ_{10} was a more sensitive predictor of all-cause mortality than NT-proBNP (33).

The authors of the subanalysis of the CORONA study (Controlled Rosuvastatin Multinational Study in Heart Failure) reached similar results. In a group of 1191 patients, univariate analysis confirmed a significantly higher total mortality at the lowest plasma CoQ_{10} concentration (0.39-0.57 µg/ml, respectively 0.45-0.66 µmol/l; p=0.03) (34). There were 14 prognostic predictors used in the multivariate analysis, which resulted from another substudy (35). This weakened the statistical power of a low CoQ_{10} value (p=ns), which the authors evaluated then rather as a marker of more advanced disease and not an independent predictor of adverse prognosis. In conclusion, however, they add that in the case of using 5 parameters from the above study by New Zealand authors, a low CoQ_{10} level would be an independent predictor of mortality in HF even in a multivariate analysis (p=0.048) (34).

In clinical practice, we can therefore use the determination of the CoQ_{10} plasma level analogously to the measurement of NT-proBNP. Significantly elevated or rising values of NT-proBNP despite treatment are, in the long term, signs of advanced HF and its worse prognosis (1). The same is practically true for low and declining CoQ_{10} levels (33, 34). Along with the knowledge about the diagnostic application, concomitant improvements in the health status and prognosis of patients taking CoQ_{10} were also recorded in the studies. This became the background for the proposal for its application in the treatment of HF (36, 37).

CoQ_{10} in the treatment of HF

Administration of CoQ_{10} is already important in patients at high risk of HF (class A according to the recommendations of the American Heart Association), where it reduces the impact of risk factors. Meta-analyses

have confirmed its antihypertensive, hypolipidemic, antiatherogenic and antidiabetogenic effects (25). Similarly, in class B (structural abnormalities of the heart without HF), the benefit of administering CoQ_{10} is proven, e.g. in patients after myocardial infarction (regression of LV remodeling) or surgical revascularization (reduction of ventricular arrhythmias, atrial fibrillation or need for inotropes) (38).

In most clinical studies, the benefit of CoQ_{10} was investigated in symptomatic (class C) and to a lesser extent in advanced (class D) HF, with functional limitation at NYHA class I to IV. These numerous studies (often with a smaller sample size) are summarized in several review articles and meta-analyses (7, 12, 23, 36, 39). Table 1 shows the largest studies with a proven benefit of CoQ_{10} treatment (in three of them it was administered for at least 1 year), neutral studies in HFrEF (no proven benefit from CoQ_{10} use) and one study evaluating the effect of CoQ_{10} in patients listed for a heart transplant (HTx) (**Table 1**).

Reduction of mortality and hospitalizations for HF

Current meta-analyses and reviews have shown that despite the lower quality of the data (different methodology, dose of nutraceutical and number of patients) in individual studies, the use of CoQ_{10} probably reduces all-cause and cardiovascular mortality as well as the number of hospitalizations for HF (12, 40-42). These findings are mainly conditioned by the results of the Q-SYMBIO study (Coenzyme Q_{10} as adjunctive treatment of chronic heart failure: a randomised, double-blind, multicenter trial with focus on SYMptoms, BIomarker status [Brain-Natriuretic Peptide (BNP)], and long-term Outcome [hospitalizations/mortality]) (**Table 1**). Taking CoQ_{10} (ubiquinone) at a dose of 300 mg per day led to a significant relative reduction of total (42%) and cardiovascular mortality (43%) and a decrease in hospitalizations for HF (41%) after two years (37).

In an older multicentre study in patients with HFrEF, a trend in the reduction of all-cause mortality (23% relative reduction), a significant decrease in hospitalizations for HF and accompanying serious complications was noted with a lower dose of CoQ_{10} (**Table 1**). About 20% of patients treated with ubiquinone and about 40% of patients in the placebo arm required at least one hospitalization within 1 year. With the therapy of 1000 patients, it would thus be possible to prevent 200 hospitalizations for HF per year (43).

A meta-analysis of 23 clinical trials (2250 patients with HFrEF) found with greater than 95% probability an economic benefit from CoQ_{10} treatment compared to standard HF therapy alone (42).

Changes in the NYHA class, NT-proBNP and LVEF

A higher degree of functional limitation according to the NYHA classification is an independent predictor of mortality and is associated with a higher risk of rehospitalization for HF (2, 3). CoQ_{10} treatment in both multicentre trials and several smaller studies resulted in a significant reduction in NYHA class by an average of 0.5 to 1 grade (7, 37, 43).

Changes in the NT-proBNP level were not statistically significant in the Q-SYMBIO study, although after 16 weeks there was an obvious trend towards its decrease compared to placebo (1883...1499 pg/ml vs 1692...1891 pg/ml; mean values). Differences in LVEF were also insignificant. One of the reasons could be the lower level of CoQ_{10} at the end of the study (compared to the measurement after the first 16 weeks; 2.0 vs 3.0 μg/ml), probably caused by poorer compliance with the therapy (37).

In a subgroup of patients enrolled in European centres (n=231), on the contrary, a steadily elevated level of CoQ_{10} was found (on average 3.42 and 3.55 μg/ml after 3 months and 2 years, respectively). The substudy confirmed the data from the whole group, i.e. significant decrease in mortality and hospitalizations for HF by using ubiquinone 100 mg 3 times a day. However, at the reached level of CoQ_{10} (3.55 μg/ml), a significant increase in LVEF compared to placebo was simultaneously noted (from an average of 33 to 39 vs 35%, p = 0.02) (**Figure 2**). Similarly, the difference in the decrease of NT-proBNP after 3 months was more significant (p=0.05) (50).

Based on these findings and data from meta-analyses, it can be concluded that CoQ_{10} can improve LVEF (in older studies there was a 3-4% increase at low doses) (12, 39). A more significant increase along with clinical improvement can be achieved with a daily dose of CoQ_{10} of 300 mg and higher if needed (see below) (51).

Table 1 Selected clinical studies* of HF patients treated with CoQ_{10} (according to 37, 43-49)

Author, year, type of study	Population, therapy (dose, duration)	Results
Morisco C et al. (1993) • multicentre, prospective • randomized • double-blind • placebo controlled • parallel group	• 641 patients with HFrEF • NYHA III-IV • CoQ_{10} 50 mg 2-3x/day (2 mg/kg/day) • 1 year	↓ hospitalizations for HF (n = 73 vs 118)** ↓ pulmonary edema (n= 20 vs 51)** ↓ cardiac asthma (n = 97 vs 198)**; **p<0.001 ↓ ventricular arrhythmias, NYHA; p<0.05 ↓ all-cause mortality (5 vs 6.5%, p=ns)
Baggio E et al. (1994) • multicentre • open • noncomparative	• 2664 patients with HF • NYHA II-III • CoQ_{10} 50-150 mg/day (78% patients taking 100 mg) • 3 months	↓ BP sitting position: 148/84...143/83 mmHg*** respiratory rate 21.2...20.6/min*** HR sitting position: 80...77/min***, ***p<0.05 ↓ clinical signs (p<0.01): cyanosis, oedema, HJR, pulmonary rales, hepatomegaly ↓ symptoms (p<0.01): dyspnoea, nocturia...
Mortensen et al. (2014) *Q-SYMBIO study* • multicentre, prospective • randomized • double-blind • placebo controlled • parallel group	• 420 patients with HF • NYHA II-IV (88% NYHA III) • CoQ_{10} 100 mg 3x/day • 2 years	↓ primary endpoint: cardiovascular deaths + hospitalizations for HF + VAD implantation + urgent HTx; 15 vs 26%, p=0.003 ↓ CV mortality: 9 vs 16%, p=0.03 ↓ all-cause mortality: 10 vs 18%, p=0.02 ↓ hospitalizations for HF: 8 vs 14%, p=0.03 ↓ NYHA ≥ 1 grade: 58 vs 45 %, p=0.03 CoQ_{10} plasma level 1.1±0.1..2.0±0.2 μg/ml
Zhao Q et al. (2015) • single-centre, prospective • randomized • double-blind • placebo controlled • parallel group	• 102 patients with HFrEF • NYHA II-IV • CoQ_{10} 30 mg/day • 1 year	↑ LVEF: 46±6% vs 43±5%, p<0.05 ↓ LVEDD: 53±3 mm vs 54±4 mm, p=ns ↓ AFib incidence: n = 3 vs n = 12; p=0.02 ↓ plasma inflammatory markers p<0.05
Permanetter B et al. (1992) • single-centre, prospective • double-blind • placebo controlled • crossover design	• 25 patients with IDCMP • NYHA I-III • CoQ_{10} 33.3 mg 3x/day • 4 months (treatment period)	Non-significant changes in: • ECG, incidence of cardiac arrhythmias • LVEF at rest/during exercise, LV diameters • CO, exercise tolerance
Watson PS et al. (1999) • single-centre, prospective • double-blind • placebo controlled • crossover design	• 30 patients with HFrEF • NYHA not listed • CoQ_{10} 33 mg 3x/day • 3 months (treatment period)	Non-significant changes in: • LVEF, hemodynamic parameters • quality of life (Minnesota questonnaire) CoQ_{10} plasma level 0.9±0.3..2.0±0.9 μg/ml
Khatta M et al. (2000) • single-centre, prospective • randomized • double-blind • placebo controlled • parallel group	• 55 patients with HFrEF • NYHA III-IV • CoQ_{10} 200 mg/day • 6 months	Non-significant changes in: • LVEF (radionuclide ventriculography) • peak oxygen consumption • exercise duration CoQ_{10} plasma level 0.95±0.6..2.2±1.2 μg/ml
Berman M et al. (2004) • single-centre, prospective • randomized • double-blind • placebo controlled • parallel group	• 32 patients listed for HTx (HFrEF) • NYHA III-IV (advanced HF) • CoQ_{10} 60 mg/day • 3 months	↑ 6MWT: 382 vs 177m, p<0.0001 ↓ NYHA: 2.4 vs 3.6, p=0.01 ↓ frequency of nocturia: 1.5 vs 3.5; p=0.01 ↓ dyspnoe (p=0.04) and fatigue (p<0.001) CoQ_{10} in plasma (median) 0.22..0.83 μg/ml

*the largest HF studies with proven benefit of CoQ_{10} therapy, neutral studies in HFrEF patients (gray color), study in patients listed for HTx. Explanations: AFib – atrial fibrillation, BP – blood pressure, CO – cardiac output, CoQ_{10} – coenzyme Q_{10}, CV – cardiovascular, ECG – electrocardiogram, HF – heart failure, HFrEF – heart failure with reduced ejection fraction, HJR – hepatojugular reflux, HR – heart rate, HTx – heart transplant, IDCMP – idiopathic dilated cardiomyopathy, LVEDD – left ventricular end-diastolic diameter, LVEF – left ventricular ejection fraction, 6MWT – 6-minute walking test, NYHA – New York Heart Association, Q-SYMBIO – Coenzyme Q_{10} as adjunctive treatment of chronic heart failure: a randomised, double-blind, multicentre trial with focus on SYMptoms, BIomarker status and long-term Outcome, VAD – ventricular assist device

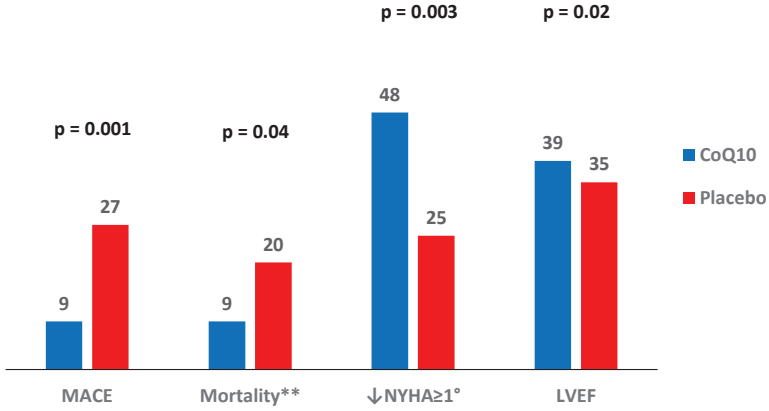

Figure 2 Effect of CoQ_{10} treatment* in the European population of the Q-SYMBIO study (according to 50)
*values in the graph are given in %, **all-cause mortality. CoQ_{10} – coenzyme Q_{10}, Q-SYMBIO – Coenzyme Q_{10} as adjunctive treatment of chronic heart failure: a randomised, double-blind, multicentre trial with focus on SYMptoms, Biomarker status and long-term Outcome, LVEF – left ventricular ejection fraction, MACE – major adverse cardiovascular events (unplanned hospitalization due to worsening of HF, cardiovascular death, urgent cardiac transplantation or implantation of mechanical circulatory support), NYHA - New York Heart Association. Note: plasma level of CoQ_{10} was higher in the treatment group (n=108) than in the placebo arm (n=123) after 2 years of therapy – 3.55 vs 0.76 μg/ml, p<0,001.

Advanced HF

The prevention of the HF progression to an advanced stage is to preserve as many viable cardiomyocytes as possible, i.e. the initiation of CoQ_{10} therapy already in the early stages of the disease (11, 44, 52).

However, CoQ_{10} treatment has an indisputable benefit even in patients waiting for HTx and in severely symptomatic ones. In a group of 32 patients listed for HTx, administration of 60 mg of liposomal ubiquinone for 3 months led not only to a significant increase in its plasma level, but also to improvement in symptomatology, physical fitness and quality of life (**Table 1**). On the other hand, no significant changes were noted in the echocardiogram or cardiac biomarkers. The reason could be a low dose of CoQ_{10} due to the advanced stage of the disease, a short treatment interval or an increased amount of fibrosis in the myocardium (49). However, depending on the method of CoQ_{10} use and the clinical response, there are also documented cases of a significant improvement in LVEF and other parameters. This made it possible to continue conservative therapy without the need for HTx (53-57).

In an open study of 7 dispensary patients in NYHA class IV, a significant improvement in LVEF (from an average of 22 to 39%) was noted after increasing the dose of CoQ_{10} and changing from the oxidized (ubiquinone) to the reduced (ubiquinol) form. In three patients, the LVEF was improved to normal values, in one the LVEF reached the level of 50% and one patient had a confirmed increase from 10 to 20% (with simultaneous regression of the LV end-diastolic diameter from 11.5 to 7.7 cm). The two remaining patients experienced a transient improvement in LVEF followed by a decrease to the original values after overcoming a severe influenza infection (55).

HFmrEF and HFpEF

For the use of CoQ_{10} in the treatment of HFmrEF, no data are yet available, although a group of patients from previously analyzed groups would fulfill the criteria for this subgroup of HF (58). In the Q-SYMBIO study, patients with higher LVEF values were also included (7% had LVEF ≥ 45%). However, a subanalysis for HFmrEF or HFpEF has not yet been published, although the greatest benefit was noted in the entire cohort precisely in patients with LVEF ≥ 30% (p=0.065) (37).

In patients with diastolic HF secondary to hypertrophic cardiomyopathy, treatment with CoQ_{10} (ubiquinone) 200 mg daily improved NYHA class, LV diastolic function, and mitral regurgitation (all by 1 grade). Increased exercise capacity (longer distance reached in the 6-minute walk test) and regression of the left ventricular walls (on average approximately 23%) were also recorded (59).

In one of the few studies in HFpEF, only a trend towards improved myocardial relaxation and regression of left atrial volume compared to placebo was found in a group of 30 patients (CoQ_{10} daily dose was 300 mg). The reason could be the short duration of the study (30 days), insufficient absorption (the level of ubiquinol was not determined) or the high percentage of patients treated with statins (80%) (60).

A similar result (minimum trend towards an improvement in diastolic function or a decrease in NT-proBNP) was also published by Israeli authors who evaluated the effect of taking 300 mg of CoQ_{10} for 4 months in 39 patients with HFpEF. Similarly, the plasma concentration of ubiquinol was not measured. Treatment with statins (in more than 70% of patients) and beta-blockers (in the treatment vs placebo group, 84 vs 50%, respectively, p=0.02) may also have contributed to the result (61).

On the contrary, in a randomized, double-blind and placebo-controlled study with 139 patients treated with CoQ_{10} and/or D-ribose, several beneficial effects were found in their individual and combined use. In the subgroup of patients treated with ubiquinol at a dose of 600 mg (n=35) only, compared to the placebo group (n=38), an improvement in quality of life, an increase in LVEF (+7.1%), a decrease in natriuretic peptide type B - BNP (by 72 pg/ml) and an increase in ATP was achieved ($p<0.001$ for all changes) (62).

The largest cohort investigating the effect of CoQ_{10} in HFpEF included 142 patients who developed HF after about 7 years of statin therapy (with no other identifiable cause). Simultaneous cessation of statin therapy and initiation of ubiquinol (300 mg per day, increase in plasma 0.8...6.6 µg/ml) led to a significant improvement of the clinical condition and findings in the echocardiogram after almost 3 years. From the initial 8%, at the end of the monitored period, 79% of patients were in NYHA class I, and at the same time, the incidence of adverse effects of hypolipidemic treatment decreased significantly ($p<0.01$). In 34% of patients, LV diastolic function normalized and in another 25%, it significantly improved ($p<0.0001$). In 6% of the patients in the group who had detected HFrEF, LVEF increased from an average of 35 to 47% ($p<0.02$). Switching from a statin to CoQ_{10} did not result in an undesirable increase in mortality (26).

Principles of optimal CoQ_{10} treatment in HF

In order to achieve the needed therapeutic effect, it is extremely important to choose the right type and form of the remedy as well as the correct method of use. From a technological point of view, fermentation production is the best, as its produces the so-called all-trans Q, identical to naturally occurring CoQ_{10} (25).

Type of remedy, dosage form and method of administration

Generally, higher bioavailability is reported when using ubiquinol compared to ubiquinone (however, the quality of the product is crucial), preparations based on emulsion and containing CoQ_{10} in lipid nanoparticles (22, 63). The highest absorption is proven when using capsules made of soft gel ("softgels") from certified manufacturers, which contain CoQ_{10} soluble in water and in fats, or an oil emulsion with decrystallization processing of the remedy (22, 64).

CoQ_{10} is not naturally soluble in water, therefore it is slowly absorbed from the small intestine, passes in the form of chylomicrons into the lymph, then into the bloodstream and liver. From there, after binding to lipoproteins, it is transported to the tissues (21). It is therefore advisable to take CoQ_{10} with food that contains at least a small amount of fat (25). This increases absorption by about 3-fold (22). Peak plasma concentrations of CoQ_{10} are reached about 6 hours after ingestion, and the elimination half-life is about 33 hours (11). It is excreted primarily in bile and feces, to a small extent in urine (30). To achieve the expected therapeutic result, it is necessary to take CoQ_{10} for at least 3 months without interruption. In the case of a good effect, the treatment lasts for a long time (22). It should be discontinued gradually, otherwise there is a risk of deterioration of myocardial function and HF symptoms (53, 65).

It is clear from clinical practice that high-quality ubiquinone with high bioavailability can be the drug of first choice. Not only is it more affordable compared to ubiquinol, but it also has stronger evidence-based medicine (EBM) based on clinical studies. In case of insufficient therapeutic effect or low plasma level of CoQ_{10} despite the recommended (or increased) dose, it is correct to replace ubiquinone with ubiquinol (**Figure 3**).

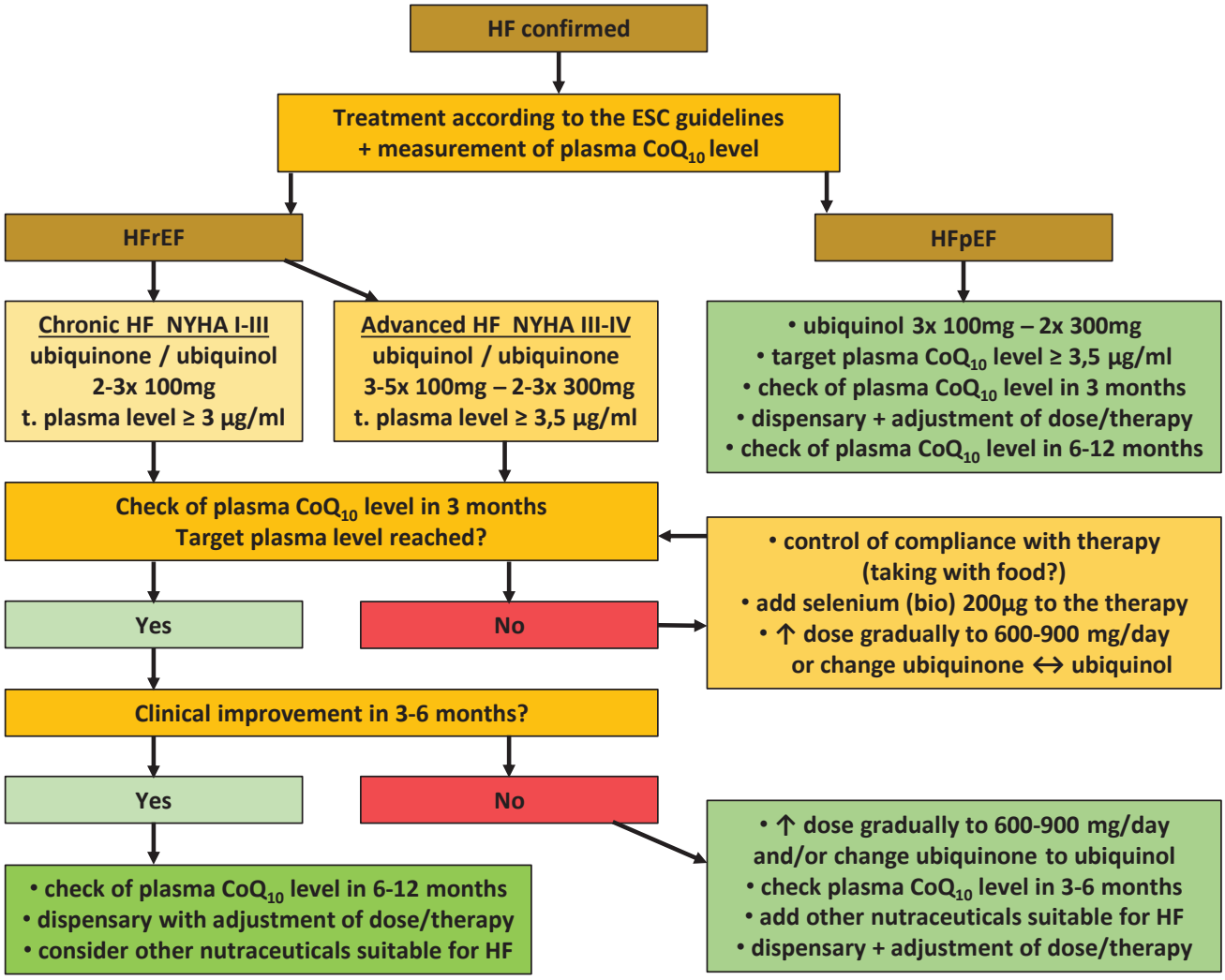

Figure 3 Proposal of an algorithm for the HF treatment using CoQ_{10} (according to 11,13,17,23,26,30,37,55,62,70,71,73)
CoQ_{10} – coenzyme Q_{10}, ESC – European Society of Cardiology, HF – heart failure, HFrEF – heart failure with reduced ejection fraction, HFpEF – heart failure with preserved ejection fraction, NYHA – New York Heart Association, t. – target

This strategy can also be tried vice versa if ubiquinol therapy does not work for the patient (due to individual variability in absorption of both CoQ_{10} forms) (17).

Selenocysteine is important for the conversion of ubiquinone to active ubiquinol, but its amount is often reduced in patients due to a lack of selenium in the diet or e.g. due to medication (statins reduce synthesis of selenoproteins in addition to CoQ_{10}). In a Swedish study (Ki-Sel-10), after 4 years of treatment with ubiquinone (200 mg) and organic selenium (200 µg) in the population over 70 years of age a significant decrease in cardiovascular mortality (5.9 vs 12.6%, p=0.015) and NT-proBNP as well as better myocardial function was found (66). The beneficial effect of this combination of nutraceuticals in the treatment of HF was also confirmed by the study of Iranian authors (decrease in NYHA grade and 4% increase in LVEF after 3 months of treatment) (67).

Target dose and monitoring of plasma CoQ_{10} level

The strategy of treating HF using CoQ_{10} with the correction of its plasma level to the physiological range has been shown to be incorrect (55). The rise in plasma

does not accurately reflect changes in the amount of CoQ_{10} in the target tissues. In a group of 40 patients with LV systolic dysfunction (EF approx. 45%), after a 4-week use of 150 mg ubiquinone, there was a more than 100% increase in the plasma concentration of CoQ_{10} (from an average of 0.7 to 1.8 μg/ml, p=0.001). However, the increase in the myocardium was only at the level of approximately 30% (68). Similarly, in another study, with increase of around 130% in plasma CoQ_{10} levels, an approximately 40% increase in the myocardium was noted (**Figure 1**) (31). The reason is probably the accumulation in the tissues by the diffusion mechanism, i.e. by the action of the concentration gradient between the plasma and the target tissue (21).

Therefore, the basis for the treatment of HF with CoQ_{10} is to achieve a plasma concentration of more than 3 μg/ml (optimally above 3.5 μg/ml), which is mostly possible with the use of 200-300 mg of high-quality ubiquinone or ubiquinol per day (17, 23, 55). In the beginning, it is advisable to start with lower doses – 50 mg in the morning and in the afternoon (CoQ_{10} can rarely cause insomnia). With a dose of 100 mg 3 times a day and an effective plasma level of CoQ_{10}, studies have confirmed a reduction in mortality, HF hospitalizations and symptoms, as well as improvement in the function of the LV and mitochondria, and a decrease in pro-inflammatory markers (17). If there is a favourable course of HF, the dose can be reduced (e.g. to 150-200 mg per day) with further adjustment according to plasma levels and current health status (**Figure 3**).

Thinned, echodense, akinetic, or dyskinetic zones of aviable myocardium have less potential for improvement with CoQ_{10} treatment. On the other hand, in the case of viable and hypokinetic segments, there is often an increase in their functions, which is manifested by hemodynamic and clinical improvement (55). Treatment with ubiquinone (using 100 mg softgel capsules 3 times a day) resulted in a significant increase in LVEF at rest (from 37 to 44 vs. 40%, p=0,0023) and also in the exercise test with dobutamine (58 vs 49%, p<0.0001). An increase in contractility was observed especially in initially hypokinetic (+25%) and akinetic (+33%) segments, in comparison to dyskinetic ones (+6%) (69). In another study, with a dose of 200 mg of ubiquinone, the same average plasma level (3.25 μg/ml) was achieved. There were significant changes in invasively measured parameters detected after 12 weeks – an increase in stroke index (31...36 ml/m2, p<0.005) and a decrease in the mean pulmonary artery pressure (27...21 mmHg, p=0.02) (70).

Therefore, it appears that a sufficiently high level in the plasma is the key parameter in the successful therapy of HF with CoQ_{10}, regardless of the type of administered remedy (14). It is advisable to take laboratory samples to monitor the plasma CoQ_{10} level before starting treatment, after 1-3 months (saturation of the organism takes 1-3 weeks), after half a year and then every 6-12 months or according to clinical course, changes in CoQ_{10} dosage and other drugs with potential interactions (**Figure 3**) (71). The field of the therapeutic use of CoQ_{10}, including laboratory diagnostics (measurement the concentration in whole blood, plasma, platelets as well as respiration and energy production in the mitochondria) has been addressed for a long time at the world scientific level by the Pharmacobiochemical Laboratory of the 3rd Department of Internal medicine under the leadership of prof. Gvozdjáková (29, 72). It is commercially possible to measure the plasma level of CoQ_{10} from the serum at Unilabs Slovensko, s.r.o. (the price of the analysis is 43 EUR).

Contraindications and adverse effects

CoQ_{10} is a natural substance and contraindications for its use are unknown (25). Due to the lack of data, it is not recommended for healthy women during pregnancy and breastfeeding and for children (14, 25, 63). However, administration to pregnant or lactating women with cardiovascular disease is safe (14). In a randomized, double-blind, placebo-controlled study in women at high risk of preeclampsia, CoQ_{10} (ubiquinone) significantly reduced its incidence (14.4 vs 20%, p=0.035). Apart from mild gastrointestinal symptoms (more in the placebo group), no adverse effects occurred during around 19 weeks of therapy (until successful delivery) (74). In children with dilated cardiomyopathy, a positive effect of CoQ_{10} (both ubiquinone and ubiquinol) was similarly reported without health risk during approximately 6 months of treatment (75, 76).

Adverse effects of CoQ_{10} are very rare and mild (especially when taking softgel capsules) (77). The most common are skin reactions (urticaria, etc.) or gastrointestinal symptoms (loss of appetite, nausea, etc.) (25, 44,

63). In the Q-SYMBIO study, the incidence of adverse events in the treatment arm was significantly lower (13 vs 19%) (37). A maximum amount of 1,200 mg of CoQ_{10} per day (divided into multiple doses) is considered safe (24). The longest follow-up comes from the study of Swedish authors, where a significant reduction in mortality without side effects still persisted after 12 years of treatment with CoQ_{10} (200 mg ubiquinone) and selenium (200 µg), which lasted 4 years (28 vs 39%, p=0.001) (78).

Drug interactions

Rare cases of decreased warfarin effect have been reported (24). In other studies, these interactions were not confirmed (e.g. in the Q-SYMBIO, 25% of patients were treated with anticoagulants) (37, 55). In any case, in patients treated with warfarin, it is safer to check coagulation parameters twice a week for 2 weeks after starting or ending CoQ_{10} treatment (25).

The synthesis of CoQ_{10} is significantly reduced (by 40-50%) when taking statins, regardless of the type (both hydrophilic and lipophilic), length of administration and intensity of their dosage (low, medium, high) (79). In the CORONA study, rosuvastatin (10 mg) reduced the CoQ_{10} level by an average of 42% (p<0.0001), which in the subgroup of patients with the lowest value (0.35 µg/ml) led to an increase in morbidity and mortality indicators (on the border of significance using a low power test, p=0.14-0.26) (34). In another study, treatment with atorvastatin 10 mg only (placebo arm) had no benefit, but atorvastatin therapy with the addition of 200 mg CoQ_{10} (treatment group) showed a significant increase in LVEF (from 19 to 24%, p=0.003) and a decrease in NYHA class (from 2.7 to 2.3 grade, p=0.025) (80). Thus, CoQ_{10} treatment can not only reduce the adverse effects of statins (e.g. myalgia), but also reverse myocardial damage as a result of their use (26, 81). In HF patients already treated with statins for another indication, it is recommended not to discontinue them (1). In that case, however, it is necessary to administer CoQ_{10} in a dose of at least 200 mg per day in order to reduce their negative metabolic impact on the myocardium (14).

There was also found a decrease in the plasma level or effect of CoQ_{10} in patients treated with beta-blockers (propranolol, metoprolol), oral antidiabetics (biguanides, sulfonylurea derivatives), phenothiazines, anthracyclines or tricyclic antidepressants (25). On the other hand, when CoQ_{10} is administered with standard HF treatment, including SGLT2i or sacubitril/valsartan, no adverse interactions have been reported (57, 61).

Combination of CoQ_{10} with other nutraceuticals

Treatment with other nutraceuticals (amino acids, vitamins, minerals) in high doses is often necessary to reverse the hypercatabolic state in chronic HF, in addition to CoQ_{10} (77). Combined therapy has a synergistic effect on myocardial function, HF symptoms, quality of life and patient prognosis (32, 58, 82-83).

In addition to the combination with selenium, it is useful to administer CoQ_{10} with L-carnitine (support of mitochondrial metabolism and detoxification), D-ribose (essential component of ATP), magnesium (enzyme activation) and taurine (regulation of calcium homeostasis) (10, 11, 40, 62, 83). Suitable supplements are also omega-3 polyunsaturated fatty acids (stabilization of mitochondrial membranes and antioxidant effect), hawthorn extract (coronary dilation and mild inotropic effect) and essential amino acids, such as L-arginine (vasodilation and energy production) (3, 11, 65, 84, 85).

Another strategy for increasing energy in a failing myocardium is to enhance the number of mitochondria, in the future e.g. by mitochondrial transplantation (29). A more accessible method in practice today is the support of mitochondrial biogenesis through exercise and nutraceuticals (e.g. essential amino acids, vitamin D, resveratrol or pyrroloquinoline quinone – PQQ) (13, 85-87). However, the strength of EBM is lower in this area (except for omega-3 polyunsaturated fatty acids), which is the reason for an individualized approach (e.g. correction of hypovitaminosis) and further clinical research (10).

Recommendations for the use of CoQ_{10} in HF therapy

CoQ_{10} has been approved by the government in Japan since 1974 under the name ubidecarenone as a medicine for HF and has long been one of the top-selling cardiovascular drugs there (48, 65, 88). In the Anatomical Therapeutic Chemical (ATC) classification system of the

World Health Organization, it is included among other cardiac drugs under the code C01EB09 (www.adc.sk). The safety profile of CoQ_{10} is excellent, which confirms its therapeutic use in children, pregnant women, the elderly and patients with HF (39, 74-76, 78).

Since October 2016, ubiquinol has been approved by the European Medicines Agency for the treatment of primary CoQ_{10} deficiency syndrome (rare diseases affecting mostly muscles, kidneys or the nervous system) (89). However, HF is classified among the so-called secondary CoQ_{10} deficiencies (90). In the European Union, CoQ_{10} in the treatment of HF is currently only registered in Hungary under the name Myoquinon® (this is the original ubiquinone from the Pharma Nord company also used in the Q-SYMBIO study) (73, 91).

In the European guidelines for the treatment of HF, there is no mention of the use of CoQ_{10} (1). The guidelines of the American Heart Association point out the positive results of the Q-SYMBIO study, but the slow recruitment of patients is mentioned as a limitation for CoQ_{10} supplementation in practice. The recommendations also refer to an older analysis by the Cochrane organization, while at the time of their creation, an updated meta-analysis with different conclusions had already been published (3, 12). In addition, in the tabular summary, the authors do not distinguish individual nutraceuticals from the point of view of benefit and risk, and a separate document is dedicated to this topic (3, 10).

The Q-SYMBIO study was also criticized for the lower number of enrolled patients (420 out of the planned 550) and adverse events that may have led to an overestimation of the positive effect of CoQ_{10} treatment (92, 93). However, these facts were already explained in the original publication. CoQ_{10} is a non-patentable substance and the smaller budget put the study at a disadvantage compared to testing new drugs from big pharmaceutical companies. The lower mortality may have been related to the patients' better functional status (NYHA II) at the time of trial enrollment (37). In addition, the values of cardiovascular and all-cause mortality in the placebo arm are in agreement, e.g. with a study evaluating sacubitril/valsartan (considering trial length) (94).

With the number of patients and the poor prognosis of HF on the one hand, and the favourable results of the Q-SYMBIO study (and other studies) on the other hand, the demand for further larger trials is also questionable from an ethical point of view (95). Similarly, the debates about the need to achieve an effective plasma concentration of CoQ_{10} can be considered over (96). The studies reported as failure of CoQ_{10} treatment are actually neutral (non-significant benefit of CoQ_{10} found) (**Table 1**). Moreover, they included only about 10% of all patients in double-blind studies published up to that time. The average plasma concentration of CoQ_{10} was also markedly lower in them compared to the studies that yielded positive results (1.97 vs 2.45 mg/l) (36).

There is a plan to conduct a large clinical study (Q10-HF) with inclusion of more than 1000 patients, the results of which may influence the recommendations in the guidelines. However, they will be available in a few years (97). Several experts therefore suggest, in terms of the available EBM, to add CoQ_{10} to the standard treatment of HF in a dose of at least 200 mg, optimally up to 300-900 mg per day (higher doses in patients in NYHA class III and IV) with the aim of achieving a plasma concentration above 3 μg/ml (11, 17, 23, 30, 50, 55, 98).

However, the financial costs make CoQ_{10} therapy practically unaffordable for patients in our country (99). The minimum price of high-quality ubiquinone in a dose of 100 mg 3 times a day is about 50 EUR per month (similar to ubiquinol in a dose of 100 mg 2 times a day). A possible solution is the official registration of this effective nutraceutical as a medicine for HF, similar to what has been done for years in Hungary or Japan (73, 88). This would subsequently enable reimbursement of CoQ_{10} therapy from the health insurance, which, however, will be effectively returned in the form of a decrease in the costs of care for patients with HF (42, 43, 100).

Summary

CoQ_{10} is a physiological antioxidant whose adequate intramyocardial concentration is essential for sufficient ATP production, especially in the failing myocardium.

With a correctly chosen form (soft gel capsules containing water- and fat-soluble CoQ_{10}, or decrystallized one in an oil emulsion), use (with food containing a small amount of fat), dose (on average 3 times 100 mg per day in order to reach the plasma level at least 3 μg/ml) and the length of treatment (long-term, at least 6 to

12 months), it is possible to expect a reduction in mortality, hospitalization for HF, improvement in LVEF and quality of life of HF patients with minimal risk of non-serious adverse effects (12, 23, 30).

Due to the absence of recommendations in the current guidelines, it is possible to proceed in accordance with the principles of EBM in the individual management of patients according to data from randomized clinical trials, which confirm the beneficial effect of both forms of CoQ_{10} – ubiquinone and ubiquinol – when added to the standard treatment of HF (37, 58, 62, 69).

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