ISSN: 0975 -8542

Journal of Global Pharma Technology

Available Online at: www.jgpt.co.in

RESEARCH ARTICLE

Thiamine, Riboflavin and Magnesium Level Correction in Improving the Quality of Life of Patients with Chronic Heart Failure

Fatima Dzalaeva[1*], Alexandr Tsymbal[1], Natalia Andriutsa[1], Oxana Kartashova[1], Ekaterina Vaseva[2]

[1.] *Sechenov First Moscow State Medical University (Sechenov University), Moscow, Russian Federation.*

[2.] *Tyumen State Medical University, Tyumen, Russian Federation.*

***Corresponding Author: Fatima Dzalaeva**

Abstract

Data are presented on the effectiveness of treating patients with chronic heart failure (CHF) with vitamins B_1, B_2 and magnesium (Mg) added to the standard complex therapy. The group of patients with cardiovascular diseases (CVDs) consisted of 143 patients with CHF I-III functional class according to NYHA (New York Heart Association Functional Classification), as a complication of coronary heart disease (CHD). To determine the preferred doses of vitamins B_1 and B_2, we studied the dynamics of the concentration of thiamine (B_1) and riboflavin (B_2) in blood plasma and their daily excretion with a single intake of vitamins by healthy volunteers at doses of 10, 20 and 30 mg. To determine the preferred magnesium-containing drug, Mg concentration dynamics in the blood plasma of healthy volunteers were studied when taken orally in an equal dose in the form of Mg oxide and in the form of Mg orotate. The study involved 80 healthy volunteers. In order to improve the quality of life for patients with CHF and increase tolerance to physical exertion, it is advisable to add Mg in combination with vitamin B_1 and B_2 in the standard complex therapy. When Mg salts are added to the standard complex treatment of CHF, it is preferable to use Mg orotate. When using vitamin B1 (thiamine), it is not advised to increase the daily dose of more than 10 mg/day, since this leads to a progressive increase in the excretion of this vitamin B_1 and vitamin B_2.

Keywords: *Chronic heart failure, Therapy, Mg salts, Thiamine (B_1), Riboflavin (B_2).*

Introduction

Prevention and treatment of diseases of the cardiovascular system stays an essential problem to date. Classically, the end of almost all diseases of the cardiovascular system or its damage in other pathological processes in the body is chronic heart failure (CHF) [1]. CHF is a syndrome that develops as a result of impaired ability of the heart to fill and/or empty, occurring under conditions of imbalance of the vasoconstrictor and vasodilating neurohormonal systems and manifested by a complex of symptoms: shortness of breath, weakness, palpitations, increased fatigue and fluid retention in the body (edematous syndrome).

The prevalence of CHF in Europe varies from 1 to 2% in the general population, reaching 10% in people over 70 years of age [2].

According to the EPOCHA study, in the Russian Federation heart failure is diagnosed in 7-10% of cases, while its prevalence significantly depends on the diagnosis criteria adopted for patient selection [3, 7]. Observation of a representative sample of the European part of the Russian Federation (EPOCHA-CHF) revealed a significant increase in the number of CHF patients over the past 16 years from 4.9 to 8.5%. The absolute number of patients suffering from CHF increased more than 2 times from 1998 (from 7.18 to 12.35 million people), and patients with severe HF from 1.8 to 3.1% (from 1.76 to 4.5 million people) [8].

The latest data, based on the information about hospitalized patients, indicate that HF frequency in European countries decreases, and more so when HF with a low ejection

fraction than with HF with a preserved ejection fraction [9, 10]. According to modern data, an increase in CHF incidence in Russia is closely associated with age: for example, more than 65% of Russian patients with CHF are aged 60+. At the same time, over the past 18 years, CHF patients have become significantly older; their average age has increased on average from 64±11.9 years to 72.8±11.9 years.

Against the background of a registered increase in the age of patients with CHF, the gender composition did not change; the proportion of women in the total cohort was 72%, men - 28% [11, 8].The prevalence of risk factors for CVDs in patients with CHF (average 4.7 per patient) [11], including insufficient control of blood pressure [12, 13] and heart rate [14, 15], causes an early development and progression of CHF [8].

The main reasons for the development of CHF in the Russian Federation, as well as in Europe and the USA, are hypertension (95.5%) and IHD (69.7%) [8] As well as their combination, which occurs in more than half of CHF cases [16].The contribution of these nosologies to the etiological structure of CHF progressively increases over time. Over the past 10 years, myocardial infarction (19.7%) and the presence of diabetes mellitus (22.7%) have become "competing" reasons of CHF; there is a tendency to an increase in the number of CHF cases with atherosclerotic lesions of the aortic valve.

As the HF etiology, diagnosis of myocarditis (3.6%) and dilated cardiomyopathy (0.8%) is significantly underestimated in the general population of patients with CHF and is veiled by IHD: however, the frequency of dilated cardiomyopathy as the cause of the disease in patients with CHF III – IV FC reaches 5% of cases, according to a Euro Heart Survey study (Russian sample), and 5.4% according to the results of the EPOCH-CHF study [17].

Diseases such as chronic obstructive pulmonary disease (13%), atrial fibrillation (12.8%) and acute cerebral circulation (10.3%) remain important causes of CHF. Moreover, the combination of the permanent form of atrial fibrillation and arterial hypertension has recently become increasingly important in CHF development [18, 19]. Thus, the wide prevalence of risk factors, the increase in the number of etiological causes of CHF at the current stage form the development of a treatment strategy for comorbidity in CHF as a priority task [20, 21]. Neurohumoral disorders of metabolic processes, closely related to vitamins imbalance, which are part of coenzymes and take part in various vital processes and play a leading role in the etiology and pathogenesis of CVDs and, in particular, CHD. Vitamins are known to be a substrate of oxidation associated with the generation of ATP, energy accumulators, membrane stabilizers, and actively participate in the transport of ions [22].

Thiamine (B_1) as coenzyme pyruvate dehydrogenase participates in the glucose oxidative metabolism and the intracellular ATP synthesis [23]. Thiamine deficiency manifests itself as a dry or wet form of beriberi syndrome [24, 25]. In cardiac patients thiamine deficiency can significantly worsen the symptoms of pre-existing HF.

According to different authors, the prevalence of thiamine deficiency in HF varies in a wide range (from 3 to 91%), which is due to the difference in the patients examined and methods for determining thiamine [26]. So, a prospective single-centered study of 150 patients by Hanninen et al found that 33% of patients with CHF had thiamine deficiency compared with 12% in the control group. Therefore even a small thiamine dosage (1.5 mg/day) in patients with thiamine deficiency was effective for its correction [27].

Currently, there are only two small randomized, placebo-controlled studies that found that the use of thiamine in patients with CHF statistically significantly increased the left ventricle ejection fraction (LVEF), increased diuresis, natriuresis and quality of life [28, 29].A single randomized study of 49 patients with acute HF showed that intravenous administration of 100 mg of thiamine did not lead to a decrease in dyspnea (after 4 h). Hospitalization rate reduction and its duration has not been established [30].

Of particular interest are two systematic reviews that confirm the positive thiamine effect in patients with congestive heart failure on the contractility of the left ventricle (LV) [31, 32]. Therefore, to date there are no multicenter, placebo-controlled randomized studies that can prove the

prognostic role of correcting thiamine deficiency in HF.

However, the above data suggests that the use of thiamine increases LVEF in CHF. Speaking about the role of vitamin B_1 in carbohydrate metabolism and energy supply to the myocardium, this thiamine function is carried out in close synergy with vitamin B_2 (riboflavin) and lipoic acid.

All three micronutrients are equally necessary for the oxidative decarboxylation reactions of pyruvic acid, the key element in the aerobic oxidation of glucose. In addition, lipoic acid and vitamin B_2 have pronounced antioxidant properties and protect the myocardium and vascular endothelium from oxidative damage. Serum Mg in serum ≤2 meq/l increases the risk of death in patients with CHF [33]. Hypomagnesemia can cause myocardial fibrosis and increases platelet aggregation, which affects cardiovascular mortality. Low levels of Mg in serum may be a marker of HF progression. The effect on Mg levels is exerted by drugs taken by patients with HF, in particular diuretics.

Patients with CHF it may be advisable to study the Mg blood level, and in case of its deficiency - take oral medications containing Mg. Thus, vitamin preparations and these containing macro- and microelements constitute an important group of pharmacological substances used to treat and prevent CVDs. However, the data on their use effectiveness, found in the literature, are contradictory. Currently, there are no evidence-based recommendations on the choice of the optimal complex and the dosing regimen for CHF.

There is insufficient data on pharmacokinetic studies determining the absorption of various Mg salts, and the effect of taking loading doses of B group vitamins on their plasma levels and excretion is poorly studied. There is little objective data on the use of Mg salts and vitamins of group B for CHF therapy.

Materials and Methods

To determine the preferred doses of vitamins B_1 and B_2, we studied the concentration dynamics of thiamine (B_1) and riboflavin (B_2) in blood plasma and their daily excretion during a single dose of vitamins by healthy volunteers at doses of 10, 20 and 30 mg. To determine the preferred Mg-containing drug, the dynamics of Mg concentration in the blood plasma of healthy volunteers were studied when taken orally in an equal dose in the form of Mg oxide and in the form of Mg orotate. The study involved 80 healthy volunteers, 40 men and 40 women, when they were included in the study. Following criteria were met (age range 18-45, average age 35.3±5.8), no chronic diseases, no deviations in the total and biochemical, blood and urine analysis, no traumatic brain injuries in anamnesis. The exclusion criteria were a body mass index >25 kg/m^2 and <19 kg/m^2, chronic CVDs, as well as diseases of the respiratory and digestive systems, history of abdominal cavity operations, clinically significant abnormalities in general and biochemical blood and urine analysis.

During the month preceding the tests, the volunteers did not take vitamin and Mg drugs. All healthy volunteers included in the study signed a voluntary informed consent to participate in it. The plasma thiamine (B_1) and riboflavin (B_2) concentration was studied with drug administration form of mono-preparations in doses of 10, 20 and 30 mg (60 volunteers in total, 10 people for each vitamin and each dose).

Blood samples were taken immediately before taking a single vitamin preparation (about 8 am) and 2, 4, 6, 24 hours after that. In order to study the excretion of vitamins in these same patients, a urine study was conducted before taking the vitamin preparation and 5 times thereafter for the next 24 hours at time intervals of 8-12 hours, 12-16 hours, 16-20 hours, 20-24 hours and 24 8 h. Determination of the content of thiamine and riboflavin in biological fluids (urine, blood plasma) was carried out using high performance liquid chromatography, described by Lopes-Anaya and Mayersohn, Shimadzu instrument (LC-6A, detector SPD-6A); diasorb column - 130-C16T (4 x 250 mm, 7 µm), dispenser loop volume 100 µl.

In 20 people, the dynamics of the content of Mg ions in the blood plasma was studied when taking Mg oxide and Mg orotate in doses of 500 mg (10 people for each drug). Blood sampling was carried out from the cubital vein in the amount of 5 ml immediately before taking the drug and after 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 and 24 hours after that. Determination of Mg in serum was carried out by atomic absorption

spectrophotometry using Analytik Jena AG apparatus - novAA® 350. A group of patients with diseases of the cardiovascular system who studied the clinical efficacy of combining standard complex therapy with vitamins B_1, B_2 and Mg orotate, amounted to 143 patients with CHF I-III functional class after NYHA (New York Heart Association Functional Classification) complicating the course of coronary heart disease (CHD). The diagnosis of heart failure was established on the basis of the recommendations of the European Society of Cardiology (Cleland JGF, Erdman E, Ferrari R et al, 1995). A prerequisite was the stability of the state for at least 44 weeks before being included in the study (Table 1). The study included 62 men and 81 women; whose average age was 54.6±6.3 years, body weight 62-88 kg, average duration of the disease at the time of inclusion in the study was 11.2±5.1 years.

Table 1: Clinical characteristics of patients included in the study

Mean age	**54.6±6.3 years**
Mean CHF duration	11.2±5.1 years
FC CHF	
I	9 (6.3%)
II	57 (39.9%)
III	77 (53.8%)
LV EF	29±12
> 40	42 (29.4%)
20-40	91 (63.6%)
<20	10 (7.0%)

Patients are randomly divided into four subgroups. The control (I) group included patients who received only standard complex CHF therapy, which included ACE inhibitors (angiotensin converting enzyme inhibitors), ARA II (angiotensin II receptor antagonists), diuretics, aldosterone antagonists, and adrenoblockers, heart glycosides, and necessary, nitrates. In the second group, along with the standard therapy, Mg orotate was administered.

The latter was used for 10 days at a daily dose of 3000 mg, and then the dose was reduced to 1500 mg per day and taken throughout the remaining observation period. In the third group of patients, along with standard therapy, mono-preparations were administered: vitamin B_1 in a dose of 10 mg and B_2 in the same dose. A fourth group of patients received along with standard therapy Mg orotate in the same way, mono-preparations of vitamins B_1 and B_2 at doses of 10 mg Duration monitor patients in all comparison groups was 12 weeks.

Dynamic and clinical observations based on regular visits by patients, when tolerance to physical exertion according to a 6-minute walk test, quality of life was studied (Minnesota questionnaire) were evaluated. For a comparative analysis of the main clinical manifestations of CHF, rating scale of clinical state for CHF (RSCS) was used. Echocardiographic studies were performed on a LOG1Q-400 MD apparatus (General Electric) using the standard procedure. The following indicators were determined: the LV end diastolic volume (EDV), the end LV systolic volume (ESV), the systolic volume (SV) and the ejection fraction (EF) were calculated. The main hemodynamic parameters were studied using transthoracic echocardiography (EchoCG) according to a standard protocol. Statistical processing of the results was carried out using STATISTICA 6.0. Other methods used: calculating averages, standard deviations, linear regression and correlation analysis, delta%, deviations from the mean values.

Results and Discussion

Thiamine (B_1) and riboflavin (B_2) concentration dynamics in plasma and their daily excretion after a single intake of vitamins by healthy volunteer's .Magnesium concentration dynamics (Δ %) in blood plasma of volunteers during the study is shown in Figure 1. The concentration of plasma Mg before it was taken by volunteers as part of an Mg-containing drug was 18.73±2.8 μg/ml and 19.33±2.7 μg/ml in the groups treated with Mg oxide and Mg orotate, respectively.

30 minutes after the start of the study, volunteers taking Mg orotate showed a statistically significant increase in concentration ($p < 0.001$) to 21.19±1.6 μg/ml (9.6 Δ%); in the use group of Mg oxide, the concentrations of cations Mg in plasma increased less, to 19.29±1.5 μg/ml (4.6 Δ%) .After 1 hour from the start of the study, Mg concentration in blood plasma in volunteers

of both groups reached even higher values and was 19.96±1.7 μg/ml (6.6 Δ%) while taking Mg oxide and 21.49±1.4 μg/ml (11.2 Δ%, p <0.05) - Mg orotate. The maximum increase in the Mg concentration in the blood plasma of volunteers using Mg orotate is 21.69±1.9 μg/ml (12.2 Δ%), noted 1.5 hours after it was taken, and statistically significantly higher (p <0.05) maximum Mg concentration in the volunteers blood plasma using Mg oxide, 20.04±2.1 μg/ml (7.0 Δ%) registered 10 hours after the start of the study. Mg concentration in the blood plasma of volunteers while taking Mg orotate remained high during the whole study time, gradually decreasing after 10 hours of testing to a value (24h point) to 19.83±1.3 μg/ml (2.6 Δ %). Thus, when taking Mg in the form of orotate, statistically insignificant, but higher Mg concentrations in comparison with those (at the same time points) when taking Mg oxide are created at all points of the pharmacokinetic curve, except for the 24 hour point from the start of the study, for which Mg plasma concentration when using Mg oxide is slightly higher than that when taking Mg orotate. When Mg salts are added to the standard complex treatment of patients with CHF, it is preferable to administer Mg orotate.

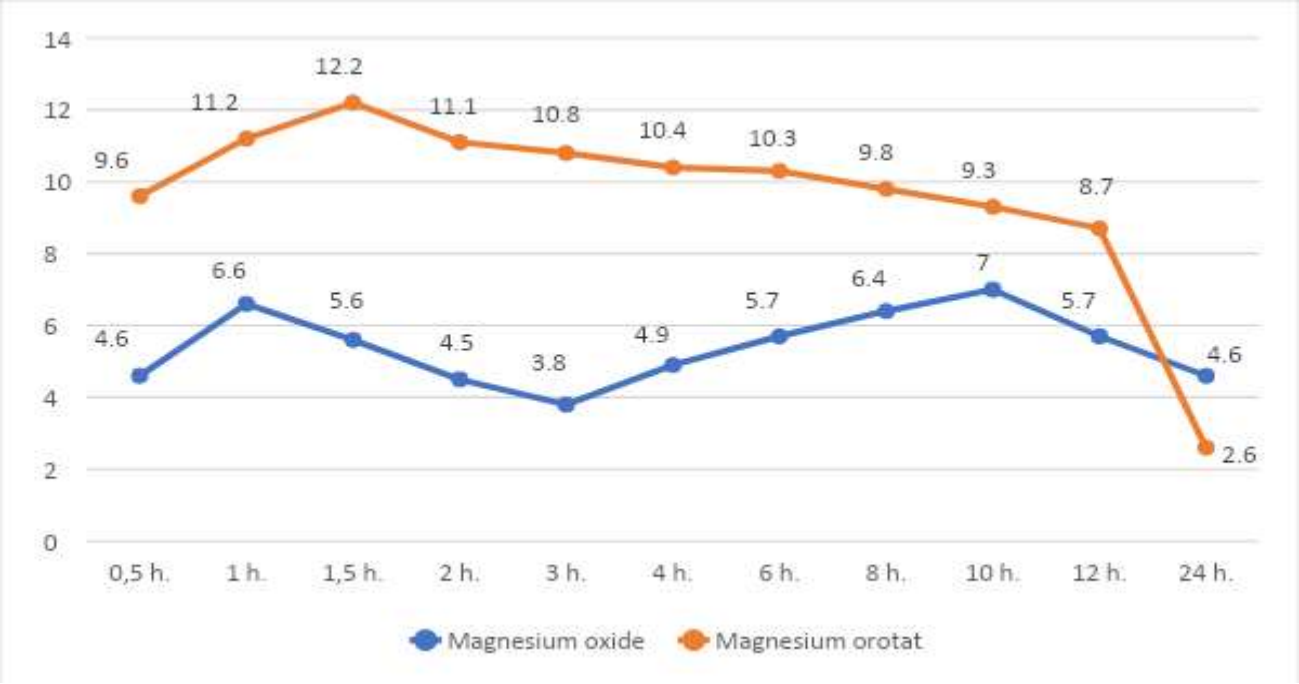

Figure 1: Mg concentration dynamics (Δ %) in blood plasma of volunteers taking Mg oxide and Mg orotat

Prior to the healthy volunteers taking mono-preparations of thiamine and riboflavin at doses of 10, 20 and 30 mg, once-initial plasma levels of thiamine were 3.2±0.5 ng/ml, 2.9±0.6 ng/ml and 2.7±0.55 ng/ml, riboflavin - 13.11±2.52 ng/ml, 12.27±1.65 ng/ml and 12.54±1.52 ng/ml for the indicated doses, respectively. C-max was determined in all cases 2 hours after the start of the study (Table 2).When taking 10 mg of thiamine C-max was 5.45±1.1 ng/ml (70.43 Δ%; p <0.05), 20 mg- 6.11±0.8 ng/ml (110.52 Δ%, p <0.005), 30 mg -8.13±1.0 ng/ml (201.21 Δ%, p <0.05).

With further research, there was a decrease in the concentration of vitamin B_1 and the final stage (after 24 hours) when taking thiamine in a dose of 10 mg, the value of its concentration was 3.95±0.5 (p <0.005), which is more than 20% (23.33 Δ %) above the baseline. When taking 10 mg of riboflavin C-max in plasma was 25.36±3.7 ng/ml (Δ% 93.56 p <0 05), 20 mg - 23.94±2.2 ng/ml (Δ% 95.14, p <0 05), 30 mg - 39.67±3.4 ng/ml (Δ% 216.35, p <0 05).Subsequently, when receiving 10 and 20 mg of riboflavin, its plasma concentration in healthy volunteers decreased, and by the end of the study, in the second case, it was 19.45±2.5 ng/ml, which is more than 50% (Δ% 58.53) differed in the direction of increase from the initial value. When receiving 30 mg riboflavin, riboflavin concentration in the blood plasma of healthy volunteers changed in waves, remaining at a high enough level up to 6 hours from the start of the study, and reached the lowest value (22.94±1.8 ng/ml, Δ% 82.92) its completion (24 hours).

Thus, an increase in the dose of taken vitamin B_1 (thiamine) correlates with the value of its maximum plasma concentration

.The correlation coefficient was 0.96. When receiving B_2 (riboflavin) at a dose of 10 and 20 mg, no statistically significant difference in the value of the maximum concentration of riboflavin in the blood plasma was detected. When receiving riboflavin at a dose of 30 mg, the magnitude of the C-max value is statistically significantly higher than this value when taken at doses of 10 and 20 mg.

Table 2: Plasma concentration of thiamine and riboflavin (ng/ml) when taken

Dose	Baseline values of concentration		C-max after 2 hours from the start of the study	
	B_1	B_2	B_1 (Δ %)	B_2 (Δ%)
10 mg	3, 2±0.5	13.11±2.52	5.45±1.1 (70.43)*	25.36±3.7 (93.56)*
20 mg	2.9±0.6	12.27±1.65	6.11±0.8 (110.52)**	23.94±2.2 (95.14)*
30 mg	2.7±0.55	12.54±1.52	8.13±1.0 (201.21)*	39.67±3.4 (216.35)*

* -p <0.05, ** - p <0.01

Indicators of urinary excretion of thiamine and riboflavin when taking loading doses vitamin B_1 are presented in Table 3. In the group of volunteers who took a single dose of thiamine in the form of a mono-preparation, its average daily urine excretion before taking vitamin (baseline) was 17.25±3.7 μg/h. The average daily excretion of thiamine at a dose of 10 mg was 33.41±7.2 μg/h; the maximum excretion occurred at the 2nd time period (12-16 h) after taking thiamine and was 53.87±5.6 μg/h (Δ% 212.3 with respect to the initial value).

The average daily excretion of thiamine at a dose of 20 mg was 41.32±9.1 μg/h, the maximum excretion occurred in the 1st time period (8-12 h) and amounted to 82.01±7.3 μg/h, (Δ% 375.4), in the later time intervals, the excretion gradually decreased and by the end of the study (8-24 h) it was 26.53±4.3 μg/h (Δ% 53.8). The average daily excretion of thiamine when it was taken in a dose of 30 mg was 68.74±9.4 μg/h, the maximum excretion value also falls on the 1st time period (8-12 h) and is 106.57±13.4 μg/h (p <0.005, Δ% 517.8). In the course of further research, the value of thiamine excretion was systematically reduced, reaching minimum values by the end of the study. In the same group, the average daily urine excretion of riboflavin before taking thiamine was 16.22±2.88. The average daily excretion of riboflavin when taking thiamine at a dose of 10 mg was 19.97±3.6 μg/h. The period of maximum excretion fell on the second time period (12-16 h) and amounted to 29.46±5.5 μg/h (Δ% 81.6). The average daily excretion of riboflavin when taking thiamine at a dose of 20 mg was 23.14±5.7 μg/h, the maximum excretion was also noted in the second time interval (12–16 h) and amounted to 37.52±7.1 μg/h (p <0 005, Δ% 131.3). The average daily excretion of riboflavin when taking thiamine at a dose of 30 mg was 28.72±7.1 μg/h, the maximum excretion was observed in the first time period (8-12 h) and amounted to 44.13±7.4 μg/h (Δ% 172, one).

Thus, an increase in the dose of thiamine leads to a statistically significant increase in its average daily excretion. At the same time, there is a direct correlation between the dose of taken thiamine and its average daily excretion with urine (r = 0 93). Acceptance of a loading dose of thiamine leads to an increase in riboflavin excretion in the urine during the day, without confirmed statistical certainty. Therefore, the lowest average daily excretion was observed when taking 10 mg of thiamine, and the C-max value is comparable to C-max when receiving 20 mg of thiamine. This circumstance makes the use of thiamine at a dose of 10 mg predominant.

Table 3: Urinary excretion of thiamine and riboflavin (μg/h) when taking loading doses of vitamin B_1

Dose	B_1 average daily excretion	B_2 average daily excretion	B_1 maximum excretion	B_2 maximum excretion
10 mg	33.41±7.2	19.97±3.6	53.87±5.6	29.46±5.5
20 mg	41.32±9.1	23.14±5.7	82.01±7, 3	37.52±7.1
30 mg	68.74±9.4	28.72±7.1	106.57±13.4	44.13±7.4
Initial value	17.25±3.7	16.22 2,88±±	21,24,1	±19,122,7

Indicators of urine excretion of riboflavin and thiamine when receiving loading doses of vitamin B_2 are shown in Table 4. The group of volunteers taking single dose of riboflavin as monotherapy average excretion in the urine before receiving vitamin (baseline

value) amounted to 15.85±3.5 mg/h. The average daily excretion of riboflavin when taken in a dose of 10 mg was 58.54±7.7 μg/h, the maximum excretion occurred in the 2nd time period (12-16 h) and amounted to 182.98±22.3 μg/h (Δ% 1054.45, p <0.05). The average daily excretion of riboflavin when it was taken in a dose of 20 mg was 38.84±7.2 μg/h, the maximum excretion occurred in the 1st time period (8-12 h) and amounted to 154.61±14.3 μg/h (Δ% 875.5).

The average daily excretion of riboflavin when it is taken in a dose of 30 mg was 76.87±11.56 μg/h, the maximum excretion in the 1st time period (8-12 h) was 246.72±23.8 μg/h (Δ % 1456.6).In the same group, the average daily excretion of thiamine in the urine before taking riboflavin was 18.12±2.4 μg/h (baseline). The average daily excretion of thiamine with 10 mg riboflavin was 25.26±1.6 μg/h (p <0.05), the maximum excretion during the second time period (12-16 h) was 39.21±3.4 μg/h (Δ% 116.4). The average daily excretion of thiamine when taking riboflavin at a dose of 20 mg was 31.51±3.1 μg/h, the maximum excretion in the 4th time interval (20-24h) - 40.64±4.4 μg/h (Δ% 124 3). The average daily excretion of thiamine when taking 30 mg of riboflavin was 34.95±2.7 μg/h, the maximum excretion in the 4th time interval (20-24 h) - 44.63±5.4 μg/h (Δ% 146.3).

Thus, excretion of riboflavin also depends on the loading dose of vitamin B_2 (riboflavin), but this relationship is not directly proportional. When taking 10 mg of riboflavin, excretion values are recorded higher than when taking 20 mg, but lower than those with receiving 30 mg riboflavin. Taking loading doses of riboflavin markedly increases the excretion of thiamine in comparison with the values obtained prior to the study.

Table 4: Urinary excretion of riboflavin and thiamine (μg/h) while taking loading doses of vitamin B_2

Dose	B_2 average daily excretion	B_1 average daily excretion	B_2 maximum excretion	B_1 maximum excretion
10 mg	58.54±7.7	25.26±1.6	182.98±22.3	39.21±3.4
20 mg	38.84±7.2	31.51±3.1	154.61±14.3	40.64±4.4
30 mg	76.87±11.56	34.95±2.7	246.72±23.8	44.63±5.4
Initial value	15.85±3.5	18.12±2.4	17.67±2, 8	20.43±2.5

CHF treatment evaluation with vitamins B_1, B_2 and Mg added to the standard complex therapy. 4 groups were formed among CHF patients for extended outpatient observation: 1 (control) - standard complex CHF therapy only, 2 + standard Mg orotate therapy, 3 - standard treatment + mono-preparations vitamins B_1 and B_2,4 - standard treatment + Mg orotate + mono-preparations of vitamins B_1 and B_2. CHF average functional class in the studied (2-4) and control (1) groups initially was 2.7±0.12, 2.6±0.18, 2.7±0.14, and 2.6±0, respectively. 17 - That is, patients with a severe degree (FC III) CHF prevailed. In the course of treatment, there was a decrease in the functional class of CHF in all groups of patients, as a result of which the number of patients with primary (FC I) and moderate degree of CHF (FC II) in all groups increased significantly.

But in the control (1st) group, the decrease in the functional class of CHF in patients occurs much more slowly and to a lesser extent than in other comparison groups (2-4), where standard therapy was accompanied by the use of Mg and B group vitamins (B_1, B_2) or a combination of the preparation of Mg with vitamins of group B_1, B_2.

The earliest and most pronounced FC decrease is observed in the 4th group (Mg orotate + B_1+ B_2). Already from the second week of therapy in this group there is a noticeable decrease CHF FC (from 2.7±0.14 to 2.3±0.11, Δ% 14.82). After treatment (Table 5), average CHF FC significantly (p <0.01) decreased in all the studied groups in the first to 1.8±0.12 (Δ% -30.8%), p <0.001), in 2nd- to the 1st group - up to 1.5±0.18 (Δ% -44.4%, p <0.01), in the 3rd - up to 1.4±0.19 (Δ% -46.2%, p <0.001) and in the 4th - up to 1.3±0.22 (Δ% -51.9%).

The most pronounced changes occurred in the group where, along with the standard therapy, the Mg preparation was used in combination with the B group vitamins. During the study, RSCS dynamics were studied in various treatment options (Table 5), reflecting the clinical condition of the patients. As can be seen from the table, the average number of points at the beginning of the study was in group 1, 2, 3 and 4 were 6.37±3.3, 5.87±3.3, 6.27±3.4 and 7.83±2, 0,

respectively, which indicated the prevalence of patients with CHF FC III in each of the study groups.

During the course of treatment of CHF, the average number of points on the RSCS scale significantly decreased ($p < 0.001$), and the difference in points after 6 weeks of therapy, compared with baseline figures expressed as a percentage of the initial state (Δ%), was 1, 2, 3 and 4 groups, respectively, - 5.76%, - 11.93%, 14.79%, - 26.16% ($p < 0.001$). The most pronounced positive dynamics was observed in the 4th group, while over the same period of time (6 weeks), the improvement in the condition of the patients in the 2nd and 3rd group was comparable, and did not have a significant difference ($p > 0.05$).

After 12 weeks of therapy, the results for the research groups (scores for RSCS) 1-4 were - 18.94%, -50.10%, -53.68%, 54.63% ($p < 0.05$), respectively .The dynamics of clinical indicators in the treatment of patients in group 4 (against the background of the use of Mg in combination with vitamins B_1 and B_2), after 12 weeks of therapy, differed significantly from the data obtained for groups 1, 2 and 3. In group 4, an earlier and pronounced positive trend ($p < 0.05$) of the patients' condition was observed practically from the second week of therapy.

The latter circumstance indicated a decrease in the severity of symptoms of decompensation in patients in group 4. First of all, this is due to the Mg positive effect, which is entering into reversible chelate-like bonds with organic substances, providing catalysis of biochemical reactions and combining this effect with the positive effect of vitamins (B_1 and B_2) taken on the heart muscle due to changes in glycolytic processes in the myocardium.

Table 5: Dynamic state compared groups of patients to change FC (NYHA) scale and RSCS for CHF patients with different therapy

Groups / timing		CHF FC (average)	RSCS score	Δ% (RSCS points)
Group 1 (control)	Initial	2 6±0.17	6.37±3.31	
	2 weeks	2.5 + 0.2	6,26 ± 3,4	-1,83
	4 weeks	2.3±0.1	6.24±3.2	-2 , 13
	6 weeks	2.2±1.4	6.01±3.1	-5.76
	8 weeks	2.1±1.2	5.65±2.7	-11.35
	10 weeks	1.9±1.0	5,29±3.0	-16.98
	12 weeks	1.8±0.12	5.17±2.9	-18.94
Group 2 (Mg orotat)	Initial	2.7±0.12	5.87±3.3	
	2 weeks	2.6±0.9	5.70±3.0	-2.84
	4 weeks	2.4±0.7	5.60±1.9	-4.63
	6 weeks	2.1±0.6	5.17±2.4	-11.93
	8 weeks	1.9±0.8	4.88±1.7	-16.76
	10 weeks	1.7±0.9	4.28±1.2	- 27.08
	12 weeks	1.5±0.18	4.08±1.8	-50.10
3 group (B_1 and B_2)	Initial	2.6±0.18	6.27±3.4	
	2 weeks	2.4±0.7	5.97±2.3	-4.79
	4 weeks	2.3±1.0	5.82±2.0	-7.09
	6 weeks	2.1±1.6	5.33±1, 9	-14. 99
	8 weeks	1.8±0.6	5.11±2, 3	-18.44
	10 weeks	1.6±0.9	4.21±1.8	-32.83
	12 weeks	1.4±0 , 19	2.90±1.9	-53.68
4 group (Mg orotate + B_1 and B_2)	Initial	2.7±0.14	7.83±2.0	
	2 weeks	2.3±0.11	6 67±1.8	-14.80
	4 weeks	2.1±1.6	6.28±1.8	-19.77
	6 weeks	1.9±0.6	5.78±1.7	-26.16
	8 weeks	1.7±0.9	5.46±1.9	-30.17
	10 weeks	1.4±0.9	4.94±2.0	-36.81
	12 weeks	1.3±0.22	3.55±1.5	-54.63
Groups / timing		CHF FC (average)	RSCS score	Δ% (RSCS points)
Group 1 (control)	Initial	2 6±0.17	6.37±3.31	
	2 weeks	2.5 + 0.2	6,26 ± 3,4	-1,83
	4 weeks	2.3±0.1	6.24±3.2	-2 , 13
	6 weeks	2.2±1.4	6.01±3.1	-5.76
	8 weeks	2.1±1.2	5.65±2.7	-11.35
	10 weeks	1.9±1.0	5 , 29±3.0	-16.98
	12 weeks	1.8±0.12	5.17±2.9	-18.94
Group 2 (Mg orotat)	Initial	2.7±0.12	5.87±3.3	
	2 weeks	2.6±0.9	5.70±3.0	-2.84
	4 weeks	2.4±0.7	5.60±1.9	-4.63
	6 weeks	2.1±0.6	5.17±2.4	-11.93

	8 weeks	1.9±0.8	4.88±1.7	-16.76
	10 weeks	1.7±0.9	4.28±1.2	- 27.08
	12 weeks	1.5±0.18	4.08±1.8	-50.10
3 group (B_1 and B_2)	Initial	2.6±0.18	6.27±3.4	
	2 weeks	2.4±0.7	5.97±2.3	-4.79
	4 weeks	2.3±1.0	5.82±2.0	-7.09
	6 Initial	2.1±1.6	5.33±1, 9	-14. SO
	8 weeks	1.8±0.6	5.11±2, 3	-18.44
	10 weeks	1.6±0.9	4.21±1.8	-32.83
	12 weeks	1.4±0 , 19	2.90±1.9	-53.68
4 group (Mg orotate + B_1 and B_2)	Initial	2.7±0.14	7.83±2.0	
	2 weeks	2.3±0.11	6 67±1.8	-14.80
	4 weeks	2.1±1.6	6.28±1.8	-19.77
	6 weeks	1.9±0.6	5.78±1.7	-26.16
	8 weeks	1.7±0.9	5.46±1.9	-30.17
	10 weeks	1.4±0.9	4.94±2.0	-36.81
	12 weeks	1.3±0.22	3.55±1.5	-54.63

When evaluating the dynamics of the 6-minute walk test, the average number of meters (I-III FC CHF), which patients underwent upon admission to the hospital, was in group 1 - 232.61±10.4, in 2 - 231.17±10.9, in 3 - 232.78±9.8 and in 4 - 233.57±8.9. From the above values it can be noted that the 6-minute walk test scores in all four comparison groups were initially comparable. According to the data of Table 6, a significant increase in walking distance during the treatment process was established in all groups of patients. On the 2nd week there is a difference in this indicator between the groups with a predominance of an increase in the values in the group of use of magnesium orotate and mono-preparations of group B vitamins (respectively, groups 1 through 4: 254.65±12.3; 257.69±11.2; 258.08±11.3; 279.68±10.5 m). This dynamics was observed throughout the study phase after 12 weeks, the greatest difference compared with the values prior to therapy, was noted in group 4 (Δ% 91.27).

Table 6: Dynamics of 6-minute walk test performance (m)

Period	Group 1 (control)	Group 2	Group 3	Group 4
Initial values	232.61±10.4	231.17±10.9	232.78±9.8	233.57±8.9
2 weeks	254.65±12.3*	257.69±11.2	258.08±11.3	279.68±10.5*
Δ%	9.48	11.47	10.01	11.97
4 weeks	285.76±8.5*	297.75±13.5	305.23±11.8	328.67±14.5*
Δ%	22.85	28.80	31.12	40.72
6 weeks	317.58±17.2*	324.76±17.3	329,56±15,2*	363,45±13,5
Δ%	36,52	40,49	41,58	55,61
8 weeks	336,62 17,9±	±367,1513,6*	377,31±17.9	398.66±10.8*
Δ%	44.71	58.82	62.09	70.68
10 weeks	351.25±16.3*	383.38±18.7	389.38±21.4	415.62±19.4*
Δ%	51.00	65.84	67.27	77.94
12 weeks	364.63±13.6	396.37±20.1	404.76±20.8*	446.75±21.7*
Δ%	56.76	71.46	73.88	91.27
Period	Group 1 (control)	Group 2	Group 3	Group 4
Initial values	232.61±10.4	231.17±10.9	232.78±9.8	233.57±8.9
2 weeks	254.65±12.3*	257.69±11.2	258.08±11.3	279.68±10.5*
Δ%	9.48	11.47	10.01	11.97
4 weeks	285.76±8.5*	297.75±13.5	305.23±11.8	328.67±14.5*
Δ%	22.85	28.80	31.12	40.72
6 weeks	317.58±17.2*	324.76±17.3		
329,56±15,2*363,45±13,5 Δ				
8 weeks	336,62 17,9±	±367,1513,6*	377,31±17.9	398.66±10.8*
Δ%	44.71	58.82	62.09	70.68
10 weeks	351.25±16.3*	383.38±18.7	389.38±21.4	415.62±19.4*
Δ%	51.00	65.84	67.27	77.94
12 weeks	364.63±13.6	396.37±20.1	404.76±20.8*	446.75±21.7*
Δ%	56.76	71.46	73.88	91.27

* - $p < 0.05$

An important indicator of the effective CHF treatment is the definition of Health related quality of life (HRQoL) indicators: level of a patient's functioning, his state of health and well-being, based on his subjective perception [34]. Of the disease specific methods for evaluating HRQoL in CHF, the MHFLQ questionnaire (Minnesota Living with Heart Failure Questionnaire) is most common [35]. In a series of studies, high validity, reproducibility of this questionnaire and its sensitivity to HRQoL changes during

treatment have been proven [36]. The MHFLQ data correlate well with clinical data (symptoms, NYHA FC, 6-minute walking distance) in patients with HF of various etiologies [37, 38, 39].

The average number of MLHFQ points in all groups before the start of the study was comparable and ranged from 1 to 4 group 84.24±6.2, 83.12±7.1, 85.31±5.8 and 83.78±7, 4 respectively. After 6 weeks from the start of the study, there was a significant decrease in the number of points in groups 2-4 to 65.40±5.4 (Δ% -21.32, p <0.001), 64.45±6.3 (Δ% -24, 45, p <0.001) and 59.78±4.3 (Δ% -28.65, p <0.001) points, respectively. In the control group, the improvement in the quality of life was minimal — up to 76.71±4.6 points (Δ% -8.94). After 12 weeks of therapy, there was a fairly high level of improvement in the quality of life in the studied groups (2-4) - 47.00±6.6 (Δ% -43.45), 39.73±3.5 (Δ% -53, 43) and 34.46±5.7 (Δ% -58.87) points, respectively .While in the control group, this indicator was significantly lower - 64.76±7.3 (Δ% -23.12) points. According to MLHFQ, complex therapy of CHF in combination with Mg orotate and B vitamins (B_1 and B_2) at a dose of 10 mg leads to an improvement in the quality of life of patients with severe CHF.

Conclusion

With an increase in the daily dose of thiamine, its daily excretion increases in proportion to the dose taken. When taking Mg in equal doses of Mg oxide and Mg orotate in all points of the pharmacokinetic curve, the concentration of Mg when taken as orotate exceeds the concentration of Mg when taken as oxide only, except for a 24-hour point. The inclusion of vitamin B_1 (thiamine) and B_2 (riboflavin) and Mg in complex CHF therapy leads to a significant improvement in the clinical condition (on RSCS scale) and patients' life quality (on MLHFQ scale).Thus, to improve the quality of life of patients with CHF and increase tolerance to physical exertion, it is advisable to add Mg in combination with vitamins B_1 and B_2 as part of standard complex therapy.

When Mg salts are added to the standard complex treatment of CHF, it is preferable to add Mg orotate. When using vitamin B_1 (thiamine), it is not advisable to increase the daily dose of more than 10 mg/day, since this leads to a progressive increase in the excretion of this vitamin and vitamin B_2.

References

1. Mareev V Yu, Fomin IV, Ageev FT (2018) Clinical recommendations of the Society of Specialists in Heart Failure, the Russian Cardio logical Society and the Russian Scientific Medical Society of Physicians. Heart failure: chronic and acute decompensated. Diagnosis, prevention and treatment. Cardiology, 58(S6): 164.
2. Mosterd A, Hoes AW (2007) Clinical epidemiology of heart failure. Heart, 93(9): 1137-1146.
3. Shakirova RM, Galyavich AS, Kamalov GM (2005) Prevalence of cardiovascular diseases and diabetes mellitus and their relationship with symptoms of chronic heart failure in the Republic of Tatarstan. Russian Heart Failure Journal, 6(2): 72-73.
4. Smirnova EA (2010) Prevalence and etiology of chronic heart failure in Ryazan Region. Russian journal of cardiology, (2): 78-83.
5. Artemieva EG, Malenkova V Yu, Frolova EV (2011) The prevalence of arterial hypertension at chronic cardiac insufficiency in Chuvash Republic. Medical almanac, 16: 51-54.
6. Babanskaya EB, Menshikova LV, Dats LS (2012) Epidemiology of chronic heart failure in Irkutsk. Byulleten' Vostochno-Sibirskogo nauchnogo centra SO RAMN, 5-1: 25-28.
7. Sergeeva EM, Malishevsky MV, Vasina AA, Mishchenko TA, Kuzmina YS, Raemgulov RA (2015) Chronic heart failure treatment in primary municipal health services in Tyumen. Medical science and education of the Ural, 16(4): 32-34.
8. Fomin IV (2016) Chronic heart failure in Russian Federation: what do we know and what to do. Russian journal of cardiology, 8: 7-13.
9. Owan TE, Hodge DO, Herges RM, Jacobsen S., Roger VL, Redfield MM (2006) Trends in prevalence and outcome of heart failure with preserved ejection

fraction. New England Journal of Medicine, 355(3): 251-259.

10. Gerber Y, Weston SA, Redfield MM, Chamberlain AM, Manemann SM, Jiang R, Roger VL (2015) A contemporary appraisal of the heart failure epidemic in Olmsted County, Minnesota, 2000 to 2010. JAMA internal medicine, 175(6): 996-1004.
11. Fomin IV, Badin YV, Polyakov DS, Belenkov YN, Mareev VY, Ageev FT, Koziolova NA (2013) Prehypertension: how often this carDiovascular conDition occurs in citizens of European Russia (epoch-ah, 2002-2007). Sovremennye tehnologii v medicine, 5(2): 38-46.
12. Kapanadze LG, Gerasimova VV, Mareev Yu V, Rogoza AN, Mareev V Yu (2013) Factors influencing 5-year survival in patients with mild and moderate CHF: Role of office BP and parameters of 24-h BP profile in disease prognosis. Russian Heart Failure Journal, 14 (6): 353-361.
13. Troitskaya Ye A, Kotovskaya Yu V, Kobalava Zh D (2015) Prognostic value of high intervisit variability of systolic blood pressure in patients with chronic heart failure with reduced ejection fraction. Materials of the IV All-Russian Conference "Contradictions of Modern Cardiology: Disputed and Unresolved Issues". MICE Partner, 138.
14. Fomin IV, Polyakov DS (2014) ß-Blockers: the lack of task implementation or the unwillingness of doctors in the Russian Federation to optimize the treatment? System hypertension, 11(1): 56-63.
15. Glezer MG, Chesnikova AI, Giliarevskiĭ SR, Perepech NB, Astashkin EI, Lopatin I, Vasiuk I (2014) Decrease in heart rate in patients with coronary artery disease and chronic heart failure the purpose and means. Kardiologiia, 54(4): 109.
16. Fomin IV, Belenkov Yu N, Mareev V Yu, Ageev FT, Badin Yu V, Galyavich AS, Makarova V G (2006) The prevalence of chronic heart failure in the European part of the Russian Federation-EPOHA-CHF data. Journal of Heart Failure, 7 (3): 112-115.
17. Cleland JGF, Swedberg K, Follath F, Komajda M, Cohen-Solal A, Aguilar JC, Madeira HC (2003) The Euro Heart Failure survey programme-a survey on the quality of care among patients with heart failure in Europe: Part 1: patient characteristics and diagnosis. European heart journal, 24(5): 442-463.
18. Koziolova NA, Nikonova Yu N, Shilova Ya E, Agafonov AV, Polianskaya EA (2013) Description of chronic heart failure against the background of permanent atrial fibrillation. Russian Heart Failure Journal, 14 (1): 14-21.
19. Zhirov IV, Romanova NV, Tereshchenko SN, Osmolovskaya YF (2015) Epidemiology and peculiarities of therapy of chronic heart failure in combination with atrial fibrillation. Cardiology, 55(3): 91-96.
20. Efremova EV, Shutov AM (2014) Comorbidity and prognosis of patients with chronic heart failure. Journal of Heart Failure, 15(5): 294-300.
21. Koziolova NA, Masalkina OV, Kozlova EV (2016) Regularities in development of chronic heart failure in patients with ischemic heart disease and chronic obstructive pulmonary disease associated with multiple co morbidity. Russian Heart Failure Journal, 17(3): 151-163.
22. Zhang P, Omaye ST (2001) Antioxidant and pro oxidant roles for ß-carotene, α-tocopherol and ascorbic acid in human lung cells. Toxicology in vitro, 15(1): 13-24.
23. Lonsdale D (2006) A review of the biochemistry, metabolism and clinical benefits of thiamin (e) and its derivatives. Evidence-Based Complementary and Alternative Medicine, 3(1): 49-59.
24. Rao SN, Chandak GR (2009) Cardiac beriberi: often a missed diagnosis. Journal of tropical pediatrics, 56(4): 284-285.
25. Dabar G, Harmouche C, Habr B, Riachi M, Jaber B (2015) Shoshin beriberi in critically-ill patients: case series. Nutrition journal, 14(1): 51.
26. Sica DA (2007) Loop diuretic therapy, thiamine balance, and heart failure. Congestive Heart Failure, 13(4): 244-247.
27. Hanninen SA, Darling PB, Sole MJ, Barr A, Keith ME (2006) The prevalence of thiamin deficiency in hospitalized patients with congestive heart failure. Journal of the American College of Cardiology, 47(2): 354-361.
28. Shimon H, Almog S, Vered Z, Seligmann H, Shefi M, Peleg E, Ezra D (1995)

Improved left ventricular function after thiamine supplementation in patients with congestive heart failure receiving long-term furosemide therapy. The American journal of medicine, 98(5): 485-490.

29. Schoenenberger AW, Schoenenberger-Berzins R, Der Maur CA, Suter PM, Vergopoulos A, Erne P (2012) Thiamine supplementation in symptomatic chronic heart failure: a randomized, double-blind, placebo-controlled, cross-over pilot study. Clinical research in cardiology, 101(3): 159-164.
30. Smithline HA (2007) Thiamine for the treatment of acute decompensated heart failure. The American journal of emergency medicine, 25(1): 124-126.
31. DiNicolantonio JJ, Lavie CJ, Niazi AK, O'Keefe JH, Hu T (2013) Effects of thiamine on cardiac function in patients with systolic heart failure: systematic review and metaanalysis of randomized, double-blind, placebo-controlled trials. Ochsner Journal, 13(4): 495-499.
32. Jain A, Mehta R, Al-Ani M, Hill JA, Winchester DE (2015) Determining the role of thiamine deficiency in systolic heart failure: a meta-analysis and systematic review. Journal of cardiac failure, 21(12): 1000-1007.
33. Adamopoulos C, Pitt B, Sui X, Love TE, Zannad F, Ahmed A (2009) Low serum magnesium and cardiovascular mortality in chronic heart failure: a propensity-matched study. International journal of cardiology, 136(3): 270-277.
34. Testa MA, Simonson DC (1996) Assessment of quality-of-life outcomes. New England journal of medicine, 334(13): 835-840.
35. Rector TS, Kubo SH, Cohn JN (1987) Patients self-assessments of their congestive heart failure. Part 2: Content, reliability and validity of a new measure, the Minnesota Living with Heart Failure Questionnaire. Heart Failure, 3: 198-207.
36. Reddy P, Dunn AB (2000) The Effect of ß-Blockers on Health-Related Quality of Life in Patients with Heart Failure. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy, 20(6): 679-689.
37. Garin O, Soriano N, Ribera A, Ferrer M, Pont À, Alonso J, Permanyer G (2008) Validación de la versión española del Minnesota Living with Heart Failure Questionnaire. Revista española de cardiología, 61(3): 251-259.
38. Supino PG, Borer JS, Franciosa JA, Preibisz JJ, Hochreiter C, Isom OW, Forur L (2009) Acceptability and psychometric properties of the Minnesota Living with Heart Failure Questionnaire among patients undergoing heart valve surgery: validation and comparison with SF-36. Journal of cardiac failure, 15(3): 267-277.
39. Fomin IV (2010) Epidemiology of chronic heart disease failure in the Russian Federation. Chronic heart failure. M: GEOTAR-Media, 7-77.

