



## EVALUATION OF THE EFFECTIVENESS OF CARVEDILOL IN THE TREATMENT OF PATIENTS WITH CHRONIC HEART FAILURE

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### Abstract:

The aim of the study was to determine the clinical efficacy and safety of carvedilol in patients with chronic heart failure. 50 patients with chronic heart failure (CHF) of functional class II-III (FC) and left ventricular ejection fraction (LV) of less than 45% were examined. All patients, in addition to ACE inhibitors, were prescribed carvedilol at an initial daily dose of 6.25 mg with the possibility of increasing the dose to 50 mg per day, divided into two doses. The duration of follow-up was 6 months. To determine the effectiveness of carvedilol treatment, at the beginning of the study and after 6 months of treatment, the clinical condition of patients with CHF was assessed (Mareeva V.Yu. scale, 2000), the distance of a six-minute walk and the functional class of CHF were determined, echocardiographic examination was performed and Dopplerography of the brachial artery and the humoral marker Willebrand factor were performed to assess the function of the endothelium. The inclusion of carvedilol in the treatment regimen of patients with CHF was accompanied by an improvement in the clinical condition of patients, an increase in exercise tolerance. The use of carvedilol in combination with standard therapy of patients with CHF not only improves the structural and geometric parameters of LV, improves LV systolic function and functional activity of patients, but also improves the functional state of the endothelium.

**Keywords:** chronic heart failure, sympathoadrenal system, beta blockers, hemodynamics, blood biochemistry.

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## 1. Introduction

Chronic heart failure (CHF) is one of the most common, progressive and prognostically unfavorable diseases of the cardiovascular system, as well as one of the most frequent causes of hospitalizations. An important role in the ongoing disorder observed during the development of CHF is played by a cascade of phenomena regulated by neurohumoral systems. But LV dysfunction is the main trigger for the development of CHF, and the state of the LV ejection fraction (LV) is the main factor determining the prognosis of CHF. Today, science has accumulated a sufficient amount of data on the regulatory and homeostasis-supporting properties of the endothelium - local, organ-tissue, and general, relative to the body as a whole. Based on the knowledge of the key role of the endothelium in the development of a number of diseases of the cardiovascular system, it can be assumed that it is "endothelial" diagnostic concepts and therapeutic strategies that will determine the situation in theoretical and practical cardiology in the near future. Taking into account the change in the ratio of  $\beta_1$  and  $\beta_2$  receptors in the myocardium in CHF, as well as the importance of alpha receptor blockade, the expediency of using carvedilol in the treatment of patients with this pathology is obvious. Taking into account the above, the use of carvedilol in the treatment of patients with CHF is of great interest for practical healthcare.

**The aim of the study** was to determine the clinical efficacy and safety of carvedilol in patients with chronic heart failure in outpatient settings.

## 2. Material and methods

36 patients with clinically pronounced CHF were examined, the average age was  $58.3 \pm 2.3$  years. Among the patients there were 28 men (80.0%, average age  $-66.1$

$\pm 2.6$  years) and 8 women (20.0%, average age  $-62.0 \pm 4.5$  years).

According to the criteria for inclusion in the study, all patients were with CHF P-P1 FC, had an ejection fraction (LV) of the left ventricle  $< 45\%$ , according to echocardiography, systolic blood pressure  $\geq 90$  mmHg, received conventional treatment of CHF, including: ACE inhibitors or angiotensin II receptor antagonists, if necessary - diuretics, cardiac glycosides; had no contraindications to the appointment of beta blockers.

Depending on the FC and the stage of CHF, patients were distributed as follows: II FC had 16 patients (43.3%), of which 92.3% were men and 7.7% were women; III FC — 20 patients (56.7%), among which 70.6% were men and 29.4% were women. As can be seen, among the examined patients, women had more severe CHF than men: in women, the average FC was  $-2.8 \pm 0.2$ , in men  $-2.5 \pm 0.1$ .

Analyzing the causes of CHF in the patients included in the study, it should be noted that in 63.3% of cases, the development of heart failure was associated with postinfarction cardiosclerosis, in 13.4% - with coronary artery disease, angina pectoris of tension and rest, in 13.3% due to hypertension, in 10.0% of cases - dilated cardiomyopathy.

In accordance with the study protocol, all patients were prescribed carvedilol at an initial daily dose of 6.25 mg, divided into two doses. Titration of the dose of carvedilol was carried out for 6-8 weeks. To this end, once every 2 weeks, the doctor assessed the general condition of the patient and the possibility of increasing the daily dose to 12.5 mg, 25 mg and 50 mg, divided into two doses. In patients with a body weight of more than 85 kg, it was possible to increase the dose of carvedilol to 100 mg per day. After completing the titration of the dose, the patient visited the doctor with a frequency of 1 time per month. The duration of follow-up was 6 months.

To assess the effectiveness, safety and validity of carvedilol treatment, at the

beginning of the study, after 3 months and upon its completion, a clinical examination of patients was conducted, including, in addition to standard indicators of cardiovascular system activity, a scale for assessing the clinical condition of patients with CHF (modification of Mareeva V. Yu., 2000), the distance of a six-minute walk and functional CHF class. In addition, at the beginning of the study and after 6 months of taking carvedilol, all patients underwent an echo-cardiographic study with mandatory determination of the ejection fraction (LV) of the left ventricle, a biochemical blood test (lipidogram, urea, creatinine, bilirubin, ACT, ALT, etc.).

### 3. Results and discussion

Analysis of the obtained material showed that before inclusion in the study, only 70% of patients were regularly treated, while 30% were treated irregularly, episodically — with deterioration. It should be noted that in the last 3 months before the start of the study, ACE inhibitor was received by 100% of patients, diuretics -93.3%, cardiac glycosides - 46.7%, veroshpiron(spironolactone) -16.7%, beta blockers occasionally - 20.0% of patients. As a result of regular treatment for 6 months, including the use of carvedilol, a significant improvement in the clinical condition of all examined patients with CHF was noted. The dynamics of clinical symptoms were analyzed according to the clinical condition assessment scale, using a point calculation of the results obtained or the determination of percentages of the maximum. Thus, during treatment, there was a significant decrease in scores after 3 months of treatment from  $6.6 \pm 0.4$  to  $4.1 \pm 0.2$  (by 37.9%), and by the end of the study, the number of points decreased to  $3.4 \pm 0.2$  (by 48.5%). As the presented data showed, the inclusion of carvedilol in the treatment

regimen of patients with CHF leads to an improvement in the clinical condition of patients by 48.5% over 6 months of follow-up.

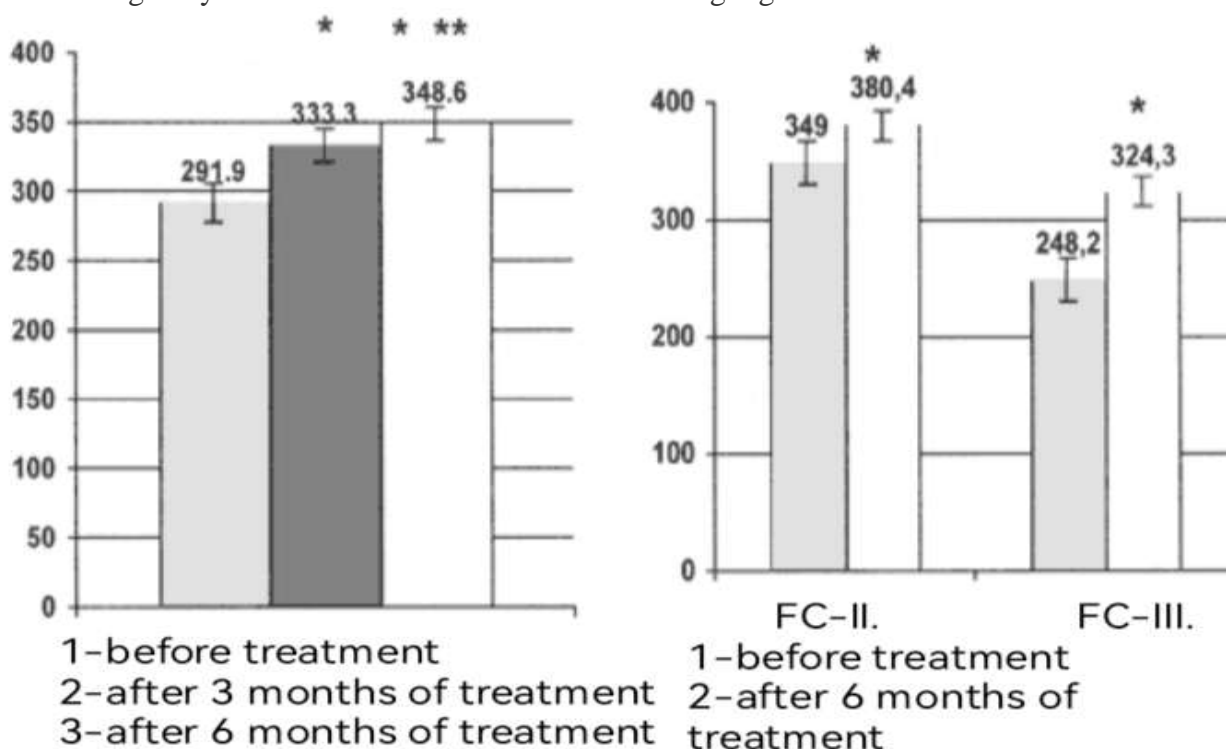
The effectiveness of therapy, including carvedilol, can also be judged by the indicators of the distance of a 6-minute walk. Against the background of treatment, there was a significant increase in the distance of a 6-minute walk after 3 months of treatment by 41.4 m (14.2%), after 6 months - by 56.7 m (19.4%). Moreover, a greater increase in the distance of a 6-minute walk was observed by the end of the study in patients with III FC - by 76.1 m (30.7%), while in patients with II FC - by 31.3 m (9.0%) (Fig. 1).

The effect of the drug is pronounced the more severe the initial status of the patients were. An increase in exercise tolerance against the background of therapy led to an increase in the number of patients with II FC by 36.7% and, accordingly, a decrease in the number of patients with III FC. At the same time, the average FC significantly decreased from 2.6 initially to 2.2 after 6 months of treatment.

It is important to note that the average daily dose of carvedilol during treatment was  $35.2 \pm 3.8$  mg, and in patients with FC II the average daily dose of the drug was  $40.4 \pm 4.3$  mg, and in patients with FC III -  $31.3 \pm 5.7$  mg.

The analysis of the effect of therapy with carvedilol on blood pressure (BP) and heart rate (HR) is of interest. Thus, the initial average level of systolic blood pressure in the general group of patients was  $136.7 \pm 2.2$  mmHg, diastolic blood pressure -  $80.2 \pm 1.5$ . After 6 months of treatment, including carvedilol, there was a significant decrease in average systolic blood pressure by 14.7%, diastolic blood pressure - by 10.8%. Heart rate during the follow-up period decreased from  $78.1 \pm 1.5$  to  $65.8 \pm 0.9$ , i.e. by 15.7%.

Fig.1 Dynamics of the 6-minute walk test during regular carvedilol treatment



Note:\* - significant differences ( $p < 0.05$ ) relative to the initial data.

\*\* - significant differences ( $p < 0.05$ ) relative to intermediate data.

An important place in the study was given to the study of the effect of therapy with carvedilol on intracardiac hemodynamics according to echocardiography. It should be noted that after 6 months of treatment, there was a significant increase in the left ventricular LV by 23.4%, a decrease in the final systolic volume (CSR) by 12.7% and the final diastolic volume of the left ventricle (CDR) by 9.0%, a decrease in the final diastolic size (CDR) by 11.9% and the final systolic size (CSR) by 6.6%.

The results obtained indicate a significant positive effect of carvedilol on left ventricular remodeling.

When analyzing the effect of carvedilol on the studied biochemical parameters, there was no negative effect of the drug on the blood lipid spectrum, carbohydrate metabolism, liver and kidney function: the results obtained before treatment and after 6 months of therapy did not significantly differ.

Attention should be paid to the results of the global assessment of the patient's condition and treatment results. It turned out that 56.7% of patients by the end of the study assessed their condition as satisfactory (the condition improved), 40.0% - as good (the condition improved significantly) and 3.3% (1 patient) - as excellent (there are no previous symptoms of CHF). The doctor's global assessment of the patient's condition and the results of treatment did not differ significantly. According to the doctor's assessment, the condition improved in 50.0% of patients, much improved in 46.7%, and 3.3% of patients had no previous symptoms of CHF.

Long-term therapy with carvedilol significantly improved the performance of patients with CHF III FC. The diameter of brachial artery at rest increased by 8.8% ( $p < 0.05$ ) of the initial ones. Systolic, diastolic and average blood flow rates increased by 2.9; 30 and 6.7% ( $p < 0.005$ ) and increased endothelium dependent vasodilation by 38.8% ( $p < 0.02$ ). The resistive and pulsative indices decreased by 5.9 and 9%. The sensitivity of the brachial

artery to shear stress significantly increased by 60% ( $p < 0.05$ ). In patients with CHF III FC, there was a significant increase in the Willebrand factor index by 25.8% ( $p < 0.05$ ) from the baseline on the background of carvedilol.

The data obtained by us are confirmed by the data of other researchers. G.Y.H. Lip and A. Blann showed a significant increase in the level of Willebrand factor in CHF and revealed a correlation of these indicators with the ejection fraction, the mass index of the left ventricular myocardium. The positive effect of carvedilol in patients with FC III CHF on the indicators of endothelial dysfunction is associated with additional  $\alpha$ -adrenoblocking and antioxidant properties of the drug and is consistent with the data of other researchers.

#### 4. Conclusions.

1. The use of carvedilol leads to a significant improvement in the clinical condition of patients with CHF (by 48.5%).

2. Carvedilol contributes to an increase in exercise tolerance (by 19.4%).

3. When using carvedilol, there was a significant increase in left ventricular LV by 23.4%, a decrease in CSR by 12.7% and BWR by 9.0%, which indicates a significant positive effect of carvedilol on left ventricular remodeling.

4. Six-month therapy with carvedilol improves endothelium-dependent vasodilation, reduces vascular tone, and increases the level of von Willebrand factor in patients with CHF.

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