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# CLINICAL EFFICACY OF A BETABLOCKERS THERAPY IN PATIENTS WITH CHRONIC HEART FAILURE ON THE BACKGROUND OF POSTINFARCTION CARDIOSCLEROSIS

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Despite the fact that betablockers (BBs) are one of the main groups of therapy of patients with acute myocardial infarction (AMI), the comparative effectiveness of various BBs in patients with postinfarction cardiosclerosis (PICS) is uncertain. There was performed comparative analysis of clinical efficacy of BBs in patients with chronic heart failure (CHF) on the background of coronary heart disease (CHD), PICS. There was evaluated the impact of metoprolol succinate, carvedilol, bisoprolol and betaxolol on blood pressure (BP), left ventricular ejection fraction (LVEF), change the functional class of chronic heart failure, and mortality in patients over 4 years. It is established that the BBs therapyblood pressure decreased equally, without significant differences between the groups (p>0,05). There was a positive effect on the increase of the LVEF all the BBs (p<0.01), bisoprolol was exerted more pronounced effect (p<0.01). Comparative assessment of BBseffectiveness showed that the reducti0on of the functional class of chronic heart failure was in the bisoprolol treatment by 43.7% (p<0.001), carvedilol by 32.3% (p<0.001), betaxolol by 27.3% (p<0.01) and metoprolol succinate by 25.6% (p<0.01). Differences between groups were significant in favor of bisoprolol. Also, our study investigated the influence of BB streatment on the mortality of patients with CHD, PICS, which was performedby year for 4 years. Depending on the duration of observation for 1year mortality was 7.4% for 2 years it was 11.6%, for 3 years it was 10.5%, for 4 year it was 24.3% (p<0.01 in all cases in comparison with the group without BBs administration). The reduction in mortality associated with treatment with beta blockers during the year was 27.5%, 2 years – 34.8%, 3 years – 67.2% and 4 years 35.9%. Thus, the administration of betablockers can significantly reduce mortality in patients with postinfarction cardiosclerosis, starting from the first year of treatment. And this positive effect persists and accumulates in the future.

Key words: chronic heart failure, drug therapy, beta blockers, mortality

**Introduction**

The concept of beta-adrenergic receptorsblockade as a therapeutic method for chronic heart failure (CHF) was developed by the Gothenburg group (Sweden) in the seventies [1, 2]. In subsequent experiments on larger selections with a placebo-controlled clinical trials there was confirmed the efficiency of the beta-adrenergic receptors blockade in the treatment of heart failure [3]. Then there were begun a series of studies that to date have presented convincing evidence for the efficacy of betablockers (BBs) as a therapeutic agent in heart failure [4, 5].

However, some questions of the mechanisms of development [6, 7] and progression of CHF in patients after myocardial infarction [8], as well as the medical administration of the BBs in this category of patients remain controversial. These include, first, the rationality of itsadministration in patients with postinfarction cardiosclerosis (PICS) at the stage of rehabilitation treatment due to a negative inotropic action on the myocardium. Also further evaluation of their effects on the left ventricular systolic [9] and diastolic dysfunction [10, 11], special aspects the actions of BBS on quality of life [12, 13], as well as the individual characteristics of the action of betablockers and their influence on mortality [14, 15] of patients is necessary.

In clinical practice, due to a cautious attitude of physicians towards the BBS modern and more effective drugs in this group are administrated less frequently than it's required. Existing varieties of beta blockers represent non-selectivedrugs, such as propranolol, timolol, and selective beta-1blockers, such as metoprolol, atenolol, bisoprolol and

betaxolol. An example of the next generation of BBSare drugs with vasodilatory and metabolic activity, its mechanisms of actions are varied, such as carvedilol with vasodilatory property and nebivolol with a pronounced antioxidant activity [16].

Clinical efficacy of BBS in patients with CHF was studied in several placebo controlled trials. Significance and efficiency of the BBSin CHF can be confirm the results of a sufficiently long (not less than 3 months) randomized clinical trials (RCTs). It should be recalled that the results of only three large and well-organized RCTs (MERIT-HF – Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure, CIBIS II – Cardiac Insufficiency Bisoprolol Study and COPERNICUS – Carvedilol Prospective Randomized Cumulative Survival) to evaluate the application of the BBS (metoprolol succinate, bisoprolol and carvedilol) in comparison with placebo showed a decrease in mortality about 35% [17]; also there is a unit comparison of the effectiveness of non-selective BBS carvedilol and the most commonly administrated beta-1selective BBS (bisoprolol, metoprolol and nebivolol) in patients with acute myocardial infarction (AMI) after percutaneous cardiac catheter intervention (PCI) [18] which not found differences impact on all-cause mortality and AMI.

Today the question of optimal BBS therapy in patients with ischemic CHFis not studied, as it requires a direct comparison of drugs in RCT$_S$. This, in turn, determines the importance of studying the influence of BBS on mortality in patients with CHF as a result of the outcome of myocardial infarction, what is the purpose of the present study.

**Materials and methods**

The clinical efficacy of the BBS in our study was studied in 168 patients. All patients suffered from myocardial infarction within the deadline more than 6 months before the examination. The patients with acute symptoms of heart failure, unstable patients with CHF and acute forms of coronary heart disease (CHD) were rejected from the study. Essential hypertension was detected in 100% (168) of patients, and its duration was 10.2 ± 1.5 years (from 4 to 16 years).

Systolic function of the left ventricle was determined by the left ventricular ejection fraction (LVEF) index. The average LVEF index of the patients was 43 ± 0.8%. To determine the functional class of CHF used the classification of New York Heart Association (NYHA). The average FC of CHF according to rating NYNA was 2.8 ± 0.06. BBS were administrated in the complex standard of pharmacotherapy of CHF: angiotensin-converting enzyme inhibitors / angiotensin receptor blockers, diuretics, and cardiac glycosides (digoxin) if it's 91ecessary. The metoprolol succinate, betaxolol, bisoprolol, and carvedilol were administrated of the BBS. The duration of the treatment ranged from 12 months to 4 years.

In a group of 168 patients, where there was the analysis of the effectiveness of the BBS treatment within one year, metoprolol succinate was administrated to 56 (33.3%) patients, carvedilol – to 35 (20.8%), bisoprolol to 43 (25.6%) and betaxolol to 34 (20.3%). Males were 110 (65.5%) and females were 58 (34.5%). The age of patients according to gender and groups, taking BBS, did not differ significantly and averaged (63.0 ± 6.0). Impact on mortality was performed annually throughout the period of supervision.

Statistical processing of the obtained data was carried out on a personal computer by methods of variation statistics using the software packages "Microsoft Excel", "Statistica" using the student's t test. The data are presented in the form (M±m). Differences were considered significant at $p < 0.05$.

**Main part**

Baseline blood pressure (ABP), systolic (SBP) and diastolic (DBP) were almost identical in all patients (table 1).

*Table 1*

**Dynamics of ABP level in the BBS therapy(M±m)**

| Drug | Number of subjects, n | ABP level, mm Hg | | | |
|---|---|---|---|---|---|
| | | Baseline ABP | | ABP after 12 months | |
| | | SBP | DBP | SBP | DBP |
| Metoprolol succinate | 56 | 174 ± 3.8 | 99 ± 4.0 | 146 ± 2.1 | 76 ± 3.1 |
| Carvedilol | 35 | 176 ± 9.9 | 97 ± 5.6 | 137 ± 4.7 | 75 ± 2.9 |
| Bisoprolol | 43 | 172 ± 8.0 | 98 ± 4.8 | 135 ± 5.2 | 78 ± 3.4 |
| Betaxolol | 34 | 168 ± 6.4 | 98 ± 4.2 | 131 ± 2.8 | 78 ± 3.3 |

Significant differences between the groups were not found. However, hypotensive effect and blood pressure reduction are most significantly manifested in patients treated with carvedilol (Figure 1).

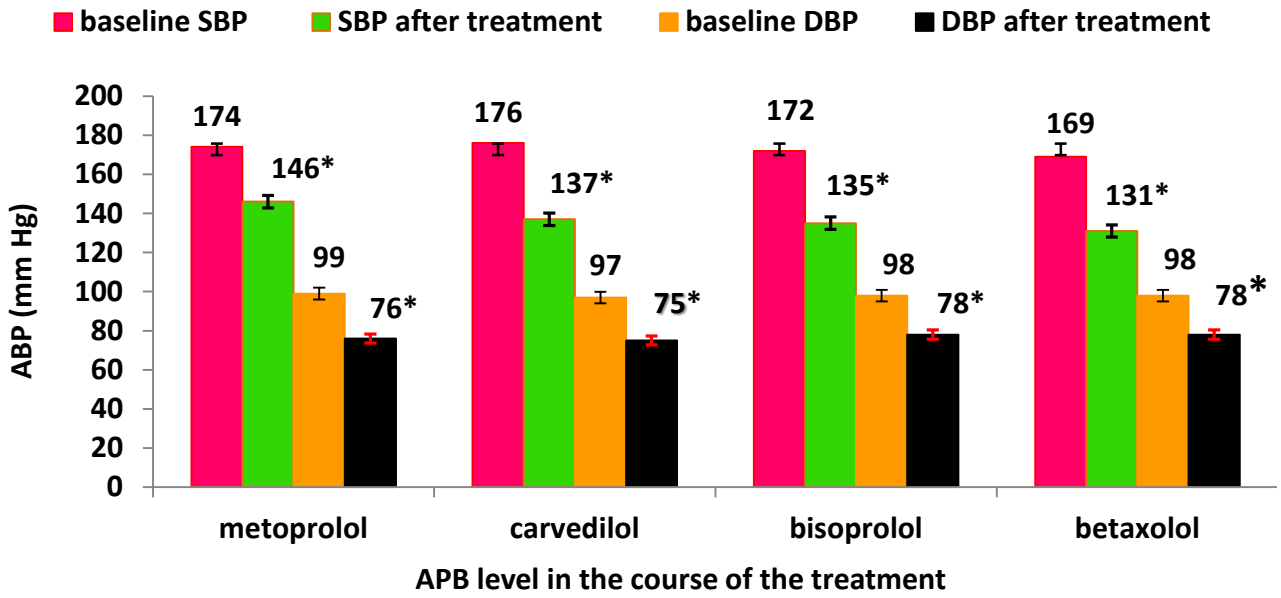


**Figure 1.** Pharmacodynamic effects of BBS in patients with CHF on the background of coronary heart disease (CHD), postinfarction cardiosclerosis (PICS) * – p<0,05 in comparison with baseline group

There was performed the assessment of BBS on the systolic function of the left ventricle of the heart. It is established that under the influence of the BBS treatment there was an increase in ejection fraction (Figure 2) to varying degrees.

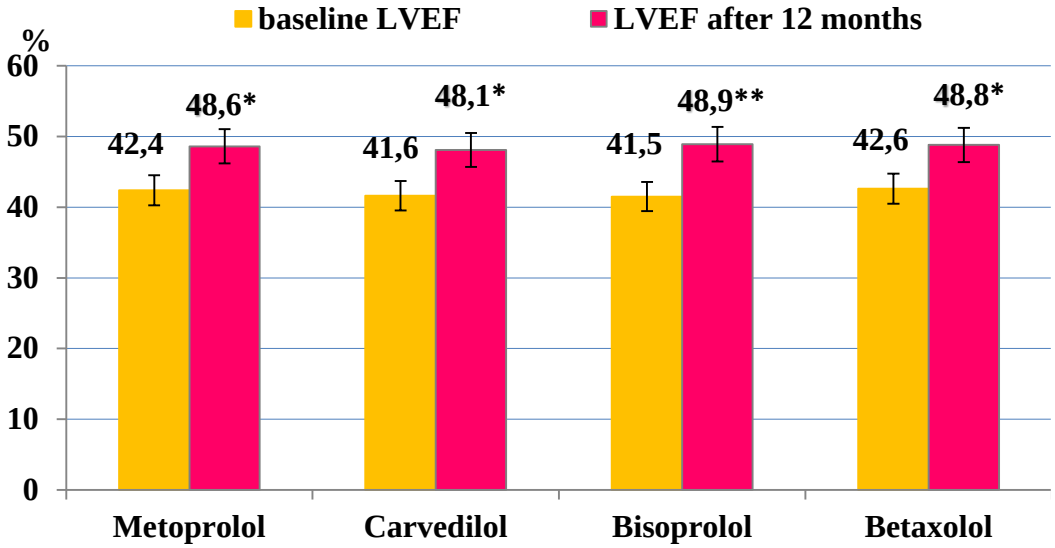


**Figure 2.** Pharmacodynamic effects of BBS in patients with CHF on the background of coronary heart disease (CHD), postinfarction cardiosclerosis (PICS). Change the LVEF in the course of the BBS treatment

Patients treated with metoprolol succinate, the baseline EF was 42.4 ± 1.8%, and in the course of the treatment it increased to 48.6 ± 1.8% or by 14.6% (p<0.05). In the group of patients treated with carvedilol, the baseline EFwas 41.6 ± 1.9%. After treatment it was 48.1 ± 2.1%, or increased by 15.7% (p<0.05). In patients group treated with bisoprolol dynamics of EF ranged from 42.6 ± 1.8% to 48.8 ± 1.8% or increased by 16.5% (p<0.01). Treatment with betaxolol has also led to an increase of the EF index from 42.6 ± 1.8% to 48.8 ± 1.8% or by 14.6% (p<0.05).

Consequently, bisoprolol had a more pronounced positive effect on the increase in the EF in patients with chronic cardiac insufficiency on the background of ischemic heart disease, postinfarction cardiosclerosis. Other betablockers: metoprolol

succinate, carvedilol, and betaxolol improve ejection fraction in a less degree. A statistically significant difference between the groups were not found.

Analysis of the impact of BBS on the course of CHF showed that the average changes of the functional class of CHF in the entire group of patients treated with betablockers, has changed from 3.0 ± 0.05 units to 2.0 ± 0.04 units (p<0.001), by 1.0 units (33.3%) (p<0.01) (table 3). In the group treated with metoprolol succinate overall average of the functional class of CHF in the course of the treatment has changed from 2.9 ± 0.05 to 2,1 ± 0.03 units (p<0.001) by 0.8 units (27.6%). Carvedilol therapy (35 patients) led to decrease of the functional class of CHF in all patients. The baseline functional class of CHF corresponded to 3.1 ± 0.05 units with a significant decrease to 2.1 ± 0.04 units (p<0.001),by 1.0 units (32.3%). Bisoprolol was treated 43 patients with coronary heart disease, postinfarction cardiosclerosis. The baseline overall average of the functional class of CHFin this group was 3.2 ± 0.06 units, and in response to treatment decreased to 1.8 ± 0.05 units, by 1.4 units (43.7%) (p<0.001). The baseline overall average offunctional class of CHF in betaxolol group was 3.0 ± 0.05 units, after treatment it decreased by 0.8 units (25%) to 2.2 ± 0,04 units (p<0.01).

*Table 3*

**Changes in functional class of chronic heart failure in patients with CHD, PICS after 12 months of therapy with beta blockers (M±m)**

| Drug | Number of subjects, n | The functional class of CHF | | p |
|---|---|---|---|---|
| | | Before treatment | After treatment | |
| Metoprolol succinate | 56 | 2.9 ± 0.05 | 2.1 ± 0.03 | <0.01 |
| Carvedilol | 35 | 3.1 ± 0.05 | 2.1 ± 0.04 | <0.001 |
| Bisoprolol | 43 | 3.2 ± 0.06 | 1.8 ± 0.05 | <0.001 |
| Betaxolol | 34 | 3.0 ± 0.05 | 2.2 ± 0.04 | <0.01 |
| All: | 168 | 3.0 ± 0.05 | 2.0 ± 0.04 | <0.001 |

Comparative evaluation of the effectiveness of BBS have shown that the decrease of the functional class of CHF was in group of bisoprolol 43.7% (p<0.001), carvedilol – 32.3% (p<0.001), betaxolol – 27.3% (p<0.01) and metoprolol succinate – 25.6% (p<0.01). Differences between groups were significant in favor of bisoprolol.

Also in our study we investigated the influence of treatment of BBS on the mortality of patients with CHD, PICS, which was arranged by the years within 4 years (table 4).

*Table 4*

**Comparative analysis of the influence of BBS therapy on mortality of patients with postinfarction cardiosclerosis**

| Patient categories | Characteristics of patients by years of supervision | | | | All |
|---|---|---|---|---|---|
| | 2012 | 2013 | 2014 | 2015 | |
| All | 80 | 90 | 85 | 84 | 339 |
| 1. Without BBS treatment, n | 49 | 43 | 38 | 39 | 169 |
| Deceased of which, n, % | 18<br>36.7% | 14<br>32.6% | 7<br>18.4% | 4<br>10.3% | 43<br>25.4% |
| 2. BBS therapy, n | 32 | 47 | 44 | 45 | 168 |
| Deceased of which, n, % | 8<br>25.0% | 5<br>10.6% | 5<br>11.4% | 3<br>6.7% | 21<br>12.5% |
| Deceased at all, n, % | 26<br>32.5% | 19<br>21.1% | 12<br>14.1% | 7<br>8.3% | 64<br>18.9% |

During the 4 years there were supervised 339 patients, of which in 2012 – 80 2013 – 90, 2014 – 85, 2015 – 84 patients. Of the 339 patients with postinfarction cardiosclerosis 168 patients (49.6%) were treated with betablockers. BBS therapy in 2012 was prescribedto 40% of patients, 2013 to 52.2%, 2014 to 56.8% and 2015 to 53.6%. Analyzing the mortality of patients with postinfarction cardiosclerosis depending on the administration of the betablockers we should say that the total number of patients died in the group treated with BBS was 21 and the general mortality was 12.5%. Among the patients was not treatedwith betablockersthere were 43 died, which accounted for 25.4% of the 171 patients (p<0.01 in comparison with the treatment group). In theBBS treatment depending on the duration of supervision of 1 year mortality was 7.4% for 2 years it was 11.6%, for 3 years it was 10.5%, for 4 years it was 24.3% (p<0.01 in all cases in

comparison with the group without the administration of BBS). The decrease of the mortality associated with BBS treatment during the year was 27.5%, 2 years it was 34.8%, 3 years it was 67.2% and 4 years it was 35.9%.

Comparative evaluation of the effect of the BBS on mortality in patients depending on the drug showed that in the group of patients treated by metoprolol succinate 8 patients were died, which accounted for 14.3% of the number of patients taking the drug. In the group taking carvedilol the number of died patients was 4 (11.4 %), bisoprololum it was 3 (6.9%) and betaxolol it was 6 patients (17.6%) (table 5).

*Table 5*

**Comparative evaluation of the effect of the BBS on mortality of patients with CHD, PICS depending on BBS**

| Drug | Statistical values | | | |
|---|---|---|---|---|
| | n | (M, %) male/female | Age, M ± m | Mortality |
| Metoprolol succinate | 56 | (62.5%) 35/21 | 65.8 ± 4 | 8 (14.3%) |
| Carvedilol | 35 | (60%) 21/14 | 63.2 ± 7 | 4 (11.4%) |
| Bisoprolol | 43 | (53.5%) 28/15 | 62.4 ± 7 | 3 (6.9%) |
| Betaxolol | 34 | (76.5%) 26/8 | 62.1 ± 5 | 6 (17.6%) |
| All | 168 | (65.5%) 110/58 | 63.0 ± 6 | 21 (12.5%) |

**Results and evaluation**

RCTs are the gold standard for delivering the foundations of therapy. Post hoc analyses, systematic reviews, and meta-analyses are post marketing tools that help refine or make sense of the collective evidence. All the small and large RCTs using BBs in CHF have answered the question of safety and efficacy very well. Studies have set out to enroll cohorts with a good spectrum of illness severity, as detailed in the NYHA class and mean LVEF. To control for confounders, studies may have controlled the heterogeneity of the other demographic and comorbid variables. Why is this important? Guidelines are shaped around the findings of large RCTs, and appear to suggest that findings from these homogeneous studies apply equally to heterogeneous «real-world» patients. This may, in fact, be the case, although examples are presenting that a broader perspective may be needed. Female sex and race have not received good representation in any RCT. Post hoc analysis from MERIT-HF and pooling of results with CIBIS II and COPERNICUS show similar survival in women and men [19, 20].

BBs therapy is not enough administrated for CHF and diabetes, and complications of diabetes, such as nephropathy, partly because of the historical problems of tolerability, adverse hemodynamic and metabolic effects, and lack of selectivity of the BBs. Heterogeneity within the class of BBs, perhaps, is the biggest problem in its prescription. It can be argued that BBs with vasodilatory properties, such as carvedilol and nebivolol theoretically may have advantages in improving metabolic profile and kidney function, as they reduce insulin resistance and not adversely impact on the blood glucose level [21, 22]. Also the question remains about the optimal dose of BBs at CHF. The results of the study of BBs as antiarrhythmic drugs are also scarce and conflicting.A rhythm-based strategy in atrial fibrillation and HF is less clear. The main pharmacological therapies that are used in maintaining sinus rhythm are either contraindicated as with flecainide, not proven with sotalol, or have long-term toxicity concerns with amiodarone. Between 10% and 35% of trial participants have comorbid atrial fibrillation, whereby the most recent 10-study meta-analysis could not demonstrate an outcome benefit with BBs [23].

The main goal of therapy in patients with coronary heart disease, postinfarction cardiosclerosis is improve long-term outcomes, that is the secondary prevention of this disease [2, 3, 24]. In our study, bisoprolol was the drug with the highest degree of a positive effect on decrease of the severity and course of chronic heart failure, and then the carvedilol and betaxolol. To a lesser extent, but quite noticeable this effect is observed in metoprolol succinate. Also the study of the influence of the BBs on the mortality of patients with CHF on the back of CHD after myocardial infarction showed the reduction of mortality for 4 years by 35.9%. Comparative evaluation of the effect of the beta-blockers on mortality in patients depending on the drug showed that in the group of patients treated by metoprolol succinate 8 patients were died, which accounted for 14.3% of the number of patients taking the drug. In the group taking carvedilol it was 4 (11.4%), bisoprolol it was 3 (6.9%) and betaxolol 6 patients (17.6%). Thus, the beta-blockers therapy can significantly reduce of mortality in patients with postinfarction cardiosclerosis, starting from the first year of treatment. And this positive effect persists and accumulates in the future.

**Conclusion**

Summing up set out on the effects of beta-blockers on the severity of CHF in patients with postinfarction cardiosclerosis, it can be argued that bisoprolol has the most positive impact on reducing of CHF, and then the carvedilol and betaxolol. To a lesser extent, but quite noticeable this effect is observed in metoprolol. Thus, the beta-blockers therapy can significantly reduce of mortality in patients with postinfarction cardiosclerosis, starting from the first year of treatment. And this positive effect persists and accumulates in the future.

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