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MODERN APPLICATION OF BETA-ADRENOBLOCKER IN PHARMACOTHERAPY OF CHRONIC HEART FAILURE AMONG PATIENTS WITH ISCHEMIC HEART DISEASE

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Abstract:
Beta-blockers (β-blockers) are among the recommended group of drugs for the treatment of chronic heart failure (CHF) and coronary heart disease. According to the results of clinical trials and meta-analyzes the long-term use of β-blockers improves the outcome of patients with CHF, reduces the risk of cardiovascular events and sudden cardiac death. During an β-blocker selection among CHF patients, it is necessary to evaluate all risk factors, as well as the individual characteristics of the considered drugs. The article highlights the issues the third-generation β-blocker "Nebivolol" modern application. They presented information about the mechanisms of action, the pharmacological profile and the cardioprotective properties of "Nebivolol" for the prevention of myocardial damage after ischemia-reperfusion and myocardial revascularization. The review presents the clinical study data concerning the effect of "Nebivolol" on LV diastolic dysfunction among CHF patients with with a preserved ejection fraction.

Key words: *Beta-blockers (β-blockers), chronic heart failure (CHF), nebivolol, nitric oxide (NO), myocardial revascularization.*

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INTRODUCTION:

Beta-blockers (β-blockers) are among the most commonly prescribed cardiovascular drugs used to treat hypertension (AH), arrhythmias, coronary heart disease (CHD) and chronic heart failure (CHF). β-blockers are recommended for the patients with stable coronary artery disease as first-line therapy based on their significant antianginal effect, as well as the extrapolation of the prognostic benefits that have been demonstrated by the patients after an acute myocardial infarction (AMI) and by the patients with CHF [1,2].

Most studies confirming the efficacy of β-blockers among the patients with CHD precede the current era of coronary revascularization, intensive anticoagulant therapy, the use of statins, more stringent target blood pressure (BP) levels and were specifically designed to evaluate their effects on stable angina (St St). The anti-anginal effect of β-blockers is based on their negative inotropic and chronotropic properties. β-blockers reduce heart rate (HR) by reducing myocardial oxygen demand. Prolonging diastolic filling and increasing vascular resistance in the non-ischemic areas of heart, β-blockers increase the coronary perfusion of the ischemic zones and improve the contractility of the viable myocardial areas. In combination, these mechanisms are the key ones to the beneficial effects of β-blockers among the patients with cardiovascular disease. They studied the use of β-blockers at cardiovascular diseases (CVD), such as stable and unstable angina, post-infarction cardiosclerosis, CHF to control heart rate during atrial fibrillation. There was a positive effect on the course of recurrent AMI and recurrent angina [3]. Also β-blockers can improve the condition of patients with CHF, reducing the load on the myocardium and affecting sudden cardiac death (SCD) by reducing the likelihood of arrhythmias [4]. It should be noted that today the intake of β-blockers is prolonged among the patients after myocardial revascularization by the method of aorta coronary artery bypass graft (ACABG), even among the patients with a preserved ejection fraction (EF) of the left ventricle (LV). However, there is not enough evidence of their effectiveness during the postoperative period and the clarification of patient group personalization is required for their prescription [5]. The problem of a personalized approach in pharmacotherapy is particularly relevant, since some β-blockers can cause counterproductive side effects, such as type 2 diabetes, bronchial obstruction and dyslipidemia [6,7]. In several studies, the number of authors has shown that the central role of β-blockers cannot be justified among the patients with relatively low risk, who have high-quality control over their cardiovascular risk factors and who receive evidence-based basic therapy [8,9]. It was noted that among the patients undergoing ACABG, preoperative β-blocking therapy reached 80-93% during the previous few years [8].

In order to assess the association of therapy by β-blockers with the decrease of St St frequency or cardiovascular events (CVS), IMAGINE analysis was performed among the patients after ACABG, which included the patients with low risk and normal LV systolic function. The results of this analysis suggest that β-blockers do not have an additional positive effect after ACABG on the reduction of cardiovascular disease frequency or the return of angina during observation for 32 months on the average [10]. The neutral effects of β-blocker therapy among a particular patient category may be based on several potential explanations. Thus, myocardial ischemia is eliminated among most patients after revascularization, and therefore the risk of CVD is reduced and the advantage of β-blockers is less significant for the occurrence of these events. Earlier studies also did not show the benefits of metoprolol intake in terms of physical exertion or myocardial ischemia among the patients revascularized by ACABG [11]. During the study of the patients with a low risk of cardiovascular disease, they found that the mortality from cardiovascular diseases was <1.4% as compared with a median follow-up for 3 years, and the incidence was only 9.4%. These data are similar to the results obtained by the patients with cardiovascular risk factors without an established coronary lesion, which emphasizes the low frequency of cardiovascular diseases among this population [12,13]. The study with the pathology of the coronary arteries SIGNIFY showed that ivabradine, added to the recommended drug therapy to reduce heart rate, did not improve the result among the patients with coronary artery disease without the clinical signs of CHF. They revealed the data showing the increase of cardiovascular disease risk among the patients with St St of the functional class II or higher. Considering that the primary cardiovascular effect of ivabradine is the heart rate reduction, these results demonstrate that the increased heart rate is only a risk marker, but not an invariable determinant of the results among the patients with coronary heart disease without the clinical signs of heart failure [14]. Thus, the neutral results of SIGNIFY provide the information that indirectly confirms the concept that sympathetic tone modulation is usually ineffective after revascularization among the patients with low risk. Other studies have found a favorable relationship between β-blocker means and cardiovascular deseases among the patients with recent AMI and

CHF [15,16]. It should be noted that β-blockers are more widely recommended among the patients after an acute myocardial infarction and among the patients with CHF, based on the extrapolation of the effect on the prognosis [17,18]. Conflicting data are presented in other studies, in which they noted that among the patients with the history of AMI, the intake of β-blockers was not associated with CVD decrease [13]. Also, β-blocker therapy was not associated with the best 3-year clinical outcomes among the patients with AMI who underwent percutaneous coronary intervention and had intact LV EF > 50% [19]. β-blockers are especially effective among the patients with LV dysfunction. The best results were observed among the patients with LV EF ≤ 40% who take β-blockers unlike the patients without β-blocking therapy [20]. The presented data suggests that the protective effects of β-blockers are limited, and are rather prescribed for the patients with recent AMI, ongoing myocardial ischemia, or with significant LV dysfunction.

Thus, to date, there is no evidence to support the indiscriminate use of β-blockers among the patients who are asymptomatic, have an intact LV function after a successful revascularization, and receive evidence-based therapy for patients with coronary heart disease. This is reflected in the latest recommendations of the American Cardiological Association for the treatment of stable coronary heart disease with the recommendation class IIb for these patients [21]. The recommendations of the European Society of Cardiology do not mention a specific recommendation on the use of β-blockers among the patients with asymptomatic IHD and low risk [22]. It should be noted that there are no data today on the effect of β-blockers among the category of patients with CHF and intermediate LV EF of 40-50%, and the study of personalized pharmacotherapy approaches remains relevant and significant.

Since β-blockers in modern cardiology continue to be one of the most widely used groups of drugs for the prevention and the treatment of CVDs, they include a variety of pharmacological properties. These include the drugs that block the action of adrenaline and noradrenaline, affecting β1-adrenergic and β2-adrenergic receptors, and are considered non-selective (propranolol, nadolol, sotalol). For example, propranolol has side effects mainly due to its ability to block β2-adrenergic receptors, especially at the level of the respiratory system, and to overcome the blood-brain barrier despite the fact that it is effective for hypertension treatment [23]. This has led to the development and the introduction of second-generation drugs with a selective effect on β1-cardiac receptors, but not affecting vasodilation (atenolol, bisoprolol, betaxolol, metoprolol, talinolol, oxprenolol, acebutolol, and celiprolol). In general, traditional β-blockers have a lower clinical effect as compared to other classes of drugs. It is noteworthy that they have little impact on the quality of life and adversely affect the metabolism of carbohydrates and lipids. The blockade of β1-adrenergic receptors can cause dyslipidemia, since these receptors are involved in the mechanism of lipolysis in adipocytes. Thus, pharmacological studies of this type of drugs continued in the attempts to synthesize β-blockers with an additional characteristic of peripheral vasodilation induction. Research has led to the development of third-generation β-blockers, which differ in the mechanisms by which they provide vasodilation. This is labetalol (nonselective blocker and α1-adrenoceptor), carvedilol (nonselective blocker of β1β2 and α1-adrenoceptors), dilevalol (nonselective blocker of β-adrenergic receptors and partial agonist of β2-adrenoceptor), nebivolol (β1-adrenergic blocker with the activation of endothelial nitric oxide (NO)). Thus, pharmacological and hemodynamic differences between conventional non-vasodilating β-blockers and vasodilating β-blockers have important consequences, especially during the treatment of complicated hypertension associated with diabetes or cardiometabolic syndrome. The effect on endothelial dysfunction can be a major factor contributing to these differences.

Carvedilol is the most studied and used third-generation β-blocker with vasodilating effects. Carvedilol is the antagonist of α1 – adrenergic receptors, and it has a combined antagonistic effect on both β1 and β2 receptors [24, 25]. Carvedilol has additional endothelium-dependent vasodilating properties among the patients with hypertension or CHF. The additional vasodilating effect of carvedilol is conditioned by its effect on endothelial function potentiating the release of prostaglandins and NO [26]. However, β2-receptor blockade causes side effects, such as fatigue and dizziness, which limits its use.

Nebivolol is a third-generation β-blocker with the highest selectivity for cardiac β1-adrenergic receptors and the highest selectivity of β1, β2 - adrenergic receptors as compared to other β-blockers. Nebivolol does not affect α-adrenergic receptors and is devoid of its own sympathomimetic activity. Taking into account these characteristics of nebivolol, it has the properties of systemic vascular resistance and peripheral vascular resistance effective reduction, the increase of cardiac output (CO) and stroke volume (SV), and heart systolic and diastolic function

improvement [27,28]. At the same time, nebivolol is highly β1-selective at the doses of ≤ 10 mg per day. They determined that these effects are conditioned by the increase of endothelial synthase endothelium NO using the means of a stimulating effect mediated through β3 agonism [29].

Different pharmacological profile of nebivolol is associated with a number of hemodynamically significant effects: 1) β1-adrenergic blockades, the decrease of heart rate, the improvement of systolic and diastolic blood pressure, myocardial contractile function; 2) NO-mediated vasodilation, which leads to peripheral vascular resistance decrease, the increase of SV, EF and the maintenance of CO [30]; 3) vasodilation and the reduction of oxidative stress, contributing to the beneficial effects of nebivolol on the metabolism of glucose and lipids [31]; 4) the decrease of volume and the aggregation of platelets by residual adenosine diphosphate reduction – the induced platelet aggregation [32].

These signs suggest a potentially high efficacy of nebivolol during the treatment of hypertension and CHF. Endothelially-dependent arterial and venous vasodilating properties of nebivolol are important, which are largely explained by the synergy of NO production [33,34]. It is important to note that the participation of α-adrenergic receptors in these effects is excluded, thereby showing that the mechanism of nebivolol action proceeds differently in contrast to the mechanism of carvedilol action. Favorable endothelial effects of nebivolol have been demonstrated in a number of studies during the comparative analysis with non-vasodilating β1-selective blockers (atenolol, metoprolol). They determined that nebivolol as compared with atenolol significantly improves the vasodilation index of small arteries [35], the parameters of oxidative stress [36] and the concentration of dimethylarginine in plasma, the endogenous inhibitor of NO production, which is directly associated with cardiovascular risk [37]. It was proved that nebivolol also stimulates the isolated formation of NO in the tissue of the myocardium [38]. The cardiac synthesis of NO with nebivolol additionally affects the cardiovascular effects among the patients with hypertension and CHF. The effect of nebivolol on cardiac NO production does not depend on the inhibition of β1-adrenergic receptors. Its effects on heart tissue are mediated through the stimulation of β3-adrenergic receptors for the secretion of NO and the promotion of neo-angiogenesis [39]. Thus, β3-adrenergic receptor has become a potential target for the treatment of CVD. The cardioprotective effects of nebivolol may be particularly useful for the treatment of the patients with ischemic and CVD by coronary reserve preservation [40]. Indeed, recent studies have shown that nebivolol prevents myocardial damage after ischemia-reperfusion due to the rapid activation of endothelial nitric oxide synthase oxygenase and the increased bioavailability of NO [41].

The recent meta-analysis of β-blocker use among the patients with CHF with and a low ejection fraction (CHF-LEF) showed that the treatment with β-blockers leads to a significant reduction of mortality as compared with placebo [42]. The patients with CHF and a good ejection fraction (CHF-GEF), had the improvement of up to 4%, as well as the decrease of SCD and CVD deaths. These benefits arose regardless of treatment duration or β-blocker class. However, the mechanisms of action by which β-blockers make a positive effect on CHF cannot be limited by β-adrenergic blockade. It has been established that β-blockers with the vasodilating effect (nebivolol, carvedilol, labetalol) can influence the regression of myocardial remodeling and arterial stiffness, which are directly related to CHF [43]. The exact role of these mechanisms, such as NO-mediated vasodilation in the case of nebivolol, is not fully understood, which requires additional research in specially designed trials. They determined that nebivolol favorably affects the course of CHF with systolic dysfunction, since it does not cause the worsening of hemodynamics (increased systolic pressure in the pulmonary artery, wedge pressure in the pulmonary artery, and HO decrease) [44]. In 12-month, randomized study the patients with CHF-GEF experienced hemodynamic improvement and exercise tolerance during the therapy with nebivolol than atenolol [45]. In the CARNEBI study (a multi-parameter comparison of carvedilol versus nebivolol and bisoprolol with moderate CHF), the patients who received nebivolol and bisoprolol for 2 months achieved better lung diffusion and exercise efficiency than in the group of patients taking carvedilol [46]. It should be noted that randomized clinical trials are conducted mainly for the patients with CHF-LEF, and only in these patients demonstrated the effective methods of treatment. Although the mortality among patients with chronic heart failure is somewhat lower than the mortality among patients with CHF-LEF, the observational studies have now shown higher mortality among these patients than in the clinical trials [47]. Conflicting data were obtained among the groups of patients with CHF-GEF. The advantage of nebivolol treatment among the patients with CHF-GEF is less evident than among the patients with CHF-LEF. For example, the therapy with nebivolol (the titration from 2.5 to 10 mg) for 5 weeks among the patients with CHF-GEF did not improve the 6-

minute walk tests, peak oxygen consumption, the functional class of CHF and the quality of life according to the Minnesota questionnaire as compared to placebo [48]. In contrast, two minor studies demonstrated a preferred hemodynamic effect with nebivolol versus atenolol and metoprolol, but the clinical results were not evaluated sufficiently [49.50]. It has been established that CHF-GEF are mainly associated with LV diastolic dysfunction (DD) and arterial stiffness increase [51].

DD on the background of IHD is represented by complex pathogenetic mechanisms. Thus, causing systemic inflammation with high circulating levels of interleukin-6 and tumor-α necrosis factor, leads to coronary microvascular endothelial dysfunction as the result of NO low bioavailability and the increase of reactive oxygen species number. Low bioavailability of NO leads to the decrease of protein kinase G activity and cyclic guanosine monophosphate, which ultimately causes cardiomyocyte hypertrophy and fibrosis with an increased rigidity and subsequent DD [52]. The stiffness of cardiomyocytes is associated with titin protein increase, which binds the strands of myocardial sarcomeres and directly affects passive relaxation. The patients with CHF-GEF have the excess of protein kinase C and the decrease of protein kinase G which lead to titin phosphorylation decrease and, consequently, to passive rigidity increase [53]. The optimal control of DD from early stages to the decompensation of CHF-GEF or CHF-LEF remains relatively empirical. Therapeutic goals include hemodynamic filling improvement, both for preload and for afterload [54]. It has been established that in the presence of diastolic dysfunction, it is important to avoid tachycardia and monitor heart rate. A lower heart rate causes LV filling time increase, thereby balancing the resistance of the rigid ventricle to diastolic filling flow and, therefore, providing the best SV. New generation β-blockers with vasodilating activity (nebivolol and carvedilol) reduce heart rate and myocardial ischemia, as well as pulse pressure and aortic stiffness better than atenolol, therefore, they are preferable during the treatment of LV DD [55]. It has been shown that Nebivolol improves DD more effectively [56].

At that some interest is demonstrated to the studies published by Galderisi et al in which they showed that coronary blood flow reserve (CBFR), which is caused by epicardial coronary stenosis and coronary microvascular dysfunction, affects both early relaxation and filling pressure, regardless of the presence or the absence of LV hypertrophy [57]. Unlike the β-blockers of the first and second generations, which have a contradictory effect on the coronary flow, the drugs of the last generation, such as nebivolol, improve CBFR, possibly reducing coronary resistance [58]. Nebivolol also improves the filling pressure by changing the ratio between the early diastolic transmitral stream and the early ring velocity E/Em, regardless of LV hypertrophy presence. After 3 months of treatment, nebivolol significantly increased the values of Em and decreased E/Em ratio, which correlated with CBFR increase. Thus, the association between the changes in CBFR and filling pressure indicates a possible mechanism for coronary microvascular function improvement and the stimulation of NO release with myocardium caused by nebivolol [59]. The effect of nebivolol on DD may also be related to treatment duration. So with the duration of therapy up to 4 weeks, the effect of nebivolol was unreliable, but it was very significant with prolonged treatment [60]. In this regard, the development of research aimed at nebivolol mechanism influence study during long-term administration is of particular interest. In general, the favorable hemodynamic profile of nebivolol and such positive effects as the preservation of HO, the decrease of peripheral vascular resistance and the improvement of LV DD, have clinically significant benefits at myocardial systolic and diastolic function disorders that appear at the beginning of the cardiovascular continuum. The meta-analysis of 2015 evaluated the efficacy of β-blockers and their effect on mortality and morbidity among the patients with CHF-GEF [61]. They determined that the treatment with β-blockers correlated significantly with lower mortality from all causes. The subgroup analysis showed that the positive effect of β-blockers on survival was found among middle-aged people (<75 years) [62]. The prophylactic effects of β-blockers in the development of supraventricular arrhythmias (SVA) were established among the patients undergoing revascularization by BS method. Andrews et al. conducted the meta-analysis to determine the effectiveness of digoxin, verapamil and β-blockers for the prevention of SVA after coronary artery bypass surgery (CABS). It was determined that digoxin and verapamil did not reduce the likelihood of SVA after BS, and the likelihood of SVA development among the patients receiving β-blockers was significantly lower as compared to control [63].

CONCLUSION:

In contrast to the work aimed at the study of the patients with CHF-LEF, there is the shortage of large scientifically based studies demonstrating morbidity and mortality, as well as the effect of pharmacotherapy on CHF course and progression

improvement among the patients with CHF-GEF. Also there is the effect of pharmacotherapy on CHF course and progression improvement among the patients with CHF-GEF. Several ongoing tests with existing and new drugs try to complete these tasks. Such as: "The comparative effects of nebivolol and carvedilol on left ventricular diastolic function among the elderly patients with heart failure and preserved ejection fraction: the study protocol for a randomized controlled study.", "The improvement of pulmonary hypertension treatment personalization associated with diastolic heart failure". Currently, the advantage of nebivolol use among the patients with chronic heart failure has not been proven and requires larger randomized clinical trials or specially planned work among certain categories of patients.

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