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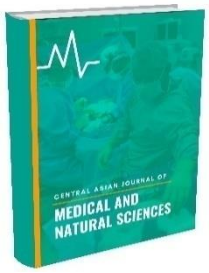

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Effects of Beta-Adrenoblockers in Patients with Cardiovascular Disease

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Abstract: The article presents a review of literature data and current clinical guidelines on the use of beta-adrenoblockers in the complex therapy of cardiovascular diseases at different stages of cardiovascular continuum.

Key words: beta-adrenoblockers, metoprolol CR/XL, cardiovascular continuum.

Introduction. Beta-adrenoblockers are the most long used class of cardiovascular drugs and have long been a major component of pharmacotherapy for almost all stages of cardiovascular continuum, the first of which in terms of chronology and role in pathogenesis and one of the most important in terms of primary prevention opportunities of the whole set of cardiovascular events is arterial hypertension (AH). Moreover, it is the example of AH, paradoxically, that can demonstrate both the evolution of views on the class of drugs as a whole and the main benefits of its individual members that influence the choice of a particular drug. In general, it can now be considered proven that there are indications for prescribing beta-blockers for AH and that the use of modern highly selective lipophilic long-acting beta-blockers such as metoprolol succinate in its delayed-release form cannot be equated with the use of "old" drugs, especially atenolol. As for contraindications and side-effects, both are not true for the entire class of beta-blockers and should also be considered when choosing therapy.

The 2013 European guidelines for the treatment of AH retained beta-adrenoblockers as first-line therapy for uncomplicated AH [1]. This means that experts do not currently deny the use of beta-adrenoblockers in the initial treatment of AH, especially if there is a clinical indication for it. Such indications are not clearly formulated in the current guidelines; the decision on the choice of therapy is left to the treating physician. However, it is known that beta-adrenoblockers are more effective in young people with signs of hyperactivity of the sympathetic nervous system - the so-called hyperkinetic type of circulation. Given the ability of beta-adrenoblockers to reduce plasma renin activity, they are also more effective in the high-renin forms of AH. Despite the fact that in persons with metabolic risk factors, especially those with metabolic syndrome, other groups of drugs are now taking precedence, this category of patients also often has signs of sympathetic nervous system hyperactivity, primarily sinus tachycardia, which also forms the clinical background for prescribing beta-adrenoblockers. It is in these situations that the choice of a particular drug is particularly

important, and in this case it should be made in favour of drugs with high selectivity or vasodilator properties. A number of epidemiological studies - the Framingham, NHANES I and CASS - have shown a positive correlation between heart rate (HR) and cardiovascular mortality. For example, the CASS study, which included a 15-year follow-up of 25 000 patients, analysed the long-term prognostic value of resting heart rate in relation to the course of coronary heart disease (CHD). It was convincingly shown that an increase in resting HR has a negative impact on quality of life and life expectancy. In contrast, a lower resting HR in patients with stable CHD is associated with a lower risk of cardiovascular complications and mortality. Current national and international guidelines on the treatment of stable angina pectoris postulate the need to achieve an optimal HR of 50-60 bpm [8]. To date, beta-adrenoblockers are still the most effective means to reduce HR.

According to the European and Russian guidelines on the treatment of AH, indications for the choice of beta-adrenoblockers as first-line therapy are a combination of AH with CHD (angina pectoris or condition after myocardial infarction) and/or chronic heart failure (CHF). Today, this tactic is absolutely justified due to the unconditional pathogenetic justification and a large evidence base for the use of beta-adrenoblockers in these categories of patients. Beta-adrenoblockers are the first-line antianginal therapy in patients with stable CHD, including STEMI. They act directly on the heart and reduce heart rate, myocardial contractility, atrioventricular conduction and ectopic activity. In addition, they can increase perfusion of ischaemic areas by prolonging diastole and increasing vascular resistance and non-ischaemic myocardial areas. Thus, the pathogenetic mechanism of the antianginal effect of beta-adrenoblockers today does not need additional argumentation, and the positive effect in relation to secondary prevention of myocardial infarction (MI) has long been turned into the gold standard of evidence-based medicine. Studies proving the protective effect of beta-adreno-blockers on the risk of recurrent heart attack and prognosis in general in patients who have had a heart attack have been published for quite some time, and their results are now rarely cited in the literature. For example, few people today can accurately reproduce the results of the Stockholm trial of metoprolol in post-MI patients, in which a total of 301 patients were shown to have an incredible, at the time, 23 % reduction in overall mortality, 55 % reduction in recurrent MI and 59 % reduction in sudden death compared to placebo. These days, these data look particularly impressive, as the number of patients in modern trials is usually in the thousands, and a reduction in overall mortality is very rarely achieved in their performance. Nevertheless, even this class of drugs, which has such a long and extensive evidence base, has not escaped attempts to critically rethink its leading place in the secondary prevention of cardiovascular events. On the one hand, it is recognized that treatment with beta-adrenoblockers leads to a 30% reduction in the risk of cardiovascular death and a 30% reduction in the incidence of MI, and that not prescribing beta-adrenoblockers for patients with CHD because of relative contraindications leads to a more than 3-fold increase in mortality compared with patients receiving therapy with this group of drugs [5]. However, on the other hand, a recent retrospective analysis of data from the REACH registry showed that in patients with risk factors for CHD alone, either a known history of CHD or known CHD without a history of CHD, beta-adrenoblocker use was not associated with a lower risk of cardiovascular events. The results of this analysis suggest that more research is needed, particularly in the context of modern cardiovascular disease regimens and the introduction of other secondary prevention drugs, such as statins and angiotensin converting enzyme inhibitors (ACEIs), into everyday practice. Research into the use of beta-adrenoblockers in CHF has also long been classic. Beta-adreno-blockers should be used in all patients with CHF with an ejection fraction of less than 40%, who have no contraindications for this group of drugs. The rationale for the use of beta-adrenoblockers in the treatment of CHF is the blockade of the sympathoadrenal system (SAS), which is in a state of chronic hyperactivation in decompensated patients and determines the poor prognosis of these patients. The activity of SAS progressively increases in parallel with the severity of CHF, and from stage II of the disease or functional class (FC II) negative de-adaptive

properties of catecholamines become predominant. Therefore, the use of beta-adrenoblockers becomes the most reasonable and effective in patients with clinically significant CHF II-IV class. It has been proved that hyperactivation of SAS contributes to a significant increase in both the risk of sudden death and death from decompensation progression. Therefore, the main purpose of beta-adrenoblockers in the treatment of patients with CHF is to improve prognosis and reduce mortality. It has now been shown that beta-adrenoblockers have a blocking effect on some other neurohormonal systems responsible for the progression of CHF - the renin-angiotensin system, the endothelin system and the cytokine system.

Conclusions: Thus, beta-adrenoblockers in the treatment of CHF are complex neurohormonal modulators that optimally complement the effects of ACE inhibitors. Recommended drugs for the treatment of CHF are carvedilol, bisoprolol, slow-release metoprolol succinate, nebivolol. According to the results of multicentre studies COPERNICUS, CIBIS II, MERIT HF, SENIORS, these drugs are proven to reduce the rate of overall and cardiac mortality, cases of decompensation of CHF and repeated hospital admissions for CHF. Suffice it to recall the MEJA1T-OT study [8], in which it was shown for the first time that adding metoprolol to treatment in patients with CHF and an ejection fraction reduction of less than 40% leads to a significant improvement in prognosis. The study included almost 4000 patients who received up to 200 mg per day with stable haemodynamics and was one of the few studies to be stopped early due to the convincing evidence of a benefit of active therapy compared to placebo. There was a 38% reduction in cardiovascular mortality, a 49% reduction in CVD mortality and a 41% reduction in sudden death. At the same time, the MEYT-ET study included patients with CHF of different etiologies, which makes it fair to recommend the use of metoprolol in patients with CHF not only associated with CHF. This is also true for patients with AH, who may develop CHF without overt manifestations of CHD or a history of MI. It is important to remember that in both CHD and CHF, beta-adrenoblockers are rarely used as monotherapy, but are usually prescribed in combination with ACE inhibitors or angiotensin II receptor blockers (ARBs) and diuretics. In congestive CVD, spironolactone is also an important component of therapy, whereas in patients with angina pectoris, a combination with calcium antagonists (CAs) is often used. However, let us return to the discussion of the prescription of beta-adrenoblockers in patients with AH. There is another category of patients for whom they are clearly indicated - those with resistant AH in whom the combination of renin-angiotensin system blockers with ACs and diuretics is not sufficiently effective. Indeed, the list of drugs recommended for the treatment of AH includes five classes - ACE inhibitors, BRAs, diuretics, ACs and beta-adrenoblockers. As the first two groups are combined with each other very rarely and only for specific indications, if the triple combination fails, beta-adreno-blockers should be prescribed as a fourth drug if they have not been previously prescribed and the patient has no absolute contraindications. It should not be assumed that the use of beta-adrenoblockers in the treatment of resistant AH is of little significance given the relative rarity of this condition. Clinical trial data.

AH - arterial hypertension, CHF - chronic heart failure, MI - myocardial infarction Unproprietary name: metoprolol. Dosage form: delayed-release coated tablets. Indications for use.

Arterial hypertension. Angina pectoris. Stable symptomatic chronic heart failure with impaired left ventricular systolic function (as adjunctive therapy to mainstream treatment of chronic heart failure). Reduced mortality and recurrent infarction rate after acute myocardial infarction. Cardiac rhythm disorders, including supraventricular tachycardia, reduced ventricular contraction rate in atrial fibrillation and ventricular extrasystoles. Functional heart disorders accompanied by tachycardia. Prevention of migraine attacks. Contraindications. II and III degree atrioventricular block, decompensated heart failure, permanent or intermittent therapy with inotropic drugs acting on beta-adrenoreceptors, clinically significant sinus bradycardia, sinus node weakness syndrome, cardiogenic

shock, severe peripheral circulatory disorders, including at risk of gangrene, arterial hypotension. Betaloc ZOC is contraindicated in patients with suspected acute myocardial infarction with HR less than 45 beats per minute, PQ interval greater than 0.24 seconds or systolic blood pressure less than 100 mmHg. Known hypersensitivity to metoprolol and its components or other (J-adrenoblockers. Intravenous administration of slow calcium channel blockers such as verapamil is contraindicated in patients receiving (5-adreno-blockers. Under 18 years of age (efficacy and safety have not been determined). Caution: Degree I atrioventricular blockade, Prinzmetal angina pectoris, bronchial asthma, chronic obstructive pulmonary disease, diabetes mellitus, severe renal insufficiency, severe hepatic insufficiency, metabolic acidosis, co-administration with cardiac glycosides. Side effects. Betaloc ZOC is well tolerated by patients, side effects are generally mild and reversible. To estimate the frequency of cases the following criteria were applied: very common (>10%), common (1-9.9%), infrequent (0.1-0.9%), rare (0.01-0.09%) and very rare (<0.01%). Cardiovascular system. Frequent: bradycardia, orthostatic hypotension (very rarely accompanied by syncope), cold extremities, palpitations; Infrequent: temporary worsening of heart failure symptoms, AV block of degree I; cardiogenic shock in patients with acute myocardial infarction, edema, pain in the heart; Rare: other conduction disorders, arrhythmias; Very rare: gangrene in patients with previous severe peripheral circulatory disorders.

Central nervous system. Very common: increased fatigue; Frequent: dizziness, headache; Infrequent: paraesthesia, seizures, depression, decreased concentration, drowsiness or insomnia, nightmares; Rare: increased nervous excitability, anxiety; Very rare: amnesia/memory disturbances, depression, hallucinations. Gastrointestinal tract. Often: nausea, abdominal pain, diarrhea, constipation; Infrequent: vomiting; Rare: dry mouth. Liver. Rare: liver dysfunction; Very rare: hepatitis. Skin. Infrequent: skin rash (as psoriasis-like urticaria), increased sweating; Rare: hair loss; Very rare: photosensitization, exacerbation of psoriasis. Respiratory organs. Often: dyspnea on exertion; Infrequent: bronchospasm; Rare: rhinitis. Sensory organs. Rare: visual disturbances, dry and/or irritated eyes, conjunctivitis; Very rare: ringing in the ears, disorders of taste. Musculoskeletal system. Very rare: arthralgia. Metabolism. Infrequent: increase in body weight. Blood. Very rare: thrombocytopenia. Epidemiological studies have shown that resistance to therapy, i.e. the ineffectiveness of three or more drugs at adequate doses, is common in 2 to 40% of patients in specialist departments and in more than 5% of patients with AH in general. Given the high prevalence of AH, the absolute number of individuals who need to be prescribed beta-adrenoblockers for BP control alone may be higher than the proportion who have had a MI or have CHF.

A separate group of AH patients for whom beta-adrenoblockers are indicated are those with persistent atrial fibrillation, in whom beta-adrenoblockers form the basis for reducing ventricular contractions and are used to reduce BP in the first place. This group is small but clinically significant. Long-acting drugs are indicated in these patients, e.g. metoprolol, whose dosage form is able to maintain a constant concentration in the blood, which is essential given the possibility of circadian fluctuations in atrioventricular conduction velocity. Beta-adrenoblockers, although they are one of the oldest classes of cardiovascular drugs, still hold a leading position in the treatment of cardiovascular pathology. They are applicable at almost all stages of the cardiovascular continuum, highly effective and most commonly prescribed as part of the first-line drugs. For each of the modern beta-adrenoblockers, there are clinical situations where they are most effective, and metoprolol succinate is the leader in the number of these situations.

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