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# ANTIHYPERTENSIVE THERAPY WITH BETA-BLOCKERS AT THE PRESENT STAGE OF CARDIOLOGY DEVELOPMENT

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**Key words:**

arterial hypertension, antihypertensive therapy, beta-blockers.

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**The purpose of the work** – carry out a review of published clinical studies on the effect of antihypertensive therapy with beta-blockers on the course of arterial hypertension.

**Conclusions.** Data from the literature testify that the rapid growth in recent years in the frequency of prescribing vasodilatory  $\beta$ -ABs is due to their presence of a number of advantages compared to conventional cardioselective drugs (without vasodilator properties). The advantages of vasodilating  $\beta$ -ABs include the absence of a negative effect on lipid and carbohydrate metabolism, the possibility of their safe combination with thiazide and thiazide-like diuretics, a proportional decrease in central and peripheral blood pressure, a minimal effect on bronchial patency, the absence of a negative effect on erectile function, a decrease in frequency cardiovascular complications in patients with arterial hypertension.

**Ключові слова:**

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**АНТИГІПЕРТЕНЗИВНА ТЕРАПІЯ БЕТА-АДРЕНОБЛОКАТОРАМИ НА СУЧАСНОМУ ЕТАПІ РОЗВИТКУ КАРДІОЛОГІЇ**

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**Мета роботи** – здійснити огляд опублікованих клінічних досліджень впливу антигіпертензивної терапії бета-адреноблокаторами на перебіг артеріальної гіпертензії.

**Висновки.** Дані літератури засвідчують, що стрімке зростання упродовж останніх років частоти призначення вазодилатуючих бета-адреноблокаторів ( $\beta$ -АБ) обумовлена наявністю у них ряду переваг порівняно зі звичайними кардіоселективними препаратами (без судинорозширювальних властивостей). До переваг вазодилатуючих  $\beta$ -АБ відносять відсутність негативного впливу на показники ліпідного та вуглеводного обміну, можливість їх безпечної комбінації з тіазидними і тіазидоподібними діуретиками, пропорційне зниження центрального та периферичного артеріального тиску, мінімальний вплив на бронхіальну прохідність, відсутність негативного впливу на еректильну функцію, зниження частоти кардіоваскулярних ускладнень у пацієнтів з артеріальною гіпертензією.

## Introduction

The International Society of Hypertension guidelines recommend pharmacological antihypertensive therapy for adults with systolic blood pressure (SBP) >140 mmHg and/or diastolic blood pressure (DBP) >90 mmHg or DBP between 80 and 89 mmHg, pharmacological antihypertensive treatment is recommended in case of high risk of cardiovascular complications, which is determined by a history of cardiovascular disease (CVD), diabetes, kidney disease, 10-year risk of CVD >10 %, and age  $\geq$ 65 years. High blood pressure (BP) is a leading risk factor for CVD, and hypertension is the world's leading cause of reduced life expectancy and increased disability. Starting from 115/75 mmHg, each increase of 20 mmHg in SBP or 10 mmHg in DBP is associated with a doubling of the risk of a fatal cardiovascular event. The prevalence of hypertension is high worldwide and continues to rise. At the threshold level of SBP/DBP >140/90 mm Hg, the prevalence of hypertension worldwide is 31 %, which is approximately 1.4 billion adults.

## The aim of the study

Carry out a review of published clinical studies on the effect of antihypertensive therapy with beta-blockers on the course of arterial hypertension.

## Main part

Currently, antihypertensive therapy includes the following five classes of drugs: beta-blockers ( $\beta$ -blockers), angiotensin II receptor blockers (ARBs), angiotensin converting enzyme inhibitors (ACEIs), calcium channel blockers (CCBs) and diuretics, including thiazide and thiazide-like diuretics. Beta-blockers are recommended as a priority treatment for patients with hypertension in combination with coronary heart disease, HF, or for those who need heart rate control and antiarrhythmic correction according to the guidelines of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH) [20]. However, some national guidelines, such as those of the National Institute for Health and Care Excellence

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(NICE) [16], do not recommend  $\beta$ -ARB as first-line therapy for hypertension.

These recommendations are based on the results of studies, but it should be noted that randomised controlled trials (RCTs) have contradictory results regarding the effectiveness of  $\beta$ -ARBs in the treatment of hypertension. For example, in a meta-analysis of RCTs that included patients with hypertension, blood pressure lowering with all classes of antihypertensive drugs was accompanied by a significant reduction in the incidence of stroke and cardiovascular events (myocardial infarction (MI), HF, and CVD death) [17]. The results indicate that the reduction in the incidence of cardiovascular complications is associated with a decrease in blood pressure, rather than with specific properties of the drug [17].

A Cochrane systematic review, which included 91561 patients with hypertension, concluded that  $\beta$ -ARBs are inferior to other classes of antihypertensive drugs in the prevention of CVD (fatal and non-fatal CHD, cerebral stroke, HF) and mortality [17]. An important aspect of the analysed trials is that they allowed for the prescription of one or more additional drugs to achieve the target blood pressure level. Therefore, different combined treatments are often compared, rather than two different classes of drugs.

In actual clinical practice, there are limited data to assess the clinical and prognostic efficacy of  $\beta$ -ARB monotherapy compared with each individual class of antihypertensive drugs.

For example, although M. R. Bronsert et al [3] noted that  $\beta$ -ARBs provide blood pressure reduction comparable to other classes of antihypertensive drugs, the study did not compare the effectiveness of different classes in reducing the risk of mortality or CVD-related outcomes.

In 2022, C. Foch et al. published the results of a study on the effectiveness of  $\beta$ -ARB compared with other antihypertensive drugs in reducing all-cause mortality and cardiovascular events [6]. Patients with hypertension were allocated to one of five antihypertensive monotherapy groups:  $\beta$ -ARB, ACEIs, ARBs, BCCs, and diuretics. A total of 44,404 patients were prescribed  $\beta$ -AB (75 % atenolol), 132,545 ACEIs, 12,018 ARBs, 91,731 BCCs, and 106,547 diuretics. The risk of all-cause mortality was lower in patients treated with ACEIs, ARBs, and BCCs. There were no differences in the risk of cardiovascular mortality in patients treated with  $\beta$ -ARBs, ARBs, BCCs, and diuretics, whereas patients treated with ACEIs had a lower risk [6].

There were no statistical differences in the risk of MI in patients treated with ACEIs and ARBs compared with  $\beta$ -ABs. However, in the diuretic cohort, the risk of MI was significantly lower compared with  $\beta$ -AB. With regard to the risk of stroke, there were no differences between the group of patients treated with  $\beta$ -ARBs and those treated with ACEIs, ARBs, or BCCs. However, the risk of stroke in patients treated with diuretics was lower compared with the  $\beta$ -AB cohort [6].

Another RCT showed that  $\beta$ -ARBs provide blood pressure reduction comparable to other classes of antihypertensive drugs [3]. The study also demonstrated that a 10/5 mm Hg reduction in SBP/DBP could prevent

8 deaths, 17 strokes, and 6 cases of CHD for every 1000 patients treated for 5 years, regardless of the therapeutic class used [17]. Thus, the reduction in the incidence of these complications is due to a decrease in blood pressure rather than to the specific properties of the chosen antihypertensive therapy.

Of interest is the meta-analysis of RCTs in which  $\beta$ -ARB therapy demonstrated the same efficacy as other classes of antihypertensive therapy in preventing all-cause mortality and myocardial infarction, and is less effective in preventing stroke [17]. Furthermore, a meta-analysis of clinical trials showed that first-line antihypertensive drugs, including ACEIs, dihydropyridine ARBs,  $\beta$ -ARBs, BRAs, and diuretics, were effective in reducing cardiovascular events compared with placebo; however, differences between drug classes were generally small in terms of their association with cardiovascular event reduction [19].

It should be noted that guidelines similar to the NICE recommendations are based on RCTs, which mainly studied atenolol [21]. The majority of patients treated with  $\beta$ -ARBs with high selectivity for  $\beta$ -1 receptors may have had different outcomes.

Beta-adrenergic blockers without vasodilation are associated with a lower reduction in cardiovascular events compared with other classes of antihypertensive drugs, and there is uncertainty in current guidelines regarding the use of  $\beta$ -ABs as first-line treatment for hypertension. The third-generation vasodilating  $\beta$ -ARB nebivolol has a unique beneficial effect on the central and peripheral vascular system. D. M. Huck et al. in 2022 published the results of a study that examined cardiovascular outcomes in patients with hypertension taking nebivolol compared with those taking non-vasodilator  $\beta$ -ARBs, metoprolol and atenolol [10]. The study concluded that the vasodilator  $\beta$ -ARB nebivolol was associated with fewer cardiovascular events compared with non-vasodilator  $\beta$ -ARBs [10].

The first analysis of the comparative risk of cardiovascular complications (CVC) between the  $\beta$ 1-selective antagonist/ $\beta$ 3-agonist nebivolol, a drug with vasodilatory properties, and the conventional cardioselective  $\beta$ 1-ARBs atenolol and metoprolol, which do not have such an effect, was conducted in the United States [1]. The results of this study were published in 2017. The study found an association between nebivolol and a reduction in cardiovascular events compared with atenolol and metoprolol [1]. The primary endpoint was to determine the risk of hospitalisation due to the development of various CVD events (MI, congestive chronic heart failure, stroke, angina). Patients taking metoprolol and atenolol had a 68 % and 105 % higher risk of hospitalisation due to the development of the above CVD events than patients taking nebivolol [1]. In patients treated with nebivolol, the risk of hospitalisation due to certain CVD events was significantly lower than in patients treated with atenolol, with the exception of stroke and HF (the risk of these complications was also lower with nebivolol, but the rate did not reach statistical significance) [1].

It should be noted that this RCT did not cover the issue of combination therapy of hypertension, which was the impetus for the completion of a new study in 2018 and publication of the results in the Journal of

the American College of Cardiology [5]. The aim of the study was to compare the risk of hospitalisation due to CVD in patients with hypertension who were on combination therapy, one of the components of which was nebivolol/atenolol/metoprolol. Patients with hypertension treated with nebivolol, atenolol, and metoprolol in combination with other antihypertensive drugs (one or more additional drugs) were selected from the US medical database for the period from 2007 to 2014. Follow-up lasted  $\geq 6$  months, until the patient discontinued the drug or switched to another  $\beta$ -ARB. Compared with nebivolol, patients taking atenolol and metoprolol had a significantly higher risk of hospitalisation due to CVD, 33 % and 91 % higher, respectively, mainly due to a reduction in the incidence of hospitalisation for MI and angina [5].

These results, based on the analysis of «hard» endpoints, determined the advantages of hypertension therapy based on the use of vasodilating  $\beta$ -ARBs. If the differences in efficacy when using  $\beta$ -ARBs as monotherapy can be explained primarily by certain differences in the pharmacological properties of vasodilating and non-vasodilating drugs, then in combination treatment it is also necessary to take into account the fact that non-vasodilating  $\beta$ -ARBs in combination with renin-angiotensin system blockers have an insufficient additive effect on blood pressure lowering [12]. Thus, the results of the studies demonstrated that patients on mono- or combination antihypertensive therapy based on nebivolol had a lower risk of hospitalisation due to CVD than patients treated with atenolol or metoprolol.

The study by D. M. Huck et al. in 2022 is of significant scientific interest because it was not limited to first-line  $\beta$ -AB monotherapy and included a much longer follow-up period (median 3.7 years) [10]. Importantly, the main conclusion of this study was the beneficial effect of nebivolol on blood vessels [10]. Nebivolol induces vasodilation through stimulation and inhibition of endothelin-1-mediated vasoconstriction by nitric oxide [4, 7, 15], which creates theoretical prerequisites for better SBP control. It should be noted that in this study, there was no significant difference in the median SBP in patients treated with nebivolol compared with other non-vasoactive  $\beta$ -ARBs [10]. Another comparative study of nebivolol and metoprolol also found no difference in brachial BP, but demonstrated a favourable effect of nebivolol on central aortic BP and left ventricular wall thickness [11].

Central aortic blood pressure and central arterial stiffness have been shown to be better prognostic factors for cardiovascular events than brachial blood pressure [2, 11].

In the Cochrane review of  $\beta$ -blockers in hypertension, older generation drugs were inferior to renin-angiotensin system inhibitors and CCBs in reducing stroke [21], but the unique vasodilator properties of nebivolol may significantly affect the incidence of cardiovascular complications. Nebivolol may have a favourable effect on cardiovascular risks, as it has a significant impact on central blood pressure control and aortic stiffness, regardless of brachial blood pressure levels.

Nebivolol has been shown to have a beneficial antioxidant effect and improves glucose and lipid metabolism compared to other  $\beta$ -ARBs [7]. The

favourable effect of nebivolol on total and low-density lipoprotein cholesterol was demonstrated in a RCT comparing nebivolol with metoprolol [15].

The rapidly increasing frequency of prescribing vasodilating  $\beta$ -ARBs in recent years is due to their several advantages over conventional cardioselective drugs (without vasodilating properties). The advantages of vasodilating  $\beta$ -ARBs include the absence of adverse effects on lipid and carbohydrate metabolism, the possibility of their safe combination with thiazide and thiazide-like diuretics, proportional reduction in central and peripheral blood pressure, minimal effect on bronchial patency, no adverse effects on erectile function, and a reduction in the incidence of cardiovascular complications in patients with hypertension.

### Conclusions

Data from the literature testify that the rapid growth in recent years in the frequency of prescribing vasodilatory  $\beta$ -ABs is due to their presence of a number of advantages compared to conventional cardioselective drugs (without vasodilator properties). The advantages of vasodilating  $\beta$ -ABs include the absence of a negative effect on lipid and carbohydrate metabolism, the possibility of their safe combination with thiazide and thiazide-like diuretics, a proportional decrease in central and peripheral blood pressure, a minimal effect on bronchial patency, no negative effect on erectile function, a decrease in frequency cardiovascular complications in patients with arterial hypertension.

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