ARTERIAL HYPERTENSION IN PATIENTS WITH DIABETES MELLITUS – INDIVIDUALIZED CHOICE HYPOTENSIVE DRUGS

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Abstract. Patients with arterial hypertension and diabetes mellitus are at high risk of developing cardiovascular complications. The modern possibilities of pharmacotherapy for patients with hypertension and diabetes mellitus are considered. The evidence base for the use of various classes of antihypertensive drugs in patients of this group for the prevention of cardiovascular complications is presented.

Keywords: arterial hypertension, diabetes mellitus, prevention of cardiovascular complications, beta-blockers

The prevalence of diabetes mellitus (DM) is steadily increasing in both developed and developing countries, primarily due to type 2 diabetes, which accounts for up to 90% of all cases of the disease. The World Health Organization estimates that more than 180 million people worldwide have diabetes, and these numbers are likely to double by 2025. Most patients with diabetes die or become disabled due to cardiovascular complications (CVC). The presence of various variants of carbohydrate metabolism disorders, such as metabolic syndrome (MS) and diabetes, increases the relative risk of cardiovascular mortality, which increases significantly with the combination of metabolic syndrome and diabetes (Fig. 1) [9,11,20].

The leading cause of death in patients with type 2 diabetes are macrovascular complications, the development of which is based on atherosclerotic damage to the main arterial basins, leading to the development of coronary heart disease (CHD) and its complications, cerebrovascular disease and damage to the arteries of the lower extremities. Microvascular complications (retinopathy, nephropathy) are also characteristic of patients with diabetes due to diabetes-specific damage to microvasculature vessels associated with thickening of the basement membranes of capillaries.

The most important factors influencing the risk of cardiovascular complications in patients with type 2 diabetes are the level of blood pressure, the state of carbohydrate and lipid metabolism [7,14,19,20]. The results of a large clinical study UKPDS (U.K. Prospective Diabetes Study) made it possible to identify the most significant risk factors and arrange them in descending order of importance: increased levels of low-density lipoprotein cholesterol (LDL); increased blood pressure (BP); smoking; low levels of high-density lipoprotein cholesterol (HDL); increased levels of glycosylated hemoglobin (HbA1c) [24].

The main goals of treatment for patients with diabetes are to reduce cardiovascular mortality and the risk of developing macro- and microvascular complications. Prevention of cardiovascular complications in patients with diabetes should be aimed at the entire range of risk factors for cardiovascular complications, including lifestyle changes (smoking cessation, regular exercise, weight control, adherence to dietary recommendations), glycemic control with minimal risk of hypoglycemia (level glycated hemoglobin < 6.5%, fasting plasma glucose less than 6.0 mmol/L (108 mg/dL), postprandial plasma glucose less than 7.5 mmol/L (135 mg/dL)), blood pressure and level control blood lipids [1,16,21].

In this regard, the issues of rational choice of medicines, which allow not only to improve the clinical condition of patients, but also to reduce cardiovascular risk, are of particular relevance.

Features of hypertension in patients with diabetes. The risk of developing cardiovascular complications increases by 2 times in patients with diabetes who have hypertension, compared with patients with diabetes who have normal blood pressure levels. In patients with type 1 diabetes, the development of hypertension is directly related to the progression of nephropathy. In type 2 diabetes, the development of hypertension in 80% of cases precedes the development of the disease. Most often, these patients exhibit “essential” hypertension, which is a manifestation of peripheral insulin resistance syndrome.

Elevated blood pressure is associated with a 2–3-fold increase in the absolute risk of cardiovascular mortality in patients with type 2 diabetes compared with individuals without diabetes [7,14,19]. This is evidenced by the results of the MRFIT (Multiple Risk Factor Intervention Trial) study [20]. Another study reported that 35 to 75% of cardiovascular and renal complications in patients with diabetes may be associated with hypertension [9]. All this has led to the fact that patients with diabetes, even without clinical manifestations of atherosclerosis, are equal in risk of developing cardiovascular complications to patients with an established diagnosis of coronary artery disease [19].

The course of hypertension in patients with type 2 diabetes has a number of distinctive features. These patients are more likely to exhibit an increase in pulse pressure, which is associated with a higher risk of developing cardiovascular complications. They are more likely to experience hypertension at night. The absence of a decrease in blood pressure at night is a phenomenon associated with more frequent target organ damage, in particular the heart and kidneys. Patients with diabetes are more prone to orthostatic hypotension, which complicates adequate control of blood pressure levels. They often experience an inadequate increase in blood pressure during physical activity and impaired autoregulation of blood pressure. These differences, in particular, largely determine the higher risk of developing cardiovascular complications in patients with diabetes and hypertension [7,14].

Since the presence of hypertension increases the already initially increased risk of developing cardiovascular complications in diabetes, this category of patients requires strict control of blood pressure levels and achievement of its target values. In accordance with the recommendations of the Russian Medical Society of Arterial Hypertension and the All-Russian Scientific Society of Cardiology (RMOAG/VNOK), the target blood pressure level for patients with diabetes is <130/80 mmHg. [3]. European recommendations set lower blood pressure values - less than 125/75 mmHg. for patients with signs of renal failure or with proteinuria more than 1 g/day [16]. The estimated benefit of reducing SBP below 120 mmHg. Art. in patients with diabetes was not confirmed. According to the results of the ACCORD Blood Pressure Clinical Trial (Action to Control Cardiovascular Risk in Diabetes - 4733 patients, follow-up duration - 4.7 years), intensive blood pressure control (target SBP less than 120 mm Hg) in patients with type 2 diabetes does not have prognostic benefit compared with SBP less than 140 mm Hg. [22]

The choice of antihypertensive drugs is of particular importance, since the presence of diabetes in a patient imposes a number of restrictions on the use of a particular drug. It is necessary to take into account the range of its side effects, possible effects on carbohydrate and lipid metabolism, as well as the presence of concomitant vascular complications in the patient. Therefore, antihypertensive drugs in the treatment of patients with diabetes must meet increased requirements, namely:

• have high antihypertensive activity with a minimum of side effects;

• do not disrupt carbohydrate and lipid metabolism;

• have cardioprotective and nephroprotective effects;

• do not worsen the course of other (non-vascular) complications of diabetes.

In accordance with the recommendations of the RMOAG/VNOK, five classes of antihypertensive drugs with a proven effect on the degree of cardiovascular risk and do not have significant differences in the severity of the antihypertensive effect are currently recommended for the treatment of patients with hypertension - these are ACE inhibitors, angiotensin II receptor antagonists (ARBs), beta-blockers (BAB), calcium antagonists (CA) and thiazide diuretics (Table 1). Each class has its own application features, advantages and limitations associated with the possibility of developing undesirable reactions [3].

According to modern international recommendations, drug therapy for patients with diabetes and hypertension should include angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor antagonists (ARBs) [6,9,13,16,21].

Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers.

The advisability of using ACE inhibitors (captopril, enalapril, lisinopril, perindopril, ramipril, etc.) or ARAs (losartan, valsartan, telmisartan, etc.) in patients with diabetes with hypertension is beyond doubt. There is both theoretical and practical justification for this, since blockade of the renin-angiotensin aldosterone system (RAAS) not only provides control of blood pressure levels, but also explains the whole range of non-hemodynamic effects inherent in ACEIs and ARAs, in particular, their organoprotective properties (Fig. 2) [20].

Evidence of organoprotective properties and reduced mortality as a result of treatment with various ACEIs and ARAs was obtained in a number of international multicenter randomized clinical trials, such as ALLHAT, ANBP2, CAPPP, EWPHE, HOPE, SCAT, STOP-2, UKPDS and many others (Fig. 2) [20].

A contraindication for the use of ACE inhibitors in patients with diabetes is bilateral renal artery stenosis. This complication must be kept in mind in patients with type 2 diabetes with generalized atherosclerosis.

Calcium antagonists do not have an adverse effect on carbohydrate and lipid metabolism and are widely used in patients with diabetes and hypertension. Preference should be given to the AK groups of verapamil and diltiazem, which have the ability to reduce proteinuria. Long-acting dihydropyridine antigens (amlodipine, felodipine, isradipine, etc.) can also be prescribed. Short-acting nifedipine may have adverse effects on the heart (steal syndrome and arrhythmogenic effects) and the kidneys, increasing proteinuria.

Centrally acting drugs. Central sympatholytics cause a hypotensive effect, mainly by reducing the activity of the sympathetic nervous system. Currently, drugs of the first (reserpine, methyldopa) and second (clonidine, guanfacine) generations have limited use, due to the development of adverse reactions such as dizziness, drowsiness, dry mouth.

It should be noted that methyldopa remains a first-line drug for the treatment of hypertension in pregnant women, since its safety for the embryo and fetus has been proven by many years of observations of children whose mothers received the drug during pregnancy [3,21].

he third generation of centrally acting drugs are selective imidazoline receptor agonists moxonidine (Moxogamma®) in tablets of 0.2 mg; 0.3 mg; 0.4 mg and rilmenidine 1 mg tablets.

The antihypertensive action of moxonidine and rilmenidine is based on specificity for imidazoline receptors of neurons located in the ventrolateral nuclei of the medulla oblongata. By reducing the activity of the sympathetic nervous system, imidazoline receptor agonists lower blood pressure and reduce heart rate. The antihypertensive effect of these drugs is also accompanied by additional effects associated with stimulation of imidazoline receptors in the tissues of the kidneys, adrenal glands, pancreas, adipose tissue and carotid glomeruli.

The beneficial pharmacological effects of moxonidine and rilmenidine make them useful both in monotherapy and as part of combination therapy for hypertension in patients with metabolic syndrome and diabetes mellitus. This is due to the fact that the basis of the action of these drugs is a decrease in the activity of the sympathetic nervous system, which plays an important role in the pathogenesis of hypertension, especially in patients with type 2 diabetes with severe insulin resistance, since hyperinsulinemia itself is accompanied by sympathetic activation. On the other hand, the favorable metabolic profile of imidazoline receptor agonists and their ability to positively influence glucose and lipid metabolism are important. Of important clinical significance is the fact that imidazoline receptor agonists have a beneficial effect on the metabolism of carbohydrates and lipids, weaken insulin resistance and improve glucose tolerance, and also reduce plasma levels of triglycerides and cholesterol [4,15,18].

Moxonidine in a daily dose of 0.2 to 0.6 mg and rilmenidine in a daily dose of 1 mg have high antihypertensive efficacy and good tolerability. The antihypertensive effect lasts up to 24 hours, which allows them to be prescribed once a day. The antihypertensive effect is enhanced when combined with small doses of thiazide diuretics and RAAS blockers [15].

Moxonidine and rilmenidine, unlike clonidine and other α2-adrenergic receptor agonists, have a good spectrum of tolerability. They have a weak affinity for α2-adrenergic receptors, the stimulation of which causes such side effects as sedation and dry mouth.

In accordance with the RMOAG/VNOK recommendations, imidazoline receptor agonists are recommended as one of the components of combination therapy for long-term treatment of hypertension in patients with obesity, diabetes mellitus and metabolic syndrome [3].

Thiazide diuretics (hydrochlorothiazide) have a range of undesirable metabolic effects: they impair carbohydrate tolerance, increase insulin resistance, and have a hyperlipidemic effect. Impaired carbohydrate tolerance appears 2-3 years after the start of continuous treatment with these drugs. When prescribing these drugs to patients with diabetes, it may be necessary to adjust the dose of sugar-lowering drugs. In addition, thiazide diuretics worsen the filtration function of the kidneys, reducing the glomerular filtration rate. Small doses of hydrochlorothiazide (6.25-25 mg) do not affect carbohydrate, lipid and purine metabolism, which allows them to be safely combined with other antihypertensive drugs in patients with diabetes, including as part of fixed combinations [15,21].

Thiazide-like diuretics (indapamide, indapamide retard) do not affect carbohydrate and lipid metabolism, which makes them safe to take in patients with diabetes. Indapamide at an average therapeutic dose acts as an antihypertensive drug due to its vasodilatory effect and does not have a diuretic effect. With long-term therapy, it does not affect carbohydrate and lipid metabolism, does not worsen renal function, and is even able to reduce microalbuminuria, which makes it safe for the treatment of hypertension in patients with diabetes.

Beta-blockers (BAB). The high effectiveness of using this group in patients with hypertension to reduce the risk of cardiovascular diseases is limited by their unfavorable metabolic effect on carbohydrate and lipid metabolism.

Current recommendations for the management of patients with hypertension limit the use of beta blockers as first-line drugs in patients with hypertension with multiple metabolic risk factors, including abdominal obesity and impaired glucose tolerance. Adverse metabolic effects are associated with β2-adrenergic receptor blockade. In this regard, patients with diabetes can be prescribed only beta blockers with high cardioselectivity.

Theoretical assumptions about the potential benefits of cardioselective blockers in patients with metabolic syndrome, made on the basis of experimental data, have been confirmed by clinical studies

[10,12]. In particular, in the largest study UKPDS (U.K. Prospective Diabetes Study Group), which included 1148 patients with diabetes mellitus, it was shown that in patients with type 2 diabetes suffering from hypertension, the cardioselective beta blocker atenolol significantly improves life prognosis, not being inferior in this regard to an ACE inhibitor – captopril [24].

BBs are a very heterogeneous group of drugs in their pharmacological effects, within which there are significant differences in pharmacokinetics and pharmacodynamics regarding two main indicators - cardioselectivity and lipophilicity.

A common property of all beta blockers is competitive antagonism of β1-adrenergic receptors. Along with the blockade of β1-adrenergic receptors, beta-blockers can also block β2-adrenergic receptors. Drugs used for long-term therapy of hypertension can be conveniently divided into the following groups depending on β1-adrenoselectivity, as well as the presence or absence of additional vasodilating properties:

1. Beta blockers without vasodilating properties:

a) non-selective (propranolol, nadolol, oxprenolol, sotalol, timolol, etc.);

b) β1-selective (atenolol, betaxolol, bisoprolol, metoprolol, etc.).

2. Beta blockers with vasodilating properties:

a) non-selective (carvedilol, bucindolol, pindolol, labetolol, etc.);

b) β1-selective (nebivolol, celiprolol, etc.)

A special place among beta blockers is occupied by bisoprolol (Bisogamma®), which has high cardioselectivity, superior to metoprolol, as was shown in the work of K. Brixius et al. If we take the ability to block β1 receptors in carvedilol as 1, then for metoprolol this figure will be 6, for bisoprolol – 21 [5]. Also, being amphophilic, that is, soluble in both fats and water, bisoprolol has two elimination routes - renal excretion and hepatic metabolism. This ensures greater safety of use in patients with concomitant liver and kidney damage, elderly patients, as well as a low likelihood of drug interactions.

In terms of antihypertensive effect, bisoprolol is not only not inferior to other beta blockers, but is superior to them in a number of indicators. Thus, in the BISOMET study, it was shown that bisoprolol is comparable to metoprolol in terms of the degree of reduction in blood pressure at rest, but significantly exceeds it in its effect on the level of systolic blood pressure and heart rate during physical activity [8]. The effectiveness of bisoprolol in reducing cardiovascular risk in combination with the absence of negative effects on carbohydrate metabolism has been proven in large randomized clinical studies, including the well-known CIBIS-II (Cardiac Insufficiency Bisoprolol Study II), TIBBS (Total Ischemic Burden Bisoprolol Study), DECREASE-IV, etc. [2,6,17,25].

It is important to note that bisoprolol has a good safety profile. Almost all researchers note good tolerability of bisoprolol, incl. with a combination of arterial hypertension and diabetes mellitus. It has virtually no effect on indicators such as the level of glycosylated hemoglobin, fasting glucose levels, does not cause changes in the blood lipid spectrum in patients with diabetes, and does not require dose adjustment of hypoglycemic agents [6].

The ability to take the drug once a day contributes to higher patient adherence to treatment. For hypertension, bisoprolol can be used not only as monotherapy, but also in combination with other antihypertensive drugs.

Due to the importance of achieving rapid and sustained BP control, most patients with hypertension and diabetes require combination therapy to achieve target BP, and guidelines based on risk stratification

approaches consider combination therapy as a first-line pharmacological treatment option. In many patients, monotherapy has shown to be ineffective or delayed in achieving blood pressure control, which significantly increases the incidence of heart attacks, strokes and deaths.

Taking into account two circumstances - the high tissue activity of the renin-angiotensin system and the high salt sensitivity of patients with diabetes, the most effective antihypertensive therapy is a combination of an ACE inhibitor and a thiazide-like diuretic. The results of the ADVANCE study showed that additional administration of a combination of perindopril and indapamide to patients with type 2 diabetes leads to a reduction in overall mortality by 14%, cardiovascular mortality by 18%, cardiovascular complications by 14%, and renal complications by 21% [23].

The presence of microalbuminuria in patients with type 1 and 2 diabetes is an indication for antihypertensive therapy that causes blockade of the RAAS regardless of blood pressure level, i.e., the appointment of ARB II or ACE inhibitors, including in combination with thiazide-like diuretics in small doses [21].

If monotherapy with ACE inhibitors (or ARBs) is insufficiently effective, a diuretic should be added to therapy, taking into account the glomerular filtration rate (GFR):

– with EF more than 30 ml/min per 1.73 m2 – thiazide,

– with EF less than 30 ml/min – loop.

Combined antihypertensive therapy for patients with diabetes, including an ACEI or ARB and a thiazide/thiazide-like diuretic, requires regular monitoring of CP and serum potassium levels.

Conclusion

Thus, hypertensive patients with diabetes are at high risk of developing cardiovascular complications. Prevention of the development of cardiovascular complications in this group of patients requires complex pharmacotherapy, including drugs that have proven their effectiveness in relation to cardiovascular risk and do not worsen the course of diabetes mellitus. An important place among them is occupied by biologically active substances, one of which is bisoprolol (Bisogamma®), a highly selective drug that has unique hydro-lipophilic properties, a long half-life and an associated convenient single dosage regimen. A favorable safety profile and the absence of negative metabolic effects allow its use in the treatment of patients with hypertension in combination with diabetes mellitus to reduce the risk of cardiovascular complications.

Literature

1. Algorithms for specialized medical care for patients with diabetes mellitus Edited by I.I. Dedova, M.V. Shestakova (2nd edition) Moscow 2006

2. Mychka V.B., Sergienko V.B., Gornostaev V.V. et al. Effect of bisoprolol therapy on cerebral perfusion in patients with metabolic syndrome // Arterial hypertension. Adj. to Consilium Medicum 2003 v. 09; No. 5.

3. Russian Medical Society for Arterial Hypertension (RMAS), All-Russian Scientific Society of Cardiologists (VNOK). Diagnosis and treatment of arterial hypertension. Russian recommendations (fourth revision), 2010.

4. Chazova I.E., Mychka V.B. New opportunities in the treatment of patients with metabolic syndrome (results of the ALMAZ study). Systemic Hypertension 2006(8); 2.

5. Brixius K. et al. Nebivolol, bucindolol, metoprolol and carvedilol are

devoid of intrinsic sympathomimetic activity in human myocardium // British Journal of Pharmacology 2001;133: 1330–1338

6. CIBIS-II Investigators and Committees. The Cardiac Insufficiency

Bisoprolol Study II (CIBIS-II): a randomized trial // Lancet 1999; 353: 9-13.

7. Cooper M. The prevalence of hypertension in patients with diabetes. In: Hypertension and diabetes (Ed. Mogensen CE). Lippincott Williams & Wilkins, London, 2003, 3–9.

8. Haasis R, Bethge H Exercise blood pressure and heart rate reduction 24 and 3 hours after drug intake in hypertensive patients following 4 weeks of trearment with bisoprolol and metoprolol: a randomized multicentre double–blind study (BISOMET) // Eur Heart J 1987 ; 8: 103–113.

9. Haffner M., Lehto S., Ronnemaa T. et al. Mortality from coronary heart disease in subjects with 2 diabetes and in nondiabetic subjects with and without prior myocardial infection // N. Engl. J. Med., 1999, 339, 229–234.

10. Heinemann I., Heise T., Ampudia J. et al. Four week administration of an ACE inhibitor and a cardioselective beta-blocker in healthy volunteers: no influence on insulin sensitivity // Europ. Heart J 1995; 25:595–600.

11. Hunt KJ, Resendez RG, Williams K et al. San Antonio Heart StudyNational Cholesterol Education Program versus World Health Organization metabolic syndrome in relation to all-cause and cardiovascular mortality in the San Antonio Heart Study // Circulation. 2004 Sep 7;110(10):1251-7.

12. Janka H.U., Ziegler A.G., Disselhoff G. et al. Influence of bisoprolol on blood glucose, glucosuria, and haemoglobin A1 in noninsulin dependent diabetics // J Cardiovasc Pharmacol. 1986; 8:Suppl 11:S96–9.

13. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomized trials in the context of expectations from prospective epidemiological studies // BMJ. May 23, 2009;338:b1665.

14. Parving H–H. Hypertension and diabetes: the scope of the problem // Blood pressure 2001; 10(Suppl 2): 25–31.

15. Pater C, Bhatnagar D, Berrow JP et al. A novel approach to

treatment of hypertension in diabetic patients – a multicenter, double-blind, randomized study comparing the efficacy of combination therapy of Eprosartan versus Ramipril with low dose Hydrochlorothiazide and Moxonidine on blood pressure levels in patients with hypertension and associated diabetes mellitus type 2 – rationale and design [ISRCTN55725285] // Curr Control Trials Cardiovasc Med. 2004; 5(1): 9.

16. Rydén Lars, Standl E. Guidelines on diabetes, pre-diabetes, and cardiovascular diseases. Eur Heart J 2007 Suppl 9 (suppl C): 30-74

17. Schouten O., Poldermans D., Visser L. et al. Fluvastatin and bisoprolol for the reduction of perioperative cardiac mortality and morbidity in high-risk patients undergoing non-cardiac surgery: rationale and design of the DECREASE-IV study // Am Heart J. 2004; Dec; 148:6:1047–52.

18. Sharma A M, Wagner T and Marsalek P. Moxonidine in the treatment of overweight and obese patients with the metabolic syndrome: a postmarketing surveillance study // J Human Hypertension 2004; 18: 669–675.

19. Sowers JR, Epstein M, Frohlich ED. Diabetes, hypertension, and cardiovascular disease // An Update Hypertension 2001; 37: 1053 1059.

20. Stamler J, Vaccaro O, Neaton JD, et al. for the Multiple Risk Factor Intervention Trial Research Group. Diabetes, other risk factors, and 12 year cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial // Diabetes Care 1993; 16:434–444.

21. Standards of Medical Care in Diabetes-2009. American Diabetes Association // Diabetes Care 2009: Vol.32, Suppl1, S13-60.

22. The ACCORD Study Group. Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med 2010; 362:1575-85

23. The ADVANCE Collaborative Group. Intensive Blood Glucose Control and Vascular Outcomes in Patients with Type 2 Diabetes // N Engl J Med. June 12, 2008;358:2560-72.

24.U.K. Prospective Diabetes Study Group. Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type II diabetes: UKPDS 39 // Br Med J 1998; 317: 713-720.

25. Von Arnim T Medical treatment to reduce total ischemic burden: Total Ischemic Burden Bisoprolol Study (TIBBS), a multicenter trial comparing bisoprolol and nifedipine // J Am Coll Cardiol 1995;25:231-8