

## **EFFECTIVENESS ASPECTS OF COMBINATION ANTIHYPERTENSIVE THERAPY IN OLDER PATIENTS WITH TYPE 2 DIABETES MELLITUS**

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**Abstract.** Arterial hypertension and diabetes mellitus are comorbid diseases, they are interconnected not only by common pathophysiological mechanisms of development, but also by similar cardiovascular complications. This relationship is due to the activation of the renin-angiotensin-aldosterone system, which underlies the remodeling of the cardiovascular system and the development of complications. According to current clinical guidelines, ACE inhibitors are the drugs of choice for the treatment of hypertension in combination with diabetes mellitus. The use of ACE inhibitors in patients with hypertension and diabetes is accompanied by a decrease in the relative risk of cardiovascular outcomes and mortality. This article presents the results of a clinical study of the combined drug Co-ramaz (ramipril and hydrochlorothiazide) in elderly patients with arterial hypertension and diabetes mellitus.

*Key words: hypertension, type 2 diabetes mellitus, blood pressure, endothelial function, elderly patients, fixed combination, ramipril, hydrochlorothiazide.*

**Relevance.** It is known that in patients with type 2 diabetes mellitus (type 2 DM), the incidence of arterial hypertension (AH) is 2 times higher than the general population, amounting to 60–80%, in type 2 DM [25]. In patients with type 2 diabetes, the appearance of hypertension, as a rule, indicates the development of nephropathy in them, and its frequency increases as the severity of kidney damage increases. According

to the Framingham study, severe cardiovascular complications (CVS) in combination with hypertension and type 2 diabetes are observed 5 times more. The mortality rate from CVC is 2.5–7.2 times higher, and when clinical symptoms of nephropathy appear, it is naturally 37 times higher than in comparable age groups [1]. The presence of type 2 DM in AH patients allows them to be classified as a very high-risk group [2]. In persons suffering from type 2 diabetes, elevated blood pressure values are observed 2 times more often than in patients with other diagnoses [24]. According to the results of different authors, the incidence of AH among DM patients ranges from 16.5 to 75% [19]. According to the National State Registry of DM (Russian Federation), the incidence of hypertension in type 2 DM is about 80–90% [14]. Numerous authors have proven the effectiveness of renin-angiotensin-aldosterone blockers, angiotensin-converting enzyme (ACE) inhibitors, in the treatment of hypertension and vascular complications in type 2 diabetes. The use of drugs of this class in some cases is accompanied by a hypoglycemic state and a decrease in insulin resistance. This made it possible to study their role in the mechanisms regulating the level of glycemia, the sensitivity of peripheral tissues to insulin, and the secretion of insulin by the pancreas.

As is known from numerous studies, hypertension is a widespread cardiovascular risk factor both in the general population and among the elderly [1, 2]. A number of randomized clinical trials have demonstrated an association between antihypertensive therapy and a significant reduction in cardiovascular morbidity and mortality in elderly hypertensive patients [3–11]. However, in everyday clinical practice, only a small number of elderly patients can achieve adequate control of blood pressure and effective prevention of cardiovascular complications [12, 13]. This discrepancy may be due to the fact that in the elderly, the combination of multiple cardiovascular risk factors, target organ damage, associated clinical conditions, and marked variability in blood pressure (BP) makes optimal pressure control difficult. Sustained, long-term BP control is an important goal of antihypertensive therapy in elderly patients. According to the results of recent meta-analyses of large clinical trials, the drugs of choice for this age group of

patients may be blockers of the renin-angiotensin-aldosterone system, in particular ACE inhibitors [16, 17]. These drugs have demonstrated high antihypertensive efficacy and good tolerability in elderly patients with AH and type 2 DM [18–24].

**Purpose of the study:** to evaluate the effect of combination therapy - ramipril and hydrochlorothiazide (Co-ramas 5/25) on the clinical and hemodynamic parameters of the cardiovascular system, lipid and carbohydrate metabolism, quality of life, endothelial function in patients with arterial hypertension and type 2 diabetes mellitus. old age.

**Materials and research methods.** Clinical studies were performed on the basis of the Department of Cardiology and Gerontology, with the course of interventional cardiology and arrhythmology, the Center for the Development of Professional Qualifications of Medical Workers.

III hypertension with various degrees of arterial hypertension and compensated type 2 diabetes mellitus. The diagnosis of hypertension was established according to the EOK criteria (2019), the diagnosis was verified in the presence of elevated blood pressure numbers - systolic blood pressure  $\geq 140$  mm Hg, diastolic AP  $\geq 90$  mm Hg, during, 3 consecutive visits to the doctor, as well as with blood pressure values of more than 135/85 with home measurements. The diagnostic criteria for the presence of DM were the criteria recommended by WHO [ Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia. report of WHO / IDF Consultation, 2014].

III hypertension; voluntary written informed consent of the patient to participate in the study. Exclusion criteria: symptomatic arterial hypertension, exacerbation of chronic or acute inflammatory diseases during the study, severe liver and kidney disease, recent myocardial infarction, high functional classes of chronic heart failure (III - IV).

All examined patients were divided into 2 groups by blind randomization methods. The design of the study included the use in patients of group 1 (control group, n = 40) against the background of standard therapy (hypotensive, antiplatelet, hypolipidemic, hyperglycemic) as an antihypertensive drug, the use of amlodipine at a dose of 5 to 10 mg per day, with a single dose in the morning application, 2-group

(main, n = 40) dynamic observation. Patients of the main group on the background of standard therapy (antihypertensive, antiplatelet, hypolipidemic, hypoglycemic) were prescribed a fixed combination of ramipiril with hydrochlorothiazide (Co-ramas 5/25, ASPHARMA, Turkey) as an antihypertensive drug. The groups were comparable in terms of age, gender, history of disease duration. The final surrogate points of dynamic observation were: a stable hypotensive effect reaching the target values, the absence of undesirable metabolic (in relation to carbohydrate, lipid, electrolyte metabolism), the absence of potentiation of target organ damage caused by hypertension, and the absence of undesirable side effects affecting the quality of life examined patients.

The duration of the study was 3 months (12 weeks), after which a second study was conducted. The following research methods were carried out: ECHOCG with the determination of parameters characterizing the structural and functional state of the myocardium. The following parameters of intracardiac hemodynamics were studied: end-diastolic and systolic sizes (EDD, ESD), thickness of the left ventricular (LV) walls: interventricular septum (VTRV) and posterior wall of the left ventricle (PVSLV) in diastole. Systolic function was determined by the following values: end-systolic and end-diastolic volumes of the left ventricle. IN According to recommendations (2015) ejection fraction (EF LV), defined as the ratio of the amount of blood ejected by the LV into aorta in every cardiac cycle LV volume, expressed in percent, calculated on Simpson method (Simpson J.S., 1989, called the disk method) was determined in two positions - four- and two-chamber apical positions.

Evaluation of endothelial function of the peripheral arteries, based on ultrasound techniques for measuring the diameter of the vessel and occlusal plethysmography with an assessment of peripheral vascular resistance. Vessel diameter was measured with a 7-8 MHz linear probe equipped with a Doppler function, determined by the relative increase in the diameter of the brachial artery during tests with reactive hyperemia (D.S. Celermajer, 1992). The image was evaluated in two modes: one-dimensional and two-dimensional. Measurements were made at rest and after compression, followed by an

assessment of endothelium-independent vasodilation based on the dynamics of arterial diameter recovery after compression. Dilatation of the artery by more than 10% of the initial diameter against the background of reactive hyperemia was considered a normal reaction, less than 10% to 0 was considered as a criterion for endothelial dysfunction, less than 0 as paradoxical vasoconstriction.

To study the lipid spectrum of the blood, the content of: total cholesterol (Cholesterol), triglycerides (TG), high-density lipoprotein cholesterol (HDL), low and very low-density lipoprotein cholesterol (LDL-C and VLDL-C), atherogenic coefficient (CA) was determined by the enzymatic method on biochemical analyzer " Daytona " (RANDOX, UK).

Statistical analysis was carried out using the statistical software package " SPSS 11.0". The obtained data were described as  $M \pm SD$  (M is the arithmetic mean, SD is the standard deviation) or  $M \pm m$  (m is the standard error of the mean). The statistical significance of the results obtained when comparing the mean values was determined by Student's t test ( t ) with the calculation of the error probability (P) when checking the normality of distribution by standard methods.

**Results of the study and their discussion.** Research results by assessment of the effect of combination therapy - ramipril and hydrochlorothiazide with the drug (Co-ramas 5/25) were carried out taking into account the assessment of the dynamics according to the data determined at the start of the study and after 12 weeks of therapy. The assessment was carried out taking into account clinical (Table 1.), hemodynamic parameters of the cardiovascular system, an assessment of antihypertensive efficacy was carried out in terms of achieving target blood pressure values, an assessment was made of the dynamics of the effect on endothelial function.

### **Table 1.**

## **Clinical characteristics of elderly patients with arterial hypertension and type 2 diabetes mellitus in dynamic observation groups**

Indicators	General group , n=80	1 control group (amlodipine) n =40	Group 2 main (ramipril + GHT) n =40	media n test	
				2	P
Wed. age (years)	68 , 3 ±11.2	67.9 ±10.6	65.3 ± 9.5	.58	.058
Duration of hypertension (years)	1 8.5±7.2	17.2±6.3	19.8±7.8	.20	.273
Duration of type 2 diabetes (years)	10, 3 ±7.2	11.2 ±4.3	9.8 ± 1.8	.1	.06
GARDEN (mm RT. Art.)	156.2 ±16.6	159 ±14.7	161.3 ± 17.9	.49	.485
DBP (mm RT. Art.)	90.9± 11.2	90.2±11.4	91.5±11.1	.10	.749
BP mean (mm Hg)	112.6 ±11.6	111.1±11.6	114.1±11.6	.26	.613
BMI ( kg /m <sup>2</sup> )	30.7± 4.6	30.7±3.8	30.6±5.3	.01	.921

We also studied indicators of metabolic neutrality in terms of lipid and carbohydrate metabolism (Table 2.).

An important aspect was to determine the effect of antihypertensive therapy on the quality of life in elderly patients with arterial hypertension and type 2 diabetes mellitus.

**Table 2.**

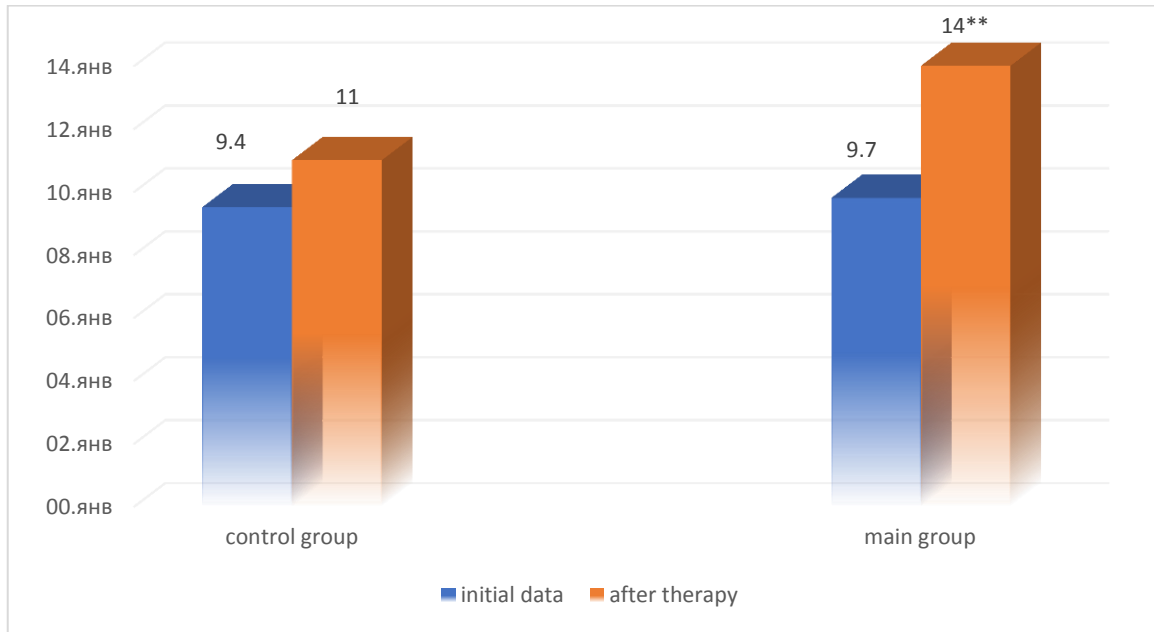
**Dynamics of blood lipid levels during therapy (M ± m )  
(baseline numerator and post-treatment denominator)**

Indicators	1 control group (amlodipine) n =40	Group 2 main (ramipril + HCT) n =40
	Exodus	Exodus
	After treatment	After treatment
Total cholesterol, mg / dl	223.0±6.5	217.5±5.0
	167.1±7.3**	194.0±7.7*
TG, mg/ dl	202.2±13.0	207.1±10.7
	165.0 ± 13.6**	188.2 ± 15*
LDL cholesterol, mg/ dl	146.2±5.9	141±4.5
	121.4 ± 4.4*	131±5.5
HDL cholesterol, mg/ dl	38.4±1.2	40.3 ± 1.2
	42.0 ± 1.7*	41.4 ± 2.4
KA, rel . units	4.0±0.3	4.1 ± 0.18
	3.1 ± 0.2	3.7 ± 0.24
Blood sugar, mmol \ l	8.4 ± 1.5	7.9 ± 1.25
	6.5 ± 0.3	6.0 ± 0.4

Note: \*  $P < 0.05$ , \*\*  $P < 0.01$  – significance of the difference relative to the initial value.

After a three-month course of treatment in patients of both groups, there was a significant decrease in the level of total cholesterol (in the main group of the group by 33% (  $p < 0.001$ ), in the control group by 12% ( $p < 0.05$ ), by 21% ( $p < 0, 01$ ) in the main group and by 8% in the control group, there is a decrease in LDL. Along with this, there is an increase in the content of HDL by 10% (  $p < 0.05$ ) in the main group and only by 3.5% in the control group . significantly decreased after therapy in patients of the main group by 22.5% (  $p < 0.01$ ) and in the control group by 10% ( $p < 0.05$ ).

Against the background of ongoing therapy in the main group of patients, there is a significant decrease in heart rate from  $86.0 \pm 7.0$  to  $65.2 \pm 4.0$  beats/min ( $p < 0.05$ ), a decrease in clinical severity according to the clinical status assessment scale from  $4, 7 \pm 2.1$  to  $2.5 \pm 1.5$  points ( $p < 0.05$ ). In the control group with HR- $85.5 \pm 8.2$  to  $73.2 \pm 5.9$  ( $p < 0.05$ ) and a decrease in clinical severity from  $4.65 \pm 2.1$  to  $2.82 \pm 1.71$  points, respectively.



Note: \*\*  $p < 0.01$  significance in relation to baseline values

**Fig.1. EZVD indicators before and after the therapy (%)**

Dynamics of indicators of endothelium -dependent vasodilation (EDVD) during therapy is shown in Fig.1. As can be seen from the figure, positive dynamics was noted in both groups, i.e. an increase in the basal diameter of the brachial artery was noted, but a more significant increase was observed in the main study group, that is, an increase in the basal diameter of the brachial artery in relation to the initial data was 44% ( $p < 0.01$ ), and in the control group by 11%. Endothelial dysfunction is largely due to the inclusion of immune mechanisms in the pathogenesis of the disease.

**Table 3**



**Assessment of ECHO CG parameters before and after behavioral therapy**

**(M±m)**

Indicators	1 control group (amlodipine) n =40		Group 2 main (ramipril + HCT) n =40	
	Befo re therapy	After Therapy	Before therapy	After Therapy
<b>TMZhP, mm</b>	1.09 ±0.14	1.0±0.14	1.19±0. 14	9.7±0.1 *
<b>TZSZh, mm</b>	1.05 ±0.11	1.02±0.1	1.18±0. 12	1.1±0.1 0
<b>KDR, mm</b>	5.34 ±0.50	5.2±0.4	5.4±0.4 8	5.0±0.4 1
<b>KSR, mm</b>	3.44 ±0.53	3.3±0.53	3.5±0.5	3.3±0.4
<b>BWW, mm</b>	141.7 ±32.0	140.1±3 0.0	143.1± 27.1	140.1± 25.1
<b>KSO, mm</b>	53.4 ±20.9	51.2±19	55.2±2 1.3	49.2±1 9.0*
<b>EF%</b>	63.6 ±31.0	64.5±31. 5	61.3±9. 7	65.3±7. 8

*Note: \* p < 0.05 significance relative to baseline*

An analysis of the results of echocardiography showed a relative positive trend after the therapy, but it should be emphasized that a significant decrease in end systolic volume (ESV) and interventricular septal thickness (IVSD) occurs in the group of patients who received combination therapy.

According to the 2009 VNOK recommendations, one of the groups of drugs recommended for people of this age group is calcium antagonists (CA) [16]. Based on this, this study directly compared the antihypertensive efficacy of the classic antihypertensive drug of the calcium antagonist long-acting drug amlodipine with the fixed combination of the ACE inhibitor ramipril with hydrochlorothiazide in elderly patients with type 2 diabetes mellitus. A meta-analysis of the SHEP, STOP-HYPERTENSION, EWPHE, CASTEL, Syst-Eur studies in elderly patients with ISAH demonstrated a reduction in the incidence of stroke, cardiovascular complications, and heart failure with active antihypertensive therapy [19, 22].

There are currently very few studies demonstrating the effectiveness of ACE inhibitors on cardiovascular morbidity and mortality in the elderly. In a randomized, double-blind, placebo-controlled HOPE study in people over 55 years of age, ramipril reduced the incidence of myocardial infarction, stroke, and mortality from them. A post-marketing study of ramipril CARE, which included people over 65 years of age, including those with ISAH, showed the efficacy and safety of ramipril, which is associated with the results obtained in this study [31, 32]. At the end of the 12-week therapy in the main group, not only more effective control of office blood pressure levels was noted, but also a significantly more pronounced decrease in pressure throughout the day. Prior to treatment, SBP in -group 1 was higher than in group 2, but the differences were not statistically significant. When analyzing the effect of drugs on office indicators of SBP and DBP, a comparable hypotensive effect was found. Significant changes in office BP were observed in both groups after 12 weeks of treatment. In particular, the antihypertensive effect of combination therapy was longer lasting, as evidenced by a significantly more pronounced reduction in blood pressure. The results obtained are consistent with the data of previous studies of therapy with the use of ACE inhibitors in people under the age of 65 years [31-34].

**Thus,** the fixed combination of ramipril and hydrochlorothiazide (Co-ramas) is not only a highly effective antihypertensive drug in patients with stage 1 and 2

hypertensions, it also has a vasoprotective effect, manifested by the restoration of the vasodilating function of the endothelium.

High efficiency throughout the day with a single dose, good tolerance with a low incidence of side effects makes the drug a popular and attractive drug for use in wide clinical practice.

IN connection with high level global cardiovascular risk and high prevalence of hypertension as one of the main factors that determine this risk, in older age it is extremely important to provide patients 65 years and older effective treatment for this disease. Features of the pathophysiology of hypertension, the presence of concomitant diseases and conditions, high risk development of adverse events in background of therapy, drug interactions, reduced adherence to therapy significantly complicate this task. IN at the same time, the possibility of safely achieving BP control with reduced risk of cardiovascular complications has been confirmed in a number of RCTs. Fixed combinations containing antihypertensive drugs with proven effectiveness, including in group of elderly patients, allow to realize this possibility in real clinical practice.

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