

**CARDIOPROTECTIVE AND METABOLIC EFFECTS OF ANTIHYPERTENSIVE THERAPY IN PATIENTS WITH SUCH COMORBIDITIES AS ARTERIAL HYPERTENSION, TYPE 2 DIABETES MELLITUS, AND OBESITY**

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Today, high rates of growth of such chronic diseases as hypertension, type 2 diabetes mellitus and obesity are noted in the world. The combination of these pathologies increases the risk of developing fatal cardiovascular complications and cardiac mortality tenfold. A reduction in systolic blood pressure of every 10 mmHg, as shown in the UKPDS study (1998), was associated with a 15% reduction in mortality. The most expedient and justified for now is the appointment for complex treatment of patients with comorbid pathology, antihypertensive drugs that inhibit excessive activation of the renin-angiotensin-aldosterone system (RAAS), in particular, ACE inhibitors and ARB II. This article highlights the main cardioprotective and metabolic properties of these groups of drugs and the specifics of their appointment, taking into account concomitant pathology.

**Key words:** arterial hypertension, type 2 diabetes mellitus, obesity, ramipril, telmisartan.

**Connection of the publication with planned research works.**

The work is a fragment of the research project “To determine the features of immunocytokine imbalance in comorbid patients with arterial hypertension and type 2 diabetes and cardiovascular and renal complications”, state registration № 0123U101711.

**Introduction.**

Presently, the world is facing high rates of occurrence of such chronic diseases as arterial hypertension (AH), type 2 diabetes mellitus (T2DM), and obesity (OB). The combination of AH and T2DM multiplies the risk of developing life-threatening cardiovascular complications tenfold [1-4]. A decrease in systolic blood pressure (BP) by every 10 mmHg has been proven to reduce mortality by 15% according to the UKPDS study (1998) [5].

The most up-to-date treatment concept in comorbid patients is an individual approach, which accounts for the presence of complications or the risk of complications with appropriate differentiated tactics [6-9]. Thus, the first step in treating patients at high risk of developing vascular complications involves normalizing blood pressure. Present-day tactics include antihypertensive therapies that are effective for a particular patient and do not cause side effects [10-12]. As for patients with moderate vascular risk, it is appropriate to use medications with metabolic neutrality, namely angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) [13, 14].

Patients with a slight increase in blood pressure, who are expected to normalize it with monotherapy, are recommended to start with ARB. Moreover, it is worth emphasizing that these medications should be used as part of combination therapy, as their nephroprotective effect has been well documented [15, 16].

Currently, antihypertensive agents that inhibit excessive activation of the renin-angiotensin-aldosterone system (RAAS), in particular ACEIs and ARBs, are the most expedient and reasonable for the complex treatment

of patients with such comorbidities as AH, T2DM, and obesity.

The major efferent mediator of RAAS is angiotensin II, but ACEIs are unable to fully inhibit angiotensin II synthesis because they do not affect alternative mechanisms of its formation and may cause some side effects (fig. 1).

ARBs considerably reduce the effects of angiotensin II regardless of its synthesis routes and do not cause bradykinin-related side effects (fig. 2).

**The aim of the study.**

To determinate the cardioprotective and metabolic effects of ACEI (ramipril) and ARB (telmisartan) in comorbid patients representing the Ukrainian population.

**Object and research methods.**

56 patients with AH, T2DM, and OB were examined and treated at the Government Institution “L.T. Malaya Therapy National Institute of the National Academy of Medical Sciences of Ukraine”.

The average age of the patients concerned totaled 64.4±1.1 years old, of whom 24 (43%) were men and 32 (57%) were women. The diagnosis of AH was set according to the recommendations of the International Society of Hypertension (ISH), 2020 [17]. The diagnosis of T2DM and obesity was based on clinical, instrumental, and biochemical criteria according to the recommendations of

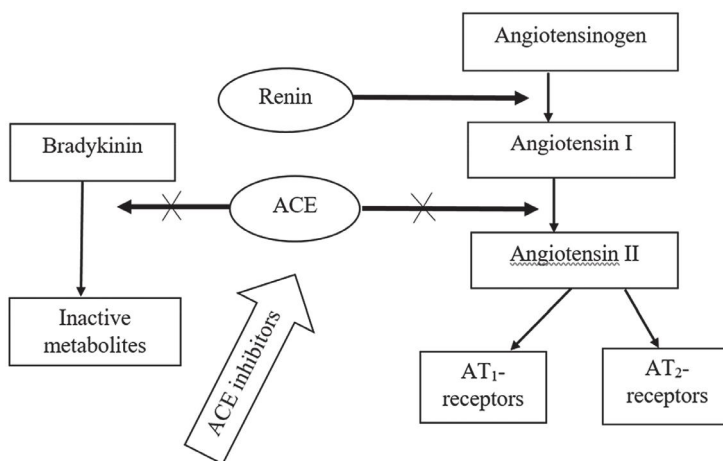


Figure 1 – Mechanism of action of ACE inhibitors.

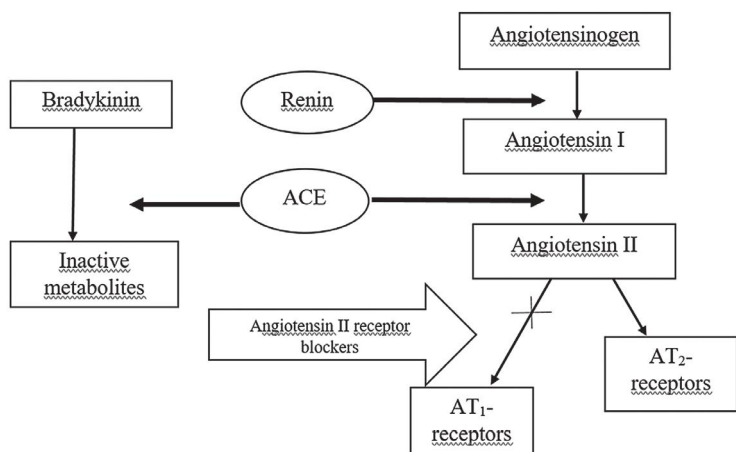


Figure 2 – Mechanism of action of angiotensin II receptor blockers.

WHO experts and the European Society of Endocrinology [18]. All patients were classified into groups: Group 1 comprised 27 patients with AH, T2DM, and grade I OB who received 10 mg of ramipril per day; Group 2 comprised 29 patients with AH, T2DM, and grade I OB who received 40 mg of telmisartan per day. All patients were also treated with standard therapy, which included bisoprolol at an average dose of 5 mg and metformin at an average dose of 1000 mg. Patients were examined before starting therapy and 3 months afterward.

The degree of compensation of carbohydrate metabolism was assessed by glucose levels according to the glucose oxidase method, and glycosylated hemoglobin (HbA1c) according to the photometric method with a commercial test system (Reagent LLC, Ukraine). Serum insulin levels were determined by an enzyme-linked immunosorbent assay using a commercial Insulin Elisa Kit test system (Monobind, USA).

The level of total cholesterol (TC) and high-density lipoprotein (HDL) was determined in heparin-stabilized blood serum by the peroxidase method using the Cholesterol Liquicolor reagent kit, and TG enzymatic colorimetric assay using the Triglycerides GPO reagent kit (Human, Germany). The atherogenicity coefficient (AC) was determined by the following equation:

$$AC = \frac{TC - HDL}{HDL};$$

$$VLDL \text{ level (mmol/L): } VLDL = \frac{TG}{2.2 \times 0.45};$$

$$HDL \text{ level (mmol/L): } HDL = TC - (VLDL + HDL).$$

An echocardiographic study was performed according to the standard method with a Radmir ultrasound machine (Ultima PRO 30), Kharkiv, Ukraine. The following parameters of the left ventricle (LV) were determined in the M-mode: end-diastolic dimension (EDD), cm; end-systolic dimension (ESD), cm; left ventricular posterior wall thickness (LVPWT), cm; interventricular septal thickness (IVST), cm. The end-diastolic volume (EDV) and end-systolic volume (ESV), ml, was estimated by the Simpson method (1991), after which the left ventricular ejection fraction (LVEF), %, was calculated.

LV myocardial mass was determined by the formula of R. Devereux et al:

$$1.04 \times [(a+b+c)^3 - c^3] - 13.6,$$

where as a – IVST; b – LVPWT; c – EDD.

The left atrium (LA) was also assessed in cm between the LA posterior wall and the posterior aortic wall in the parasternal image by the long axis.

The data were statistically evaluated using parametric methods to calculate the mean and standard deviation. Epi Info (TM) 3.5.1 software kit for epidemiological studies was used to assess the significance of clinical outcomes. Absolute risk (AR), %, relative risk (RR), and odds ratio (OR) were analyzed to calculate the confidence interval (CI) for RR and OR, as well as the reliability of the partial distribution by the chi-squared test with the Mantel-Haenszel method. Correspondence between groups with a distribution close to normal was assessed using Pearson's chi-squared test. Differences at  $p < 0.05$  were considered statistically significant.

### Research results and their discussion.

The comorbid patients with AH, T2DM, and concomitant obesity we've examined belong to the high cardiovascular risk group, among whom ACEIs reduce cardiovascular morbidity and mortality, whereas ARBs have a similar effect. Moreover, comparing the effect of these two groups of medications in a similar patient population is of great interest.

Two groups of patients were examined and treated: Group 1 consisting of 27 patients with AH, T2DM, and grade I OB who received 10 mg of ramipril per day; Group 2 consisting of 29 patients with AH, T2DM, and grade I OB who received 40 mg of telmisartan per day. It is worth noting that all patients also underwent standard therapy, which included bisoprolol at an average dose of 5 mg and metformin at an average dose of 1000 mg. Along with the prescribed treatment, patients were advised to follow the non-drug treatment recommendations, namely, diet therapy aimed at reducing body weight and lowering blood pressure to target levels. Patients were also advised to increase physical activity, mainly by walking at a fast or moderately fast pace for at least 45 minutes per day.

It was found that following complex antihypertensive treatment for three months, the levels of systolic blood pressure (SBP) (by 19.6%)  $p < 0.05$ , diastolic blood pressure (DBP) (by 15%)  $p < 0.05$ , and heart rate (HR) (by 9%) decreased significantly (table).

As for echocardiographic characteristics, the following levels decreased: EDV by 25.5%  $p < 0.05$ , ESV by 17.3%  $p < 0.05$ , EDD by 24.0%, LVMM by 8.3%; EF increased by 6% compared to the pretreatment values.

Thus, ongoing treatment of patients with comorbidities proved a positive effect of ramipril and telmisartan on structural and functional parameters of LV and EF. However, no significant differences were found between such parameters as fasting blood glucose, HbA1c, insulin, TC, TG, and HDL, while a significant reduction in LDL, AC, and BMI levels after treatment was found.

A summary of the findings suggests that patients with AH and concomitant T2DM and OB are treated equally effectively with telmisartan as with ramipril, and this medication is less likely to cause angioedema. The choice between telmisartan and ramipril will depend on physicians' preferences and individual patient sensitivity. The data obtained are consistent with global data on the beneficial effect of ACEIs. Thus, several large-scale global trials (CONSENSUS I, SOLVD, SAVE, AIRE, TRACE, etc.) have demonstrated both a significant clinical effect and an impact on hemodynamics and myocardial re-

modeling, as well as a substantial improvement in the quality of life of patients [19-21]. Multiple clinical trials involving about 150.000 patients have convincingly demonstrated that ACEIs reduce mortality and prevent the occurrence of heart attack, stroke, and heart failure in patients with high cardiovascular risk.

Several studies have shown that prolonged use of ARBs in comorbid patients was associated with a reduction in mortality or hospitalization in patients with low EF or those who could not tolerate ACEIs. Compared with ACEIs, ARBs decreased the incidence of vascular complications in high-risk patients with AH, concomitant T2DM, and OB [22-23]. The main class effect of this group of agents includes stable blood pressure control. Moreover, several studies have shown additional organ-protective effects of sartans: cardioprotective (LIFE, JIKEI-HEART), nephroprotective (IRMA II, IDNT, MARVAL, RENAAL, DETAIL), neuroprotective (MOSES, ACCESS), as well as a positive effect on glycemic control (VALUE, LIFE, ALPINE, NAVIGATOR) [24].

**Conclusions.**

Treatment of arterial hypertension in patients with type 2 diabetes mellitus and obesity with ramipril or telmisartan as standard therapy has demonstrated a positive effect on the structural and functional parameters of the left ventricle and ejection fraction (p<0.05), which may subsequently prevent the development and progression of vascular complications.

Furthermore, the neutral effect of ramipril and telmisartan on carbohydrate metabolism in the examined patients was determined.

A significant decrease in the level of VLDL was found among the lipid spectrum parameters in comorbid patients.

Complex treatment of patients with comorbidities has proven a significant reduction in body mass index.

**Table – Performance dynamics under complex treatment combined with ramipril or telmisartan in patients with AH and concomitant T2DM and obesity**

Parameter	Before treatment n=56	After a 3-month treatment	
		I group (n=27)	II group (n=29)
1	2	3	4
SBP, mmHg	159.4±3.0	128.3±0.7*	127.2±0.7*
DBO, mmHg	92.4±1.8	79.3±0.8*	79.3±0.8*
Heart rate, bpm	76.8±2.1	70.1±1.0	68.9±1.4
EDV, ml	180.4±3.3	144.4±3.9*	135.8±1.4*
ESV, ml	82.8±1.6	69.5±2.9*	67.9±1.9*
EDD, cm	6.5±0.1	5.0±0.1	4.8±0.1
ESD, cm	3.2±0.1	2.8±0.1	2.8±0.1
EF, %	47.6±0.8	50.7±0.8*	50.6±0.83*
LVMM, g	263.3±6.9	241.5±5.2*	240.8±6.9*
Insulin, μU/ml	29.3±0.5	28.9±0.4	28.8±0.4
Fasting glucose, mmol/l	7.5±0.4	7.3±0.1	7.1±0.1
HbA1c, %	7.8±0.6	7.6±0.1	7.7±0.1
TC, mmol/l	5.4±0.1	5.21±.1	5.22±0.1
TG, mmol/l	1.9±0.1	1.8±0.1	1.81±0.1
HDL, mmol/l	0.9±0.003	0.93±0.02	1.0±0.01
LDL, mmol/l	3.1±0.1	2.8±0.1*	2.90±0.09*
VLDL, mmol/l	1.7±.02	1.6±0.01	1.6±0.04
AC	3.4±0.1	3.1±0.1	3.1±0.1
BMI, kg/m <sup>2</sup>	31.3±0.2	28.2±0.2*	29.3±0.3*

Notes: \* – difference of parameters in comparison with the control is significant, p<0.05.

**Prospects for further research.**

Comorbid patients with arterial hypertension, type 2 diabetes and obesity are at high risk of developing cardiovascular complications, therefore they are subject to timely diagnosis of early signs of their development and the appointment of timely treatment. This problem requires further study in order to determine the necessary, modern, optimized treatment, taking into account the prevention of the development of cardiovascular and metabolic complications.

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### КАРДИОПРОТЕКТОРНІ І МЕТАБОЛІЧНІ ЕФЕКТИ АНТИГІПЕРТЕНЗИВНОЇ ТЕРАПІЇ У ХВОРИХ НА КОМОРБІДНУ ПАТОЛОГІЮ: АРТЕРІАЛЬНУ ГІПЕРТЕНЗІЮ, ЦУКРОВИЙ ДІАБЕТ 2 ТИПУ Й ОЖИРІННЯ

Дунаєва І. П., Кравчун Н. О., Ільченко І. А.

**Резюме.** Лікування хворих на артеріальну гіпертензію із цукровим діабетом та ожирінням потребує обліку індивідуального ризику ускладнень та застосування відповідної диференційованої тактики, призначення комплексного лікування лікарськими засобами, що гальмують надмірну активацію ренін-ангіотензин-альдостеронової системи, зокрема інгібіторів ангіотензинперетворюючого ферменту та блокаторів рецепторів ангіотензину II, що є найбільш доцільним та обґрунтованим.

*Мета роботи* – визначення кардіопротекторних та метаболічних ефектів іАПФ раміприлу та БРА II – телмісартану у коморбідних пацієнтів – представників української популяції.

*Об'єкт і методи дослідження.* Проведено обстеження і лікування 56 пацієнтів з АГ, ЦД 2 та ОЖ. Середній вік обстежених склав (64,4±1,1) років, із них чоловіків було 24 (43%), жінок – 32 (57%). Діагноз АГ встановлювали за рекомендаціями Міжнародного товариства гіпертензії (International Society of Hypertension – ISH), 2020. Діагноз ЦД 2, ожиріння встановлювали на підставі клінічних, інструментальних, біохімічних критеріїв відповідно до рекомендацій експертів ВООЗ, Європейського товариства ендокринологів. Було проведено порівняльний аналіз застосування різних схем лікування пацієнтів з артеріальною гіпертензією, супутнім цукровим діабетом 2 типу й ожирінням з використанням інгібітору ангіотензинперетворюючого ферменту раміприлу та блокатору рецепторів ангіотензину II телмісартану.

*Результати.* Встановлено, що після проведеного антигіпертензивного лікування протягом трьох місяців достеменно знизилась рівні систолічного артеріального тиску (САТ) (на 19,6%), діастолічного тиску (ДАТ) (на 15%), частота серцевих скорочень (ЧСС) (на 9%). З боку ехокардіографічних характеристик: зменшилися рівні: КДО – на 25,5%, КСО – на 17,3%, КДР – на 24,0%, ММЛШ – на 8,3%; збільшилася ФВ на 6% у порівнянні із зазначеними показниками до лікування.

*Висновки.* Лікування артеріальної гіпертензії у хворих на цукровий діабет 2 типу й ожирінням з включенням до стандартної терапії раміприлу або телмісартану продемонструвало позитивний вплив на структурно-функціональні параметри лівого шлуночка та фракцію викиду, що може в подальшому сприяти запобіганню розвитку і прогресуванню судинних ускладнень.

**Ключові слова:** артеріальна гіпертензія, цукровий діабет 2 типу, ожиріння, раміприл, телмісартан.

### CARDIOPROTECTIVE AND METABOLIC EFFECTS OF ANTIHYPERTENSIVE THERAPY IN PATIENTS WITH SUCH COMORBIDITIES AS ARTERIAL HYPERTENSION, TYPE 2 DIABETES MELLITUS, AND OBESITY

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**Abstract.** Treatment of patients with arterial hypertension with diabetes and obesity requires taking into account the individual risk of complications and the use of appropriate differentiated tactics, and therefore the appointment of complex treatment with drugs that inhibit excessive activation of the renin-angiotensin-aldosterone system, in particular angiotensin converting enzyme inhibitors and angiotensin II receptor blockers, is the most appropriate and justified.

*The purpose of our study* was to determinate of cardioprotective and metabolic effects of ACE inhibitor ramipril and ARB II – telmisartan in comorbid patients – representatives of the Ukrainian population.

*Materials and methods.* 56 patients with AH, T2DM, and OB were examined and treated. The average age of the patients concerned totaled 64.4±1.1 years old, of whom 24 (43%) were men and 32 (57%) were women. The

diagnosis of AH was set according to the recommendations of the International Society of Hypertension (ISH), 2020. The diagnosis of T2DM and obesity was based on clinical, instrumental, and biochemical criteria according to the recommendations of WHO experts and the European Society of Endocrinology. A comparative analysis of the use of different treatment regimens for patients with hypertension, concomitant type 2 diabetes and obesity using the angiotensin-converting enzyme inhibitor ramipril and the angiotensin II receptor blocker telmisartan was conducted.

**Results.** It was found that following antihypertensive treatment for three months, the levels of systolic blood pressure (SBP) (by 19.6%), diastolic blood pressure (DBP) (by 15%), and heart rate (HR) (by 9%) decreased significantly. As for echocardiographic characteristics, the following levels decreased: EDV by 25.5%, ESV by 17.3%, EDD by 24.0%, LVMM by 8.3%; EF increased by 6% compared to the pretreatment values.

**Conclusions.** Treatment of arterial hypertension in patients with type 2 diabetes mellitus and obesity with ramipril or telmisartan as standard therapy has demonstrated a positive effect on the structural and functional parameters of the left ventricle and ejection fraction, which may subsequently prevent the development and progression of vascular complications.

**Key words:** arterial hypertension, type 2 diabetes mellitus, obesity, ramipril, telmisartan.

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#### Conflicts of interest:

Author has no conflict of interest to declare.

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## PECULIARITIES OF CLINICO-PSYCHOPATHOLOGICAL MANIFESTATIONS AND SLEEP QUALITY IN PATIENTS WITH ANXIETY DISORDERS DEPENDING ON THE LEVEL OF STRESS LOAD

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*Modern scientific studies indicate a close connection between psychological distress, anxiety and impaired sleep quality. The assessment of psychopathological symptoms and components of sleep disorders in 81 patients with anxiety disorders of neurotic origin was carried out using clinical-psychopathological, psychodiagnostic and statistical methods. The psychodiagnostic method included the use of the Psychological stress measure (PSM-25), the Symptom Check List-90-Revised (SCL-90-R) and the Pittsburgh Sleep Quality Index (PSQI). All respondents, depending on the level of psychological stress, were divided into 3 groups, representative by age and gender: 1st group (n=25) – patients with a low level of stress, 2nd group (n=29) – with an average level, 3rd group (n=27) – with a high level of stress. In patients of group 1, indicators on all scales of the SCL-90-R questionnaire were significantly lower than in group 2 (p<0,05) and group 3 (p<0,01). Significant differences were found between group 1 and groups 2 and 3 on the PSQI total score and on the scales of subjective sleep quality, sleep latency, sleep duration, and sleep efficiency. Significantly higher indicators were found in group 3 compared to group 1 on the daily dysfunction scale. The severity of obsessive-compulsive symptoms, additional symptoms, hostility, interpersonal sensitivity, and phobic anxiety had a positive correlation with deterioration in sleep duration, subjective sleep quality, sleep efficiency, sleep latency, and daytime dysfunction according to the PSQI (p<0,01). Disturbances during sleep were positively correlated (p<0,01) with the somatization index. The obtained data should be taken into account when conducting personalized pharmacotherapy and psychocorrection of this cohort of patients.*

**Key words:** anxiety disorders, sleep disturbances, the level of stress load, psychopathological symptoms.