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EFFICACY OF COMBINED HYPOLIPIDEMIC AND ANTIHYPERTENSIVE THERAPY, PROGNOSTIC EFFECTS AND CLINICAL INSTRUMENTAL SELECTION CRITERIA FROM THIS THERAPY

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Abstract. The results of multifactor analysis showed that the prognostic effectiveness of combination antihypertensive therapy lisinopryl and amlodipine and hypolipidemic therapy with atorvastatin in men, patients with arterial hypertension stage II depends on a number of pathological factors that are determined during the original clinical

and instrumental examination - weight of the patient, nature of lipid spectrum blood, severity of structural lesions of the left ventricular myocardium mass and vascular endothelial function vasodilatation.

Key words: hypertension, combined antihypertensive and hypolipidemic therapy, performance criteria.

Introduction. Combined antihypertensive therapy is the main treatment strategy for hypertension (HP) [2, 5]. Since 2003, according to American and European guidelines, combined therapy has been indicated for all patients, starting with the 2nd degree hypertension, with a blood pressure of (BP) $\geq 160/100$ mmHg. The European recommendation of 2007, indicates the administration of combined therapy has been expanded, to include high and very high risk of cardiovascular complications [1, 3, 4]. Recently, the problem of determining the clinical and instrumental informative markers that would allow the allocation of groups of patients with prognostic high efficiency to a particular variant of combination antihypertensive therapy is becoming more important. Such an approach potentially provides an opportunity to conduct a thorough prevention of target organs damage and development of various cardiovascular complications in various categories of patients with HP.

Materials and Methods. The study included 97 male patients with essential hypertension stage II, chronic heart failure (CHF) and 0-stage I-II functional class (FC) aged 60 to 88 years (average age was 77.3 ± 0.8) years). Diagnosis of HP was made using the methodological recommendations of the Ukrainian Association of Cardiology in prevention and treatment of hypertension [2008]. 33 patients with HP had concomitant I degree abdominal obesity (AO), 20 were overweight, 21 with lack of body weight, 23 patients with normal weight. The disease lasted for at least 10 years. Body mass was assessed by body mass index (BMI) recommended by WHO. The optimal BMI is considered within the 18,5-24,9 units, overweight is diagnosed when it reaches 25-29,9 units and the obesity from a value of 30,0-34,9. Persons with a BMI less than 18.5 were included in the group with low BMI. All patients received a combination of antihypertensive (ACE-inhibitor – lisinopril 10 mg 1 time / day, AK – amlodipine 5 mg 1 time / day) and hypolipidemic (atorvastatin 10 mg 1 time / day) therapy. A survey that we conducted included patients before the treatment and 6 months after the treatment.

The patients examination included echocardiography – model, two-dimensional mode, pulse mode

and continuous Doppler using the apparatus "LOGIQ 500" sensor 2.5 – 3.5 MHz phased lattice, brachial artery Doppler – through ultrasonic diagnostic scanner "LOGIQ 500". The study of endothelial function was conducted using samples with reactive hyperemia (endothelium vasodilatation, EZVD) and nitroglycerin (endothelium – dependent vasodilatation, UTII). Determination of triglycerides (TG), total cholesterol and HDL in blood was performed by enzyme method using sets from the "Olveks diagnosticum" (Russia) on the machine "Stat Fax 303+" (Germany). Determining the level of glucose in the blood was carried out on an empty stomach, by glucose oxidase method using analyzer "AHKM-01", firm "Kvertimed" using reagents "Kvertimed" (Kharkiv). Determination of serum insulin was performed on the analyzer, enzyme-linked immunosorbent OD "HUMAN Rader" sets using "HUMAN" (Germany) ELISA. For more thorough analysis of prognostic efficiency of applied combined therapy we performed multivariate analysis using stepwise multiple regression (module "Multiple Regression" package StatSoft "Statistica" v. 6.0).

Results and discussion. To conduct a multivariable analysis it was employed the use of a statistical matrix, which consisted of 84 different clinical and instrumental parameters obtained by examining 97 men with stage II HP with different weight. The initial parameter analysis was applied to the total index, which described the prognostic scores effectiveness of the combination therapy for 6 months of treatment. We have developed the method of calculating the actual index. Dimensions of dynamic criteria during 6 months of treatment that were taken to calculate the total assessment prognostic indicator of efficiency, calculated as the 25 percentile in case of negative dynamics and 75 percentile - in case of positive dynamic indicator. The value of the sum of predictive efficiency evaluation consisted of the amount of points that were determined during the second examination after 6 months of treatment. Thus, theoretical minimum score was 0 and the maximum one – 14 points, the average composite score predictive efficacy of the therapy for the cohort surveyed – $6,77 \pm 0,23$ (minimum – 2, maximum –

11, median – 7 and interquartile and scope – 5 and 9).

As independent predictors we consider clinical and instrumental parameters, which were obtained at the initial examination and patients who showed a significant relationship with the source parameter analysis (total index) ($p < 0,05$). The analysis was estimated by calculating the coefficient of multiple regression (coefficient of determination – RI), adequacy - by analyzing residues (Residual Analysis) calculation of the level of significance (p). For the statistical characteristics of individual independent predictors was used a beta coefficient (β coefficient) which showed the force of the impact factor on the output parameter and the nature of the impact (positive coefficient β testified on direct and negative – for feedback). Thus, the results of the analysis showed, as a good indicator of predictive efficacy using combination antihypertensive therapy in men on HP II stage should be considered: the level of HDL cholesterol and TG in plasma value, BMI value, index of left ventricular mass in the calculation the growth rate to 2,7 (IMMLSH 2,7) increased in the value of the diameter of the brachial artery in the sample with decompression, that is EZVD. Various indicators that characterize the severity of the structural remodeling of the left ventricle is the value of IMMLSH 2,7 acted as a predictor of treatment efficacy. Definition of IMMLSH 2,7 in many studies demonstrated the most informative in the diagnosis of left ventricular hypertrophy for persons with altered body weight, since its use is offset by the impact of body-surface area of patients. Further on using linear regression equations, we have calculated the critical value for each independent predictor. For this option for the output value was taken number 9, which amounted to 75 percentile of the sum of which reflects predictive efficacy of treatment. When making estimates it was determined that for HDL cholesterol critical value was ≤ 1 mg / l, $BMI \geq 30$ kg/m², for $TG \geq 3$ mmol/l IMMLSH_{2,7} ≥ 73 g/m^{2,7} and for $EZVD \leq 8$ %.

Certainly a much bigger interest was presented from an analysis of informative forecasting combinations of different predictors that had allowed, primarily, to increase significantly a priori forecast efficiency of combination therapy in men with stage II GC. Maximum forecast informativeness was observed with a combination of four independent predictors – $IMMLSH_{2,7} \geq 73 + 3 + TG \geq BMI \geq 30 + HDL\ cholesterol \leq 1$ (RI=0,71). Results of the analy-

sis showed that the addition of 5 predictors, does not increase the informativeness of the forecast. Thus, the results of the multivariate analysis showed that the predictive efficacy of the proposed combination of antihypertensive and lipid-lowering therapy (lizinopryl + amlodipine + atorvastatin) in men in the GC second stage depends on a number of pathological factors that is determined during the original clinical and instrumental examination – the weight of the patient, nature of defection of lipid spectrum in the blood (hypertriglyceridemia and reduced HDL cholesterol), a structural lesion severity of left ventricular (characterized IMMLSH with the expectation of a growth rate of 2,7) and violation of vascular endothelial function.

Thus, the combination of such factors as $IMMLSH_{2,7} \geq 73 + 3 + TG \geq BMI \geq 30 + HDL\ cholesterol \leq 1$ with a high degree of probability (informative priori prediction is 71 %) may predict a high predictive efficiency of the proposed combination of antihypertensive therapy and provide high priori prognostic effect from treatment.

Conclusions and recommendations for further development. 1. When combined output parameters such as $IMMLSH_{2,7} \geq 73$ g/m^{2,7} $TG \geq 3$ mmol/l, $BMI \geq 30$ units. $HDL \leq 1$ mg/l we can provide high prognostic effect of treatment (lisinopryl, amlodipine, atorvastatin) in men with stage II GC;

2. Promising is a research on predictive efficacy of combination therapy of various schemes and their implementation in clinical practice.

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ЭФФЕКТИВНОСТЬ КОМБИНИРОВАННОЙ ГИПОЛИПИДЕМИЧЕСКОЙ И АНТИГИПЕРТЕНЗИВНОЙ ТЕРАПИИ, ПРОГНОСТИЧЕСКИЕ ЭФФЕКТЫ И КЛИНИЧЕСКИЕ ЭКСПЕРИМЕНТАЛЬНЫЕ КРИТЕРИИ ТЕРАПИИ

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Резюме. Результаты многопрофильного анализа показали, что прогностическая эффективность комбинированной антигипертензивной терапии лизиноприлом и амлодипином и гиполипидемической терапии atorvastатином, у пациентов с артериальной гипертензией II стадии, зависит от целого ряда патологических факторов, кото-

рые определяются в ходе первичного клинического и инструментального анализа – веса пациента, липидного профиля крови, тяжести структурных поражений миокарда левого желудочка сердца и функции сосудистого эндотелия.

Ключевые слова: артериальная гипертензия, комбинация антигипертензивной и гиполипидемической терапии, критерии эффективности.

ЕФЕКТИВНІСТЬ КОМБІНОВАНОЇ ГІПОЛІПІДЕМІЧНОЇ ТА АНТИГІПЕРТЕНЗИВНОЇ ТЕРАПІЇ, ПРОГНОСТИЧНІ ЕФЕКТИ ТА КЛІНІЧНІ ЕКСПЕРИМЕНТАЛЬНІ КРИТЕРІЇ ТЕРАПІЇ

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Резюме. Результати багатопрофільного аналізу показали, що прогностична ефективність комбінованої антигіпертензивної терапії лізиноприлом та амлодипіном і гіполіпідемічної терапії аторвастатином, у пацієнтів з артеріальною гіпертензією II стадії, залежить від цілого ряду патологічних факторів, які визначаються в ході первинного клінічного та інструментального аналізу – маси тіла пацієнта, ліпідного спектра крові, тяжкості структурних уражень міокарда лівого шлуночка та функції судинного ендотелію.

Ключові слова: артеріальна гіпертензія, комбінація антигіпертензивної та гіполіпідемічної терапії, критерії ефективності.

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