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Comparative efficacy of enalapril and valsartan in heart failure with mid-range ejection fraction

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Abstract

Aim. To compare the effectiveness of the angiotensin-converting enzyme inhibitor enalapril and the angiotensin II receptor antagonist valsartan in patients with heart failure with mid-range ejection fraction (HFmrEF) from the standpoint of the effect on the clinical picture, echocardiographic parameters and the level of the N-terminal fragment of the prohormone brain-type sodium (NT-proBNP).

Methods. 110 patients with heart failure with mid-range ejection fraction were included in the study based on the City Clinical Hospital named after N.I. Pirogov of Orenburg between 2018 and 2020. All patients were divided into two randomized groups. Patients of the first group (n=55) were prescribed enalapril, the second group (n=55) — valsartan. Each patient was followed up for 1 year. The six-minute walk test, NT-pro-brain natriuretic peptide level, echocardiography parameters were assessed in dynamics. Statistical analysis was performed by using Statistica 10.0 software, Shapiro–Wilk, Mann–Whitney, Wilcoxon tests.

Results. During the year of observation in both groups, there was a significant decrease in the functional class of chronic heart failure ($p < 0.005$) without a statistical difference between the groups ($p = 0.251$). The distance during the six-minute walk test increased from 350 (310–400) m to 490 (420–530) m ($p < 0.001$) in the first group, from 360 (330–400) m to 510 (450–520) m ($p < 0.001$) in the second group, also without significant differences ($p = 0.361$). The NT-pro-brain natriuretic peptide level decreased from 491 (410–610) pg/ml to 286 (187–350) pg/ml ($p < 0.001$) in the first group, and from 446 (376–534) pg/ml to 210 (143–343) pg/ml ($p < 0.001$) in the second, with a more significant change in the second group ($p = 0.020$). The dynamics of echocardiography parameters were comparable in the groups ($p > 0.05$), while ejection fraction normalized in 89.1% of patients received enalapril and 92.7% of patients received valsartan.

Conclusion. The efficacy of enalapril and valsartan in heart failure with mid-range ejection fraction is comparable in its effect on the clinical picture and echocardiography parameters with a more pronounced decrease in NT-pro-brain natriuretic peptide when taking valsartan during a year of follow up.

Keywords: chronic heart failure, mid-range ejection fraction, enalapril, valsartan.

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Background. Chronic heart failure (CHF) remains an urgent public health problem [1–3]. In 2016, for the first time in the recommendations of the European Society of Cardiology, CHF with mid-range values from 40% to 49% of the ejection fraction (CHFmrEF) was designated as a special subgroup [4]. Leading experts believe that the designation of a separate group of CHFmrEF will stimulate research aimed at elucidating the pathophysiology and searching for optimal methods of treatment and prevention of complications in this category of patients [4–8].

In addition, most previous randomized trials on drug therapy concern patients with low EF (<40%, less often <45%) and little related to patients with EF of 40–49% [9]. In connection with the above, it is important to transfer the patients from the "gray zone" to the normal EF zone, which is likely to help prevent the progression of heart failure and improve the prognosis, and for this purpose, renin–angiotensin–aldosterone system blockers can be used, particularly an angiotensin-converting enzyme (ACE) inhibitor enalapril and an angiotensin II receptor antagonist (ARA) valsartan, which has not been proven to date and requires confirmation.

In this regard, **the study aimed** to compare the efficacy of ACE inhibitors enalapril and ARA valsartan in patients with CHFmrEF in terms of the

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Table 1. Characteristics of the study groups.

Parameter	Data format	Group 1 (n = 55)	Group 2 (n = 55)	p
Age, years	M±σ	66.0±9.6	63.4±8.0	0.115
Sex	n (%)	M 38 (69.1) F 17 (30.9)	M 45 (81.8) F 10 (18.2)	0.121
Postinfarction cardiosclerosis	n (%)	51 (92.7)	47 (85.5)	0.180
Chronic left ventricular aneurysm	n (%)	7 (12.7)	8 (14.5)	0.376
Arterial hypertension	n (%)	45 (81.8)	42 (76.4)	0.523
Diabetes mellitus	n (%)	14 (25.5)	12 (21.8)	0.654
Grade I CHF	n (%)	10 (18.2)	11 (20.0)	0.969
Grade II CHF	n (%)	34 (61.8)	34 (61.8)	
Grade III CHF	n (%)	11 (20.0)	10 (18.2)	
SMWT, m	Me (Q_{25}–Q_{75})	350 (310–400)	360 (330–400)	0.381
NT-proBNP, pg/mL	Me (Q_{25}–Q_{75})	491 (410–610)	446 (376–534)	0.061
EF, %	Me (Q_{25}–Q_{75})	46 (43–48)	46 (44–47)	0.114

Note: *p,* difference between treatment groups; M, male; F, female; CHF, chronic heart failure; SMWT, six-minute walk test; NT-proBNP, N-terminal fragment of the prohormone of the brain-type natriuretic peptide; EF, left ventricular ejection fraction.

effect on the clinical presentation, central hemodynamic parameters, and level of the N-terminal fragment of the brain natriuretic peptide prohormone (NT-proBNP) during the follow-up.

Materials and methods. The study was conducted at the N.I. Pirogov City Clinical Hospital, Orenburg. It sequentially included 110 patients with CHFmrEF, aged 36–89 years (mean age, 64.7 ± 8.8 years), including 83 (75.5%) men and 27 (24.5%) women. The study protocol was approved by the local ethics committee of the Orenburg State Medical University of the Ministry of Health of Russia (Protocol 208 of 09/28/2018).

Criteria for the exclusion from the study were as follows: previous regular treatment with an ACE inhibitor or ARA, intolerance to renin–angiotensin–aldosterone system blockers or contraindications to their use, CHF against rhythm and conduction disorders, active oncological process, other diseases and pathological conditions (mental, infectious, etc.) affecting laboratory and instrumental signs of CHF, and patient's refusal to participate in the study.

CHFmrEF was determined based on the recommendations of the European Society of Cardiology, including the definition of NT-proBNP [4].

The CHF grade was established according to the criteria of the New York Heart Association with its objectification using the six-minute walk test (SMWT). Among all examined patients, grade I was established in 21 (19.1%), grade II in 69 (62.7%), and grade III in 20 (18.2%). The main cause of CHF was coronary heart disease. A history of myocardial infarction for >6 months was recorded in 98 (89.1%) patients, and a history of chronic left ventricular (LV) aneurysm was registered in 15 (13.6%) patients.

Among comorbid pathologies, arterial hypertension (98 patients, 89.1%) and diabetes mellitus (26 patients, 23.7%) were the most common. Before inclusion in the study, all patients received statins, antiplatelet drugs, β-blockers, and diuretics in case of signs of congestion.

Patients were distributed by the random envelop method into two groups, randomized by gender, age, CHF severity, EF, NT-proBNP, and concomitant pathology (Table 1). Group 1 received an ACE inhibitor enalapril (enap, KRKA, Slovenia) in titrated doses from 2.5 mg to the maximum tolerated or maximum dose (40 mg/day, average dose 10–20 mg). Group 2 received ARA valsartan (Valsakor, KRKA, Slovenia) with a recommended initial dose of 40 mg two times/day, which increased to 80 mg two times/day, and with good tolerance in up to 160 mg two times/day (average dose, 120–160 mg).

Central hemodynamic parameters were assessed by echocardiography on a SonoScape S8 device (Korea) according to the standard technique with EF assessment by the Simpson method and determination of the following standard parameters: end-systolic and end-diastolic dimensions (mm), LV volumes (mL), LV stroke volume (mL), dimensions of both atria (mm), volume of the left atrium (mL), thickness of the interventricular septum (mm) and posterior wall of the LV (mm) with the calculation of its relative thickness, and mass

Table 2. Changes in the grade of chronic heart failure under the influence of enalapril and valsartan.

Follow-up period	Group 1 (n = 55)			Group 2 (n = 55)			p*
	Grade I	Grade II	Grade III	Grade I	Grade II	Grade III	
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
Before treatment	10 (18.2)	34 (61.8)	11 (20.0)	11 (20.0)	34 (61.8)	10 (18.2)	0.969
3 months	31 (56.4)	22 (40.0)	2 (3.64)	37 (67.3)	18 (32.7)	0 (0.00)	0.343
6 months	32 (58.2)	21 (38.2)	2 (3.64)	38 (69.1)	17 (30.9)	0 (0.00)	0.340
9 months	33 (60.0)	20 (36.4)	2 (3.64)	40 (72.7)	15 (27.3)	0 (0.00)	0.262
12 months	35 (63.4)	18 (32.7)	2 (3.64)	42 (76.4)	13 (23.6)	0 (0.00)	0.251
p†	<0.005	<0.005	<0.005	<0.005	<0.005	<0.005	—
p§	<0.005	<0.005	<0.005	<0.005	<0.005	<0.005	—

Note: *difference between the treatment groups; †difference between indicators before and after 3 months of treatment; §difference between indicators before and after 12 months of treatment.

Table 3. Changes in test values over time with a six-minute walk test during treatment.

Follow-up period	Group 1 (n = 55)		Group 2 (n = 55)		p*
	Me (Q_{25}–Q_{75})	ΔT	Me (Q_{25}–Q_{75})	ΔT	—
Before treatment, m	350 (310–400)	—	360 (330–400)	—	0.381
3 months, m	430 (390–490)	23%	410 (390–450)	14%	0.410
6 months, m	450 (400–510)	29%	450 (410–500)	25%	0.947
9 months, m	470 (410–520)	34%	490 (430–510)	36%	0.504
12 months, m	490 (420–530)	40%	510 (450–520)	42%	0.361
p†	<0.001	—	<0.001	—	—
p§	<0.001	—	<0.001	—	—

Note: *difference between the treatment groups; †difference between indicators before and after 3 months of treatment; §difference between indicators before and after 12 months of treatment.

of the LV myocardium (g) with its indexed parameter (g/m^2).

The NT-proBNP level was determined by electrochemiluminescence immunoassay in blood serum samples using the Elecsys proBNP II test system (Roche Elecsys, Germany) on the cobas 6000 modular platform (Roche Diagnostics GmbH, Germany). The reference values were 0–125 pg/ml.

The study was performed in 2018–2020, and each patient was monitored for 1 y. Control examination with assessment of CHF grade and SMWT was performed every 3 months. Central hemodynamic parameters and NT-proBNP level were assessed before and after 1 year of treatment.

Statistical processing was performed using the Statistica 10.0 program. First, quantitative characteristics were analyzed by the graphical visualization of the distribution of variation series and calculation of the Shapiro–Wilk criterion. In cases that conformed to the normal distribution, descriptive statistics of quantitative data were presented using the arithmetic mean (M) and standard deviation (σ) as M ± σ. If the distribution deviated from the normal, quantitative data were described using the median (Me) and lower and upper quartiles (Q_{25}–Q_{75}). The significance of intergroup differences was assessed using the Mann–Whitney and Wilcoxon tests. Differences in the compared groups were considered significant at $p < 0.05$.

Results. During the follow-up, a significant decrease in the CHF grade was recorded (Table 2). Positive dynamics was established in both groups within 3 months from the start of treatment. A decrease in grade was accompanied by an increase in the walking distance when performing SMWT (Table 3). Moreover, in group 1, grade III remained throughout the follow-up period in 2 (3.64%) patients who had a history of widespread myocardial infarction with an outcome in LV aneurysm, obesity, and diabetes mellitus.

Table 4 presents the changes in central hemodynamic indices in patients with CHFmrEF before and after 12 months of treatment, which indicates that the use of renin–angiotensin–aldosterone system blockers was accompanied by an improvement in most of the studied parameters of echocardio-

Table 4. Changes in the values of echocardiography indicators in patients with chronic heart failure with mid-range ejection fraction during treatment with enalapril (group 1) and valsartan (group 2).

Indicator	Data format	Group 1 (n = 55)		Group 2 (n = 55)		p
		Baseline	After 12 months	Baseline	After 12 months	
LA. mm	Me (Q_{25}–Q_{75})	41 (39–44)	40 (37–41)	41 (39–43)	40 (36–42)*	0.950
LA volume. mL	Me (Q_{25}–Q_{75})	56 (50–66)	54 (50–56)*	55 (50–64)	52 (50–60)*	0.507
RA. mm	M±σ	43.7±7.6	41.6±7.1*	45.4±6.8	40.8±6.0*	0.492
ESD. mm	Me (Q_{25}–Q_{75})	45 (40–49)	40 (34–42)*	46 (43–49)	40 (37–43)*	0.073
EDD. mm	M±σ	59.4±6.0	54.8±6.4*	60.5±6.2	55.6±5.7*	0.497
ESV. mL	Me (Q_{25}–Q_{75})	78 (70–86)	62 (57–69)*	76 (70–95)	60 (54–64)*	0.159
EDV. mL	Me (Q_{25}–Q_{75})	140 (135–166)	136 (133–150)*	140 (130–170)	135 (133–140)*	0.374
SV. mL	Me (Q_{25}–Q_{75})	68 (61–76)	78 (71–88)*	63 (61–72)	80 (73–83)*	0.790
EF. %	Me (Q_{25}–Q_{75})	46 (43–48)	55 (51–58)*	46 (44–47)	55 (51–60)*	0.895
IVS. mm	Me (Q_{25}–Q_{75})	12 (12–13)	11 (11–12)*	12 (11–13)	11 (11–12)*	0.995
LVPW. mm	Me (Q_{25}–Q_{75})	11 (10–12)	10 (10–11)*	11 (11–12)	11 (10–11)*	0.112
RWT. units	Me (Q_{25}–Q_{75})	0.38 (0.34–0.41)	0.39 (0.36–0.42)	0.37 (0.34–0.41)	0.39 (0.36–0.42)*	0.545
LVMM. g	M±σ	296.8±61.7	242.2±59.3*	309.3±65.9	249.7±53.4*	0.483
LVMMI. g/m^2	M±σ	147.6±29.2	120.4±28.0*	154.3±32.9	125.0±26.9*	0.469

Note: *difference between parameters before and after treatment ($p < 0.05$); p, difference between the treatment groups; LA, left atrium; RA, right atrium; ESD, end-systolic dimension; EDD, end-diastolic dimension; ESV, end-systolic volume; EDV, end-diastolic volume; SV, stroke volume of the left ventricle; EF, left ventricular ejection fraction; IVS, interventricular septum; LVPW, left ventricular posterior wall; RWT, relative wall thickness of the left ventricle; LVMM, left ventricular myocardium mass; LVMMI, left ventricular myocardial mass index.

graphy without significant differences between the study groups.

Although EF values significantly increased both with enalapril (ΔT 20%, $p < 0.05$) and valsartan (ΔT 20%, $p < 0.05$) treatments, such dynamics was not registered in all patients. Thus, in group 1, EF became normal in 49 of 55 (89.1%) patients (≥50%) and in 6 (10.9%) patients, and its mid-range values remained. In group 2, EF became higher than 50% in 51 of 55 (92.7%) patients, and in 4 (7.3%) cases, it increased but remained within the mid-range values. Patients of both groups (n = 10), whose EF remained in mid-range values, had a history of myocardial infarction with LV aneurysm, while EF became >50% in the remaining patients (n = 5) with similar clinical data.

In the presence of improved parameters of central hemodynamics, the NT-proBNP level in group 1 decreased from 491 (410–610) pg/ml to 286 (187–350) pg/ml ($p < 0.001$) and from 446 (376–534) pg/ml to 210 (143–343) pg/ml ($p < 0.001$) in group 2 during the follow-up period, while valsartan contributed to a more significant decrease in the amount of NT-proBNP than enalapril ($p = 0.020$).

Discussion. Renin–angiotensin–aldosterone system blockers (such as ACE inhibitors and ARA) are recommended for all patients with symptomatic CHF and decreased EF as well as for asymptomatic LV systolic dysfunction [4, 10]. For drugs such as enalapril and valsartan, the clinical advantage and a positive effect on prognosis have been proven in several major randomized clinical trials [11–13]. In CHFmrEF, the efficiency of these drugs has not been examined, especially in comparison with each other; however, this is the focus of this study.

In this study, during treatment with both enalapril and valsartan, we registered a significant improvement in the functional and clinical states of patients as a decrease in the CHF grade recorded after 3 months and up to 1 year of follow-up. The efficacy obtained is consistent with previous studies where enalapril or valsartan in patients with reduced EF contributed to clinical improvement [11–13].

A positive effect of both enalapril and valsartan on the LV attributes of remodeling was established, such as a decrease in geometric parameters, an increase in EF, and a decrease in the size of the left atrium in both groups, indicating load reduction. Similar results were previously obtained in studies on the effect of these drugs in patients with low EF [11–13]. In addition, enalapril and valsartan therapy was accompanied by a significant decrease in the LV myocardial mass index in group 1 (ΔT, –18%) and group 2 (ΔT, –19%). Moreover, when comparing between the groups, no significant difference was found in the change in LV myocardial mass over time.

In this study, during the follow-up, the NT-proBNP level decreased in patients taking enalapril (ΔT, –42%) and valsartan (ΔT, –53%), which is quite natural in the improvement of the central hemodynamics parameters and decrease in the CHF grade and may indicate treatment success [14]. A more significant decrease in the NT-proBNP level in group 2 ($p = 0.020$) suggests that valsartan is more effective than enalapril in CHFmrEF; however, a comparable effect of both drugs on the grade, SMWT, and echocardiography parameters does not allow preference for any drug.

Despite the positive treatment results with renin–angiotensin–aldosterone system blockers, not all patients achieved a release of EF from the "gray" zone, including an improvement in clinical symptoms and an increase in the distance during SMWT. From these positions, the drug efficiency during the follow-up was significantly comparable and accounted for 89.1% for enalapril and 92.7% for valsartan, that is, the effect was not achieved in 6 (10.9%) patients in group 1 and in 4 (7.3%) patients in group 2. Analysis of factors affecting the efficiency of treatment established a significant effect of chronic LV aneurysm, and its effect was observed in only 33.3% of the cases ($p < 0.001$), which was apparently due to a more pronounced postinfarction myocardial remodeling [15].

CONCLUSIONS

1. A comparative study of ACE inhibitor enalapril and ARA valsartan in patients with CHF with mid-range EF of grade I–III showed comparable clinical efficacy and unidirectional effect on the parameters of central hemodynamics according to echocardiography, with a pronounced decrease in the level of NT-proBNP when taking valsartan during the follow-up.

2. High clinical efficiency in some patients (9.1%) was limited by LV aneurysm, and the EF remains at mid-range values.

3. The use of an ACE inhibitor enalapril and an ARA valsartan can be recommended for CHF with a mid-range EF, as well as with a reduced EF, to improve the symptoms of CHF, but from the standpoint of influencing the prognosis, longer follow-up in a larger cohort of patients is required.

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Conflict of interest. The authors declare no conflict of interest.

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