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CARDIAC MUSCLE MODELING DURING TREATMENT WITH SACUBITRIL/VALSARTAN IN PATIENTS WITH HEART FAILURE

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გულის კუნთის მოდელირება საკუბიტრილ/ვალსარტანით მკურნალობის დროს გულის უკმარისობის მქონე პაციენტებში

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რეზიუმე

მიზანი. კვლევის მიზანს წარმოადგენდა გულის კუნთის მოდელირების შესწავლა საკუბიტრილ/ვალსარტანით მკურნალობის დროს გულის უკმარისობის (HF) მქონე პაციენტებში.

მეთოდები. საკუბიტრილ/ვალსარტანის მკურნალობის ეფექტების შესაფასებლად (დაკვირვების პერიოდი – 6 თვე) შერჩეულ იქნა სხვადასხვა კლასის ქრონიკული გულის უკმარისობის მქონე 60 პაციენტი. ისინი შემთხვევითობის პრინციპით გადანაწილდნენ საკვლევ ჯგუფში. საკუბიტრილ/ვალსარტანით (24/26 მგ) მკურნალობის ფონზე 55 პაციენტმა დაასრულა კვლევა.

შედეგები. თითქმის ყველა ექოკარდიოგრაფიულ პარამეტრისთვის არ დაფიქსირებულა მნიშვნელოვანი სარწმუნო ცვლილება. სარწმუნოდ შემცირდა მე-3 და მე-4 კლასის მიტრალური სარქვლის რეგურგიტაციით დაავადებულთა პროცენტული მაჩვენებელი; ასევე სარწმუნოდ შემცირდა მე-2 და მე-3 კლასის ტრიკუსპიდური სარქვლის რეგურგიტაციით დაავადებულთა პროცენტული მაჩვენებელი. განდევნის ფრაქციის გარდა, თითქმის ყველა ექოკარდიოგრაფიული პარამეტრისთვის არ შეინიშნებოდა რაიმე სარწმუნო ცვლილება. კვლევის დასაწყისში განდევნის ფრაქციის მაჩვენებელი 34.2%-დან სარწმუნოდ გაიზარდა 37.4%-მდე მკურნალობის დაწყებიდან 6 თვის შემდეგ ($p<0.001$). შემცირდა მე-4 ხარისხის მიტრალური სარქვლის რეგურგიტაციები (MVRs), მე-2 და მე-3 კლასის MVR-ების პროცენტული მაჩვენებლები არ შემცირებულა. მიუხედავად იმისა, რომ მე-4 ხარისხის ტრიკუსპიდური სარქვლის რეგურგიტაცია (TVR) შემცირდა, მე-2 და მე-3 კლასის TVR-ების პროცენტული მაჩვენებლები სარწმუნოდ არ შემცირებულა. გაიზარდა პირველი კლასის TVR-ების პროცენტული მაჩვენებელი.

დასკვნა. საკუბიტრილ/ვალსარტანით დაავადებულთა 6-თვიანი მკურნალობის ეფექტების შეფასების საფუძველზე, შეიძლება დავასკვნათ, რომ საკუბიტრილ/ვალსარტანი აჩვენებდა უკეთეს შედეგებს გულის ექოკარდიოგრაფიულ პარამეტრებზე ზემოქმედების თვალსაზრისით, მაგრამ არ აჩვენებდა რაიმე სარწმუნო გავლენას სარქვლოვან რეგურგიტაციებზე. უფრო ძლიერი მტკიცებულებების მისაღებად აუცილებელია კვლევის გაგრძელება მტკიცებულებებზე დაფუძნებული შედეგებისა და დასკვნების მოწოდებისთვის.

Introduction. Heart failure (HF) became one of the main problems of medicine at the end of the 20th century and the beginning of the 21st century. The successful medicinal and surgical treatment of relatively common heart diseases has increased the proportion of the patients who live to a relatively old age at which the risk of the development of the heart failure is high. In the United States approximately 6.7 million people (age ≥ 20 years) were registered with a diagnosis of HF in 2017-2020, which is higher by 11.7% than the rate of 2015-2018 [1]. A comparative analysis of the 25-year periods of the Framingham Heart Study (1965-1989 vs. 1990-2014) showed that the residual lifetime risk at 50 years of age was increased by 6.1% in men, and by 3.7% - in women [2]. The HF prevalence is essentially related to age: 1.4% of the population aged 25-49 complain of HF, 2.9% - at the age of 50-59, 7.6% - at the age of 60-69,

12.7% - at the age of 70-79, and 16.1% - aged 80 and over [2-5]; at the same time the health-related quality of life also decreases [6].

It should be noted that the role of renin-angiotensin-aldosterone activation is central in the development of HF and left ventricular (LV) hypertrophy, which is the main risk factor for the development of HF and arterial hypertension [7,8]. In recent years the drug aliskiren has appeared which inhibits renin activity. Aliskiren is a direct renin inhibitor with the high specificity for the human renin. It is used to treat arterial hypertension. Luo Y and Chen Q [9] based on the results of a meta-analysis of 1973 patients from 5 randomized clinical trials, reported that the addition of aliskiren to conventional therapy reliably reduced NT-proBNP levels and plasma renin activity, improving plasma renin concentrations in patients with HF. However, data about the treatment with aliskiren are very scarce, especially in terms of long-term studies. Zhao Q et al in their review article noted that there is strong evidence for the benefits of aliskiren in the treatment of essential hypertension, and that aliskiren can significantly lower blood pressure with adequate safety [10]. However, the authors also indicated that the effects on cardiovascular and renal outcomes are implausible.

One of the primary mechanisms of sacubitril/valsartan is to increase the circulatory and myocardial nitric oxide bioavailability, leading to an increase of a cyclic guanosine monophosphate (cGMP) and an activation of protein kinase G. The final effect is a reduction of a systemic oxidative stress, apoptosis, and hypertrophy accompanied by antiplatelet and antithrombotic effects [11]. In chronic patients, the earliest effect was observed in the EVALUATE-HF study: a significant reduction of the left ventricular end-systolic and end-diastolic volumes (LVESV and LVEDV), left atrial volume index (LAVI) and E/e' ratio compared with enalapril was observed in 12 weeks [12]. Another prospective study with the blind echocardiographic analysis demonstrated improvements in the systolic and diastolic functions after 4 months of ACEI/ARB II replacement with sacubitril/valsartan in patients with a chronic HF with a preserved ejection fraction (HFpEF) who were previously optimally treated [13].

Based on the mentioned above, the aim of the study was to study the dynamics of the development of heart muscle modeling during the treatment with sacubitril/valsartan in the HF patients within 6 months after the initiation.

Methods. This study is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [14]. The cross-sectional observational study design has been chosen to assess the treatment effects of aliskiren and Sacubitril/Valsartan. All procedures performed in the study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study protocol and a draft consent agreement for participation in the study were approved by the Ethics Committee of the Institutional Review Board of Tbilisi State Medical University (#5-2020/82; October 28, 2020). Written informed consent was obtained from all individual participants included in the study. We de-identified the patients' details so that they may not be identified in any way.

Inclusion criteria were diagnosed HF, and obtained informed consent. Exclusion criteria were chronic kidney disease, liver failure, hyperkalemia, hypotension episodes in anamnesis, and refusal to participate in the study at any stage.

Study groups. To achieve the aim of the study, after obtaining the informed consent, 60 randomly selected patients with chronic HF of different classes were randomly assigned to study group; 6 patients were excluded from the study because of not coming to the intermediate visits. 54 patients (mean age - 69.5 ± 9.5 years, 40 males/14 females) who were prescribed the treatment with Sacubitril/Valsartan (24/26 mg) finished the study. All patients have been prescribed antihypertensive drugs before the study.

Study tools. The instrumental examinations and laboratory tests provided by the study protocol were performed at the beginning of the study (baseline) and at 2 points after the initiation of the treatment - after every 3 months.

All patients at all points underwent echocardiographic studies, during which the parameters of the left ventricle (end-systolic-diameter - LVESD and volume - LVESV, end-diastolic-diameter - LVEDD and volume - LVEDV, ejection fraction - EF), left atrial parameters (diameter-LAD and volume - LAV) and valvular pathologies (mitral valve regurgitation - MVR, aortic valve regurgitation - AVR, tricuspid valve regurgitation - TR) have been measured and assessed. Blood pressure (BP), pulse, saturation, respiratory rate, carbohydrate metabolism parameters (fasting glycemia - FPG, fasting C-peptide - FCP, HbA1C, HOMA-indexes), lipid metabolism parameters (total cholesterol, triglycerides, HDL-cholesterol, LDL-cholesterol, VLDL-cholesterol), blood renin, creatinine, electrolytes (potassium, calcium, sodium, chlorine) were also measured at all stages of the patient's examinations. The natriuretic peptide NT-proBNP and PAPS was also measured. The obtained baseline characteristics of the study group are given in Table 1.

Table 1. The obtained baseline characteristics of the study group.

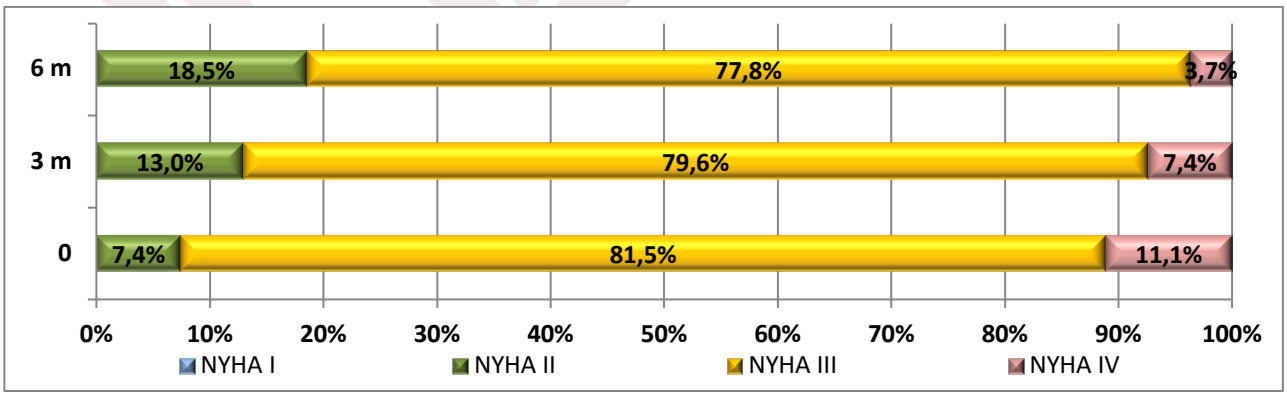
Parameter	Group 2 (n=54) Mean±SD or n= (%)
Age, years	69.5 ± 9.5
Gender (Male/Fenale)	40 (74.1%) / 14 (25.9%)
Family status (Married/Widow)	40 (74.1%) / 14 (25.9%)
Education (Middle/High School)	15 (27.8%) / 39 (72.2%)
Employment (No/Yes)	12 (22.2%) / 42 (77.8%)
HF class	
NYHA I	0 (0.0%)
NYHA II	4 (7.4%)
NYHA III	40 (74.1%)
NYHA IV	10 (18.5%)
LVESD, mm	59.0 ± 7.1
LVEDD, mm	53.4 ± 7.4
LVESV, ml	160.6 ± 57.8
LVEDV, ml	105.6 ± 41.4
EF, %	34.5 ± 4.5
Valvular pathologies	
MVR	50 (92.6%)
AVR	4 (7.4%)
TVR	43 (73.6%)
BP, mmHg	
Systolic	119.6 ± 7.8
Diastolic	63.1 ± 4.5
Pulse, bpm	78.0 ± 8.6
Saturation, %	89.7 ± 2.6
Brearth Rate, bpm	22.2 ± 0.9
Carbohydrate Metabolism	
FPG, mg/dl	112.7 ± 16.9
FCP, ng/ml	1.0 ± 0.3
HBA1C, %	6.8 ± 1.2
HOMA-B,%	109.7 ± 24.9
HOMA-S, %	45.2 ± 14.2

HOMA-IR	2.4 ± 0.6
Lipid Metabolism	
Total cholesterol, mg/dl	212.5 ± 28.5
Triglycerides, ng/ml	174.8 ± 19.0
HDL- cholesterol, mg/dl	40.5 ± 4.2
LDL- cholesterol, mg/dl	137.3 ± 19.6
VLDL- cholesterol, mg/dl	35.0 ± 3.8
Renin, ng/ml/hr	16.7 ± 2.8
Creatinine, mmol/L	75.6 ± 4.3
NT-proBNP, pg/ml	161.9 ± 43.4
PAPS, mmHg	36.7 ± 9.9
Electrolytes, mmol/L	
K	4.0 ± 0.2
Ca	1.1 ± 0.1
Na	138.9 ± 2.4

Statistical analysis. The study results were statistically analyzed using SPSS 22.0 software (IBM Corp., Armonk, NY, USA). Continuous variables are expressed as mean ± standard deviation (SD), cheked for normality by Kolmogorov-Smirnov Z-test and differences were assessed by analysis of variance (within the groups – paired t-test, between groups - independent t-test and Fisher's exact test). Categorical variables were compared using the chi-square test or Fisher's exact test. Pearson's coefficient (r) was used to evaluate the correlation between the parameters. P-values of <0.05 were considered as statistically significant.

Results. The distribution of the patients in the study group according to the NYHA class at all stages of the study is shown on Figure 1. As it is shown on Figure 1, the percentage of patients with NYHA class IV decreased from 11.1% at baseline to 3.7% after 6 months; the percentage of the patients with NYHA class III also decreased from baseline 81.5% to 77.8% after 6 months; the percentage of the patients with NYHA class II was increased at every study point and after 6 months it was 18.5%.

Figure 1. The distribution of the patients in the study groups according to the NYHA class at all stages of the study. The distribution was statistically significant (Chi2=58.86; p<0.001)



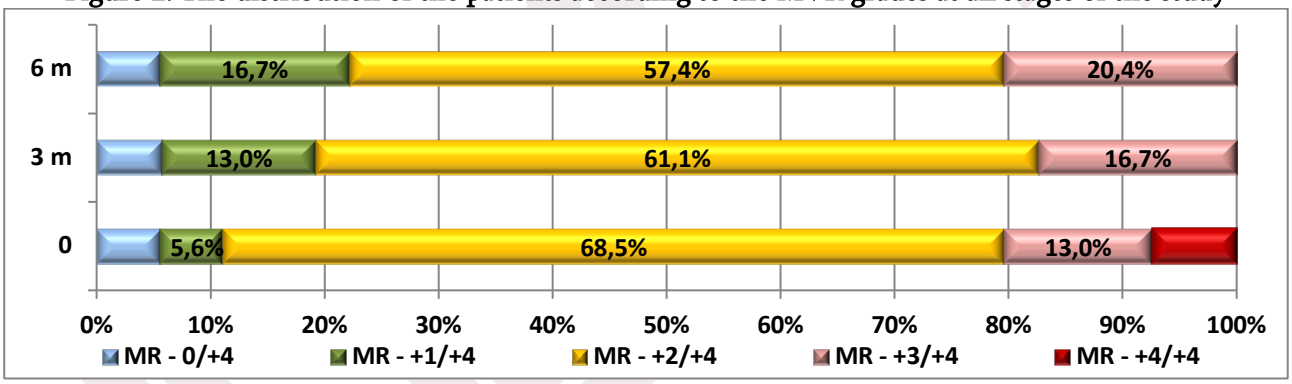
The changes of the echocardiographic parameters of the patients of the study group at all stages of the study is shown in Table 2. There were no significant changes in all echocardiographic parameters except EF. It increased significantly from 34.2% baseline to 37.4% after 6 months of the treatment initiation (p<0.001).

Table 2. The dynamics of the echocardiographic parameters of the patients at all stages of the study

	Baseline	After 6 months
	Mean (SD)	Mean (SD)
LVESV, ml	160.6 (59.1)	156.0 (52.3)
	0.43, p=0.669	
LVEDV, ml	105.6 (41.4)	103.5 (28.6)
	0.31, p=0.760	
LVESD, mm	59.0 (7.1)	58.5 (6.4)
	1.42, p=0.159	
LVEDD, mm	53.7 (7.5)	53.0 (5.3)
	0.56, p=0.577	
EF, %	34.2 (4.7)	37.4 (4.0)
	3.81, p<0.001	

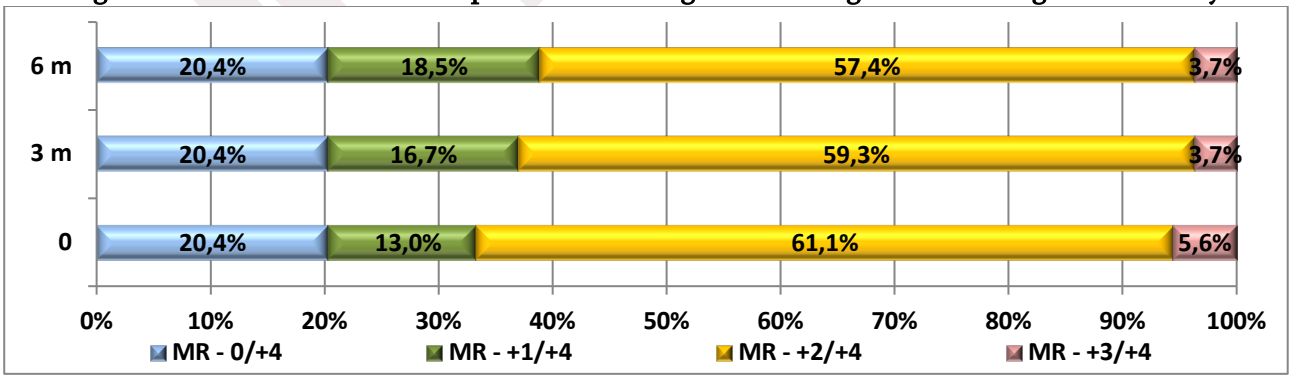
The distribution of the patients in the study group according to the degree of mitral valve regurgitation (MVR) at all stages of the study is shown on Figure 2. As it is shown on Figure 2, MVRs of grade 4 was reduced, the percentage values of the MVRs of 2nd and 3rd grades were not decreased. The distribution of the patients in the study groups according to the degree of Tricuspid valve regurgitation (TVR) at all stages of the study is shown on Figure 3. As it is shown on Figure 3, although TVRs of grade 4 was reduced, the percentage values of the TVRs of 2nd and 3rd grades were not decreased significantly. The percentage value of the TVRs of 1st grade was increased.

Figure 2. The distribution of the patients according to the MVR grades at all stages of the study



* The distribution was not statistically significant (Chi2=21.75; p=0.152).

Figure 3. The distribution of the patients according to the TVR grades at all stages of the study



* The distribution on figure 4b was not statistically significant (Chi2=10.30; p=0.850)

The values of the parameters of carbohydrate and lipid metabolism, renin, creatinine, NT-proBNP and electrolytes during the study in the group are shown in Table 3.

Table 3. The study parameters during 12 months follow-up in the group.

Parameter	Baseline	3 Months	6 Months
	Mean (SD)	Mean (SD)	Mean (SD)
Systolic BP, mmHg.	119.6 (7.8)	115.7 (4.8)*	113.4 (6.5)*
Diastolic BP, mmHg.	63.1 (4.5)	63.4 (3.5)	63.1 (4.5)
Pulse, bpm	78.0 (8.6)	77.3 (6.6)	77.0 (4.8)
Saturation, %	89.7 (2.6)	91.6 (2.2)*	92.8 (2.2)*
Breath Rate, bpm	22.2 (0.9)	21.6 (1.0)*	21.2 (0.8)*
FPG, mg/dl	112.7 (16.9)	110.2 (15.8)	108.5 (13.7)
HbA1C, %	6.8 (1.2)	6.4 (0.3)*	6.2 (0.3)*
FCP, nmol/l	1.02 (0.27)	0.98 (0.21)	0.97 (0.20)
HOMA-B, %	109.7 (24.9)	111.0 (20.4)	113.8 (21.1)
HOMA-S,%	45.2 (14.2)	45.7 (10.0)	46.1 (9.9)
HOMA-IR	2.4 (0.6)	2.3 (0.5)	2.3 (0.5)
Renin, ng/ml/hr	16.7 (2.8)	17.2 (2.2)	17.4 (2.3)
Creatinine, mmol/L	75.6 (4.3)	72.4 (9.2)	69.8 (10.3)
Total Chol, mg/dl	212.8 (28.5)	201.8 (23.0)*	195.9 (19.5)*
Tg, mg/dl	174.8 (19.0)	167.7 (22.0)	166.6 (16.4)*
HDL Chol, mg/dl	40.5 (4.2)	46.1 (6.7)*	47.4 (8.6)*
LDL Chol, mg/dl	137.3 (19.6)	122.2 (16.7)*	115.2 (24.5)*
VLDL Chol, mg/dl	35.0 (3.8)	33.5 (2.4)*	33.3 (3.3)*
PAPS, mmHg	36.7 (9.9)	34.7 (11.1)	31.9 (10.2)
K, mmol/L	4.0 (0.2)	4.1 (0.1)	4.0 (0.1)
Ca, mmol/L	1.1 (0.1)	1.1 (0.1)	1.1 (0.1)
Na, mmol/L	138.9 (2.4)	138.9 (1.9)	137.9 (1.8)
NT-proBNP, pg/ml	161.9 (43.4)	151.9 (41.3)	145.8 (35.3)*

* - significant compared to baseline value

As it is shown from the Table, the systolic BP values were significantly reduced already after 3 months and this reduction compared to the baseline value was remained after 6 months. As for diastolic BP, this parameter did not change significantly. It should be noted here that there were very few episodes of hypotensions at all stages of the study. Pulse rate did not change at any point of the study. The saturation was significantly increased after 6 months. The same picture was observed for the breath rate.

FPG did not change significantly at all points of the study. But HbA1C was decreased significantly. Fasting C-peptide levels and HOMA-indices was not changed significantly.

Among the parameters of lipid metabolism, the mean level of total cholesterol was significantly reduced after 3 and 6 months, the changes in the mean triglyceride levels were also significant at the same points; HDL-cholesterol levels were already significantly increased at 3 months and the trend of increase remained until the final stage; LDL- and VLDL-cholesterol levels began to decrease significantly at 3 months, and this trend was maintained until the final stage too; Blood rennin and creatinine levels was not changed significantly compared to the baseline values. Finally, the level of NT-proBNP decreased significantly after 6 months from the initation of the treatment.

Discussion. To discuss the obtained results, attention should be paid to the several interesting findings. Sacubitril / Valsartan significantly improved the data of NYHA class of HF after 6 months of treatment. In relation to Sacubitril/Valsartan, this is not a new finding. This was reported by Yenercag M and co-authors [16]. One of the findings refers to the regurgitations. We could not find the evidence of the effect of Sacubitril/Valsartan monotherapy on the valvular pathologies in group 2. This was noted by Martens and co-authors [13]. They concluded that sacubitril/valsartan reduced mitral valve regurgitation

more than valsartan in the patients with secondary functional mitral valve regurgitation. According to the data of another study, the authors believed that angiotensin receptor-neprilysin inhibitor can be considered as an optimal medical therapy for patients with HF and functional myocardial valve regurgitation [15].

For the left ventricular echocardiographic parameters, there were no significant changes in all echocardiographic parameters except EF. It increased significantly from 34.2% baseline to 37.4% after 6 months of the treatment initiation ($p<0.001$).

Limitations. This study has several limitations, including the inherent limitations of the study design, the relatively small sample size, and the short follow-up. Moreover, the comorbidities that could have impact on the study parameters were not specified. Future studies on larger numbers of patients with longer follow-up and a comparative double-blind randomized design are required to address these limitations.

Conclusion. Based on the evaluation of the effects of 6-months' treatment of the HF patients with Sacubitril/Valsartan, it may be concluded that Sacubitril/Valsartan shows better results in terms of impact on the heart echocardiographic parameters, but it did not show any significant effect on the valvular regurgitations. To obtain more strong evidences, it is necessary to continue the study to provide the evidence-based results and conclusions.

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CARDIAC MUSCLE MODELING DURING TREATMENT WITH SACUBITRIL/VALSARTAN IN PATIENTS WITH HEART FAILURE

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SUMMARY

Background and objectives. The aim of the study was to study the cardiac muscle modeling during treatment with Sacubitril/Valsartan in patients with heart failure (HF).

Methods. To assess the treatment effects of aliskiren (follow-up period – 6 months) 60 randomly were selected patients with chronic HF of different classes. They were randomly assigned to the study groups. 55 patients treated Sacubitril/Valsartan (24/26 mg), and finished the study.

Results. Significant changes have not observed for almost all echocardiographic parameters except EF. It increased significantly from 34.2% baseline to 37.4% after 6 months of the treatment initiation ($p<0.001$). mitral valve regurgitations (MVRs) of grade 4 was reduced, the percentage values of the MVRs of 2nd and 3rd grades were not decreased. although Tricuspid valve regurgitation (TVR) of grade 4 was reduced, the percentage values of the TVRs of 2nd and 3rd grades were not decreased significantly. The percentage value of the TVRs of 1st grade was increased.

Conclusion. Based on the evaluation of the effects of 6-months' treatment of the HF patients with Sacubitril/Valsartan, it may be concluded that Sacubitril/Valsartan shows better results in terms of impact on the heart echocardiographic parameters, but it did not show any significant effect on the valvular regurgitations. To obtain more strong evidences, it is necessary to continue the study to provide the evidence-based results and conclusions.

Keywords: Echocardiography; Heart Failure; Sacubitril/Valsartan; Valvular regurgitations.