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The Clinical Evolution of Diffuse Myocardial Fibrosis in Patients With Arterial Hypertension and Heart Failure With Mildly Reduced Ejection Fraction Treated by Olmesartan or Sacubitril / Valsartan

Aim — A 12-month evaluation of the potentialities of the angiotensin II receptor inhibitor olmesartan (Olme) and the angiotensin receptor and neprilysin inhibitor (ARNI) sacubitril/valsartan in patients with arterial hypertension (AH) and dyslipidemia in the dynamics of the following indicators of chronic heart failure (CHF): N-terminal pro-brain natriuretic peptide (NT-proBNP), left ventricular ejection fraction (LVEF), LV global longitudinal strain (LV GLS) in diffuse myocardial fibrosis (MF) previously diagnosed by magnetic resonance imaging (MRI).

Material and methods — Olmesartan medoxomil (n=56) and sacubitril/valsartan (n=63) were used for 12 months in patients with hypertension, dyslipidemia and NYHA functional class II–III CHF with mid-range LVEF (CHFmrEF). MF was diagnosed by the following MRI criteria: late gadolinium enhancement and an increased proportion of extracellular matrix (33% or more). The frequency of persisting late gadolinium enhancement and the increased proportion of extracellular matrix (33% or more) was evaluated at 12 months; changes in systolic blood pressure (SBP), diastolic blood pressure (DBP), NT-proBNP, and LV GLS were evaluated after 3, 6, and 12 months of follow-up.

Results — Baseline parameters did not differ between groups. The late gadolinium enhancement and increased proportion of extracellular matrix were present at baseline in all patients of both groups (100%; p=1.0). Already at 3 months, statistically significant decreases in SBP and DBP were observed in both groups. In addition, the LV GLS monitoring showed LV GLS significantly increased in both groups after 3 months and continued changing after 6 and 12 months. The NT-proBNP concentration significantly decreased in both groups already after 3 months and continued to decrease after 6 and 12 months. At 6 and 12 months, sacubitril/valsartan was superior to olmesartan in reducing SBP and NT-proBNP and in restoring LV GLS. At 12 months, the incidence of persisting, abnormal late gadolinium enhancement and increased proportion of extracellular matrix was significantly less in the ARNI group.

Conclusion — Olmesartan was demonstrated effective in the multi-modality therapy of CHFmrEF and MF in patients with AH and dyslipidemia. ARNI was superior to olmesartan in this regard, but further research of this issue is required.

Keywords — Myocardial fibrosis; magnetic resonance imaging; left ventricular global longitudinal strain; arterial hypertension; dyslipidemia; chronic heart failure with mid-range left ventricular ejection fraction; olmesartan; sacubitril/valsartan

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Introduction

The healthy myocardium consists of cardiomyocytes and the surrounding extracellular matrix in a ratio of 3 to 1 [1, 2]. Diffuse myocardial fibrosis (MF) is present in various chronic heart diseases, it develops as a result of excessive deposition of collagen fibers throughout the myocardium [3]. The physicochemical properties of fibers, the composition of collagen, and the amount of fibrous deposits are keys to the effect of diffuse MF on cardiac function and clinical outcomes in patients with chronic heart failure (CHF) [4].

MF is a common pathological response to damage to the heart muscle [2, 3]. Numerous stimuli can cause initial myocardial damage, which can lead to various forms of fibrosis. Myocardial inflammation, myocardial ischemia, pressure overload, volume overload, genetic mutations, and other conditions can initiate MF [5, 6]. Activated fibroblasts are a key driver of the development of MF [2]. In response to various forms of myocardial damage, myocardial fibroblasts differentiate into two subtypes: activated and profibrotic fibroblasts. Activated myocardial fibroblasts are involved in MF through dynamic interactions between collagen, extracellular matrix, and other cell types involved in the formation of fibrosis [7]. Interstitial and substitutive MF is often distinguished [2].

Plasma biomarkers such as hydroxyproline, N-terminal pro-brain natriuretic peptide (NT-proBNP), matrix metalloproteinases and tissue inhibitors of matrix metalloproteinases can be used to established MF as well as direct confirmation by biopsy [7]. However, with exception of NT-proBNP, these biomarkers are not specific for the heart and their levels may elevate when fibrosis is formed in other organs and tissues [7].

Imaging techniques used for non-invasive assessment of MF include echocardiography [8], computed tomography (CT), magnetic resonance imaging (MRI) [9], etc. Echocardiography is often used for the additional evaluation of MF. It allows detecting the effects of MF, such as ventricular wall thinning and local and global strain, including left ventricular global longitudinal strain (LVGLS). MRI with T1 mapping and late gadolinium enhancement (LGE) is used for the diagnosis of MF [10]. LGE is a differential test based on the slower elimination of gadolinium-based contrast agents from the extracellular matrix. LGE is the gold standard in MF assessment [11].

MF has lately become regarded as a promising therapeutic target, and fibrogenesis is regarded now as a dynamic process that can significantly reduce the rate of progression under certain conditions or even reverse it. Elimination of the causative agent is one of the main and most effective therapeutic approaches. However, slowing down the progression is the most realistic therapeutic strategy in modern practice. At the same time, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, aldosterone antagonists, statins turned out to have antifibrotic effects [12–14]. Olmesartan combined with a statin has showed in an animal model the additive effects of combined blockade of the AT1 receptor and HMG-CoA reductase on left ventricular remodeling in rats with the history of infarction [15], and researchers are not losing interest in its comparison with sacubitril/valsartan in various clinical scenarios [16–19].

Objective

Evaluate within 12 months the effects of the angiotensin II receptor blocker olmesartan (Olme) and angiotensin receptor-neprilysin inhibitor (ARNI) sacubitril/valsartan in patients with arterial hypertension (AH) and dyslipidemia on the following indicators of CHF: NT-proBNP, left ventricular ejection fraction (LVEF), LVGLS in diffuse MF initially established by MRI.

Material and Methods

From October 2021 to August 2022, 119 patients were included in 13 sites in 4 countries (Russia, Turkey, Kazakhstan, Kyrgyzstan), who met the inclusion criteria and were followed up for up to 12 months (until repeated contrast-enhanced MRI of the heart). All patients signed the informed consent to be included in this non-randomized prospective study.

Inclusion criteria were the presence of AH without contraindications to renin-angiotensin system inhibitors,

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CHF NYHA class II–III with mid-range LVEF (HFmrEF) caused by AH (other causes excluded), dyslipidemia (considering each of the presented lipid metabolism indicators: total cholesterol (TC) > 4.9 mmol/L and/or low-density lipoprotein cholesterol (LDL cholesterol >3.0 mmol/L), elevated NT-proBNP vs. baseline (from 450 to 3000mmol/mL), abnormal LVGLS (above 18%), LGE+ (more than 10 minutes from the administration of the agent) on contrast-enhanced MRI of the heart, increased fraction of extracellular volume (≥ 33%) on MRI of the heart.

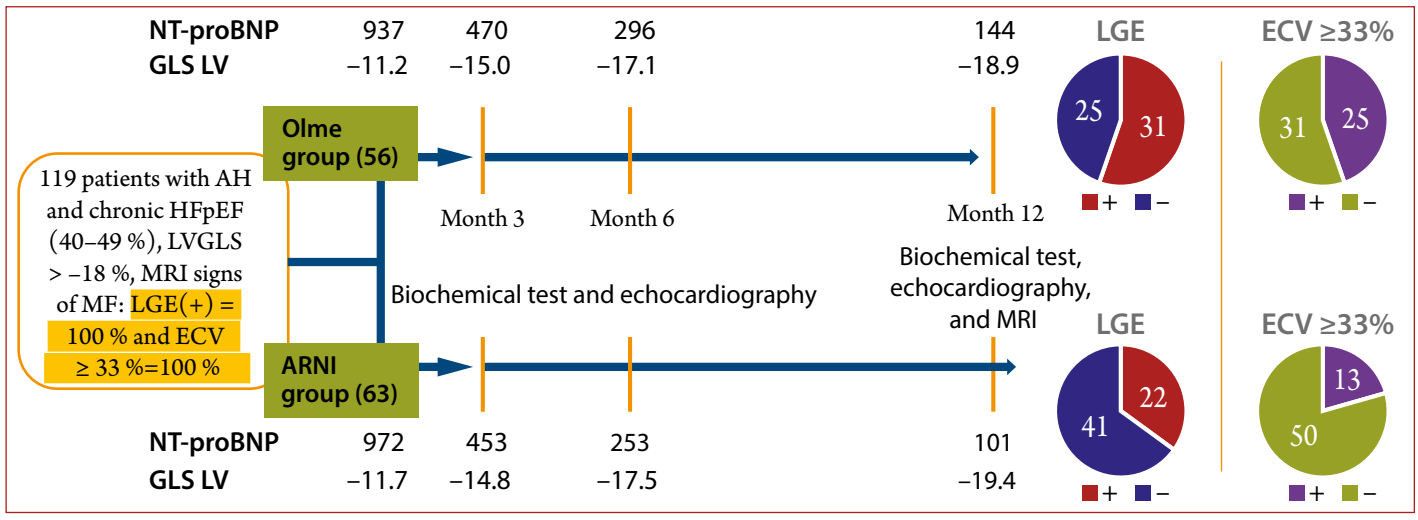
Exclusion criteria: age above 75 years, symptomatic AH, previously verified coronary artery disease (CAD; including myocardial infarction, percutaneous coronary intervention or coronary artery bypass grafting), severe congenital or acquired heart valvular disease, severe hypertrophic cardiomyopathy, Takotsubo cardiomyopathy, amyloidosis, pregnancy, any form of non-valvular atrial fibrillation, ischemic or hemorrhagic stroke, any rheumatic diseases, obesity of any stage, diabetes mellitus type 2 with glycated hemoglobin above 7.5%, severe anemia, chronic kidney disease stage 4–5 (estimated glomerular filtration rate < 30 mL/min/1.73 m^2), malignancies, any conditions requiring nonsteroidal anti-inflammatory drugs or glucocorticoids.

At the cardiologist's discretion, patients with AH due to persistent high blood pressure (BP) were transferred from enalapril, lisinopril, perindopril to olmesartan medoxomil (Cardosal/Hipersar; Olme group, n = 56) or ARNI sacubitril/valsartan (Uperio/Entresto; ARNI group, n = 63). In the first 4 weeks, the dose of olmesartan was titrated from 10 mg to 40 mg every 2 weeks, the dose of sacubitril/valsartan was selected according to the package leaflet. Dose escalation was stopped when systolic blood pressure (SBP) or diastolic blood pressure (DBP) achieved 120 mm Hg and 70 mm Hg or lower, respectively. In addition to the selected drug, according to which patients were divided into 2 groups (Olme and ARNI), all patients received treatments according to the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure [20], specifically bisoprolol or metoprolol succinate, eplerenone, dapagliflozin. Moreover, patients with baseline dyslipidemia (TC > 4.9 mmol/L and/or LDL cholesterol > 3.0 mmol/L) received lipid-lowering therapy with atorvastatin from 40 to 80 mg/day or rosuvastatin from 20 to 40 mg/day (if the target level of LDL cholesterol was not achieved in 3 months statin therapy was supplemented with ezetimibe 10 mg/day).

Complete blood count, urinalysis, and biochemical blood test were performed in all patients at baseline. 12-lead ECG, 24-hour BP monitoring, 24-hour Holter monitoring, transthoracic echocardiography with LVGLS calculation, gadolinium-enhanced MRI of the heart were carried out. Outpatient clinical monitoring and laboratory and echocardiographic monitoring were carried out in 3, 6, and 12 months. Control MRI was conducted in 12 months.

Echocardiography with the calculation of LV strain indicators was performed using the Philips EPIQ 7 machines. MRI of the heart was performed using the Ingenia (1.5T) scanners manufactured by Philips and Optima MR450w (1.5T) manufactured by GE using special surface coils for heart imaging with the required number of elements. Patients received a total intravenous dose of gadobutrol of 0.15 mmol/kg of body weight. The protocols of MRI, mapping, contrast enhancement and ECV calculations had been described earlier [5, 6] and were carefully followed by us. Extracellular volume (ECV) fraction was calculated in contrast-enhanced MRI of the heart using the following formula:

Central illustration. The Clinical Evolution of Diffuse Myocardial Fibrosis in Patients With Arterial Hypertension and Heart Failure With Mildly Reduced Ejection Fraction Treated by Olmesartan or Sacubitril / Valsartan



ECV = (1 – hematocrit {Hct}) · (1/T1 myocardium after contrast-enhancement – 1/T1 native myocardium) / (1/T1 blood volume after contrast-enhancement – 1/T1 native blood volume).

We targeted the time from 10 minutes after the injection of the contrast-enhancement agent to assess LGE.

The statistical analysis of data obtained was carried out in Statistica 12.5 (Tulsa, USA). The Kolmogorov-Smirnov test was used to assess data distribution. Normally distributed data were presented as the means ± standard deviations, and non-normally distributed data were expressed as the medians and interquartile ranges. Categorical variables were expressed as rates and percentages. Continuous variables were compared between groups using Student's t-test or Mann–Whitney U-test depending on the type of distribution. Categorical variables were compared using the chi-squared test. Two-tailed values $p < 0.05$ were considered statistically significant.

Results

Clinical data of patients and prescribed drugs with doses are presented in Table 1.

Changes in all the indicators of interest over 12 months are provided in Table 2.

After 3 months of therapy, the mean doses of olmesartan and sacubitril/valsartan were 22.3 ± 6.9 mg and 106.3 ± 29.7 mg, respectively. At the same time, mean SBP was 152 ± 13 mm Hg versus 148 ± 13 mm Hg ($p > 0.05$) and mean DBP was 91 ± 9 mm Hg versus 90 ± 8 mm Hg ($p > 0.05$), respectively. Changes in SBP and DBP for 12 months are shown in Figure 1. Differences in SBP were statistically significant only in 6 and 12 months of follow-up: 141 ± 10 mm Hg versus 133 ± 9 mm Hg ($p = 0.0482$) and 127 ± 9 mm Hg versus 119 ± 7 mm Hg ($p = 0.0289$). As for DBP, there were no statistically significant differences between groups during the follow-up period.

The condition of patients improved significantly during CHF treatment in accordance with the guidelines after 3 months and did not deteriorate during further follow-up for up to 12 months. This subjective assessment was confirmed by the positive trend of NT-proBNP, which decreased statistically significantly in both groups after 3 months, and the magnitude of this decrease was statistically significant ($p < 0.001$) at each cut-off point (in 6 and 12 months). Differences in the NT-proBNP levels between the Olme and ARNI groups appeared only in 6 months and became statistically significant only in 12 months of follow-up, showing the superiority of ARNIs over olmesartan (101 ± 33 pg/mL versus 144 ± 38

Table 1. Baseline patient data

Parameter	Olme group	ARNI group	p
Number of patients	56	63	–
Male patients, n (%)	25 (45)	30 (48)	0.7433
Median age, years (range)	57 ± 9 (34–68)	55 ± 9 (33–66)	0.2287
DM type 2, n (%)	14 (25)	13 (21)	0.6041
CKD stage 3, n (%)	13 (23)	16 (25)	0.7989
BMI, kg/m²	26 ± 3	27 ± 3	0.0721
Hemoglobin, g/L	129 ± 12	125 ± 13	0.0850
Hematocrit, %	44 ± 5	42 ± 4	0.2285
Erythrocytes, ×1012/L	4.5 ± 0.3	4.4 ± 0.3	0.0721
Leukocytes, 109/L	6.2 ± 1.7	5.8 ± 1.9	0.2310
ESR, mm/h	14 ± 5	15 ± 4	0.2285
NT-proBNP, pg/mL	937 ± 426	972 ± 541	0.6982
TC, mmol/L	5.6 ± 1.4	5.4 ± 1.3	0.4208
LDL cholesterol, mmol/L	3.7 ± 1.2	3.5 ± 1.3	0.3869
HDL cholesterol, mmol/L	1.2 ± 0.4	1.1 ± 0.4	0.1761
Triglycerides, mmol/L	1.6 ± 0.5	1.7 ± 0.4	0.2285
CRP, mg/L	5.9 ± 1.8	6.3 ± 1.3	0.1640
Potassium, mmol/L	4.3 ± 0.7	4.5 ± 0.6	0.0960
Creatinine, μmol/L	85 ± 16	80 ± 19	0.1257
Urea, mmol/L	6.6 ± 2.7	6.1 ± 2.9	0.3342
Glucose, mmol/L	5.3 ± 1.6	5.2 ± 1.3	0.7077
HbA1c, %	7.1 ± 0.3	7.0 ± 0.3	0.0721
HR, baseline, bpm	82 ± 9	80 ± 10	0.2561
SBP, mm Hg	175 ± 15	173 ± 13	0.4538
DBP, mm Hg	104 ± 8	101 ± 10	0.0757
LVEF, %	46 ± 3	45 ± 4	0.1294
LVGLS, %	-11.2 ± 1.9	-11.7 ± 2.2	0.1898
ECV, %	37 ± 3	36 ± 3	0.0721
LGE+, baseline, n (%)	56 (100)	63 (10 %)	1.0
Bisoprolol/metoprolol succinate, n	37/19	40/23	0.7758
Bisoprolol, mg	6.1 ± 2.1	6.4 ± 2.2	0.4497
Metoprolol succinate, mg	67.1 ± 37.2	60.3 ± 31.0	0.2792
Eplerenone, mg	34.5 ± 11.8	36.1 ± 13.3	0.4913
Rosuvastatin/atorvastatin, n	23/33	33/30	0.2173
Rosuvastatin, mg	26.1 ± 8.5	28.5 ± 9.8	0.1587
Atorvastatin, mg	54.5 ± 18.5	50.7 ± 15.6	0.2267

Olme, olmesartan medoxomil; ARNI, angiotensin receptor-neprilysin inhibitor; DM, diabetes mellitus; CKD, chronic kidney disease; BMI, body mass index; ESR, erythrocyte sedimentation rate; NT-proBNP, N-terminal pro-brain natriuretic peptide; TC, total cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein; CRP, C-reactive protein; HbA1c, glycated hemoglobin; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; LVEF, left ventricular ejection fraction; LVGLS, left ventricular global longitudinal strain; ECV, extracellular volume; LGE(+), late gadolinium enhancement.

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Table 2. Changes in the indicators of interest over 12 months

Parameter	Olme group	ARNI group	p
SBP, month 3, mm Hg	152 ± 13	148 ± 13	0.0965
DBP, month 3, mm Hg	91 ± 9	90 ± 8	0.5223
SBP, month 6, mm Hg	141 ± 10	133 ± 9	0.0482
DBP, month 6, mm Hg	83 ± 8	81 ± 9	0.2050
SBP, month 12, mm Hg	127 ± 9	119 ± 7	0.0289
DBP, month 12, mm Hg	76 ± 8	74 ± 7	0.1485
NT-proBNP, month 3, pg/mL	453 ± 267	470 ± 233	0.7114
NT-proBNP, month 6, pg/mL	296 ± 179	253 ± 161	0.1703
NT-proBNP, month 12, pg/mL	144 ± 38	101 ± 33	0.0207
LVGLS, month 3, %	-15.0 ± 2.1	-14.8 ± 2.1	0.6050
LVGLS, month 6, %	-17.1 ± 2.0	-17.5 ± 2.0	0.2784
LVGLS, month 12, %	-18.9 ± 2.2	-19.4 ± 2.0	0.1966
LVEF, month 12, %	49 ± 4	48 ± 4	0.1761
ECV, month 12, %	31.9 ± 2.0	31.0 ± 1.7	0.0091
ECV > 32 %, month 12, n (%)	25 (45)	13 (21)	0.0104
LGE+, month 12, n (%)	31 (55)	22 (35)	0.0252

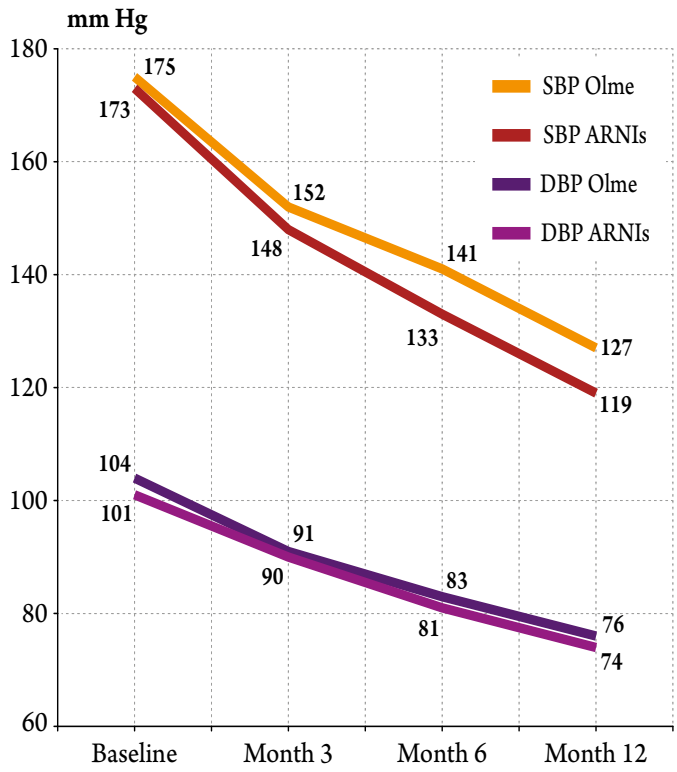
Olme, olmesartan medoxomil; ARNI, angiotensin receptor-neprilysin inhibitor; SBP, systolic blood pressure; DBP, diastolic blood pressure; NT-proBNP, N-terminal pro-brain natriuretic peptide; LVGLS, left ventricular global longitudinal strain; LVEF, left ventricular ejection fraction; ECV, extracellular volume; LGE(+), late gadolinium enhancement.

pg/mL; p = 0.0122). Changes in the NT-proBNP levels are shown in Figure 2.

Dynamic control of echocardiographic parameters, primarily LVGLS, showed a statistically significant increase (estimated in absolute values due to a negative value of LVGLS) in both groups in 3 months (Figure 3). It should be noted that, since myocardial strain is a shortening, the indicator has a negative value, and the absolute value of LVGLS increased statistically significantly in both groups at each cut-off point. LVEF increased to a mean of 49 ± 4% in the Olme group and 48 ± 4% in the ARNI group by the end of follow-up, showing a statistically significant (p = 0.0248) and similar 3% increase in both groups. CHF class decreased in 6 months by 1 class in 91% of patients in the Olme group and in 98% of patients in the ARNI group.

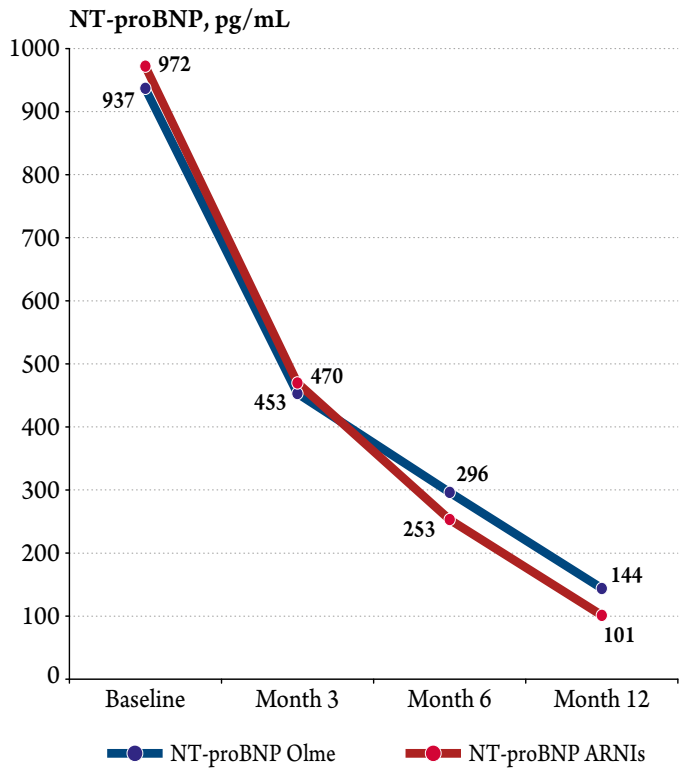
Gadolinium-enhanced MRI of the heart was repeated in all patients in 12 months. At baseline, 100% of patients in both groups had an increased fraction of extracellular volume (ECV above 32%) and all had diffuse late gadolinium enhancement (LGE+). After 12 months, diffuse late gadolinium enhancement (LGE+) persisted in 31 (55%) of 56 patients in the Olme group and 22 (35%) of 63 patients in the ARNI group (Figure 4). ARNI was statistically significantly superior to olmesartan in this term (p = 0.0252). However, both groups included

Figure 1. Changes in mean blood pressure per groups



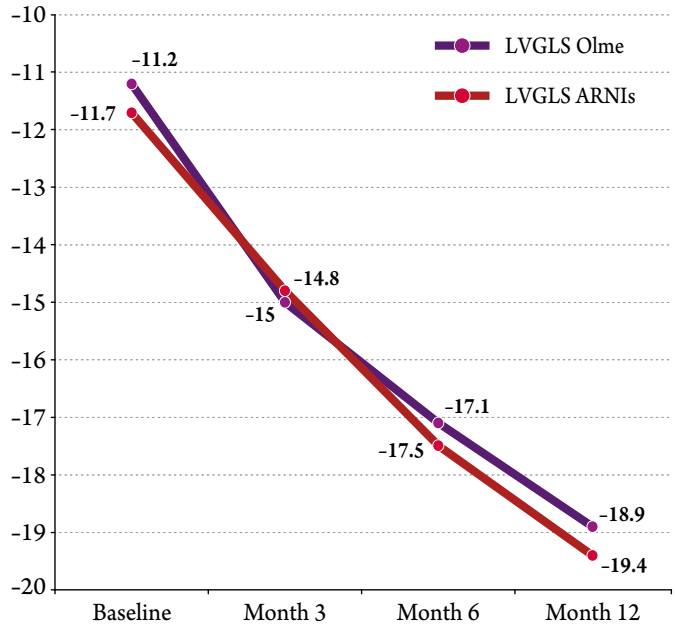
Olme, olmesartan medoxomil; ARNI, angiotensin receptor-neprilysin inhibitor; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Figure 2. Changes in NT-proBNP per groups



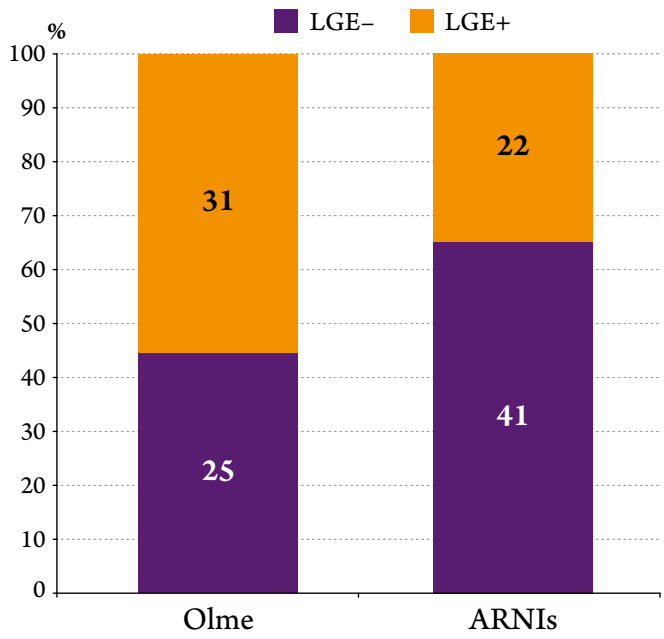
Olme, olmesartan medoxomil; ARNI, angiotensin receptor-neprilysin inhibitor

Figure 3. Changes in LVGLS per groups



LVGLS, left ventricular global longitudinal strain. Olme, olmesartan medoxomil; ARNI, angiotensin receptor-neprilysin inhibitor

Figure 4. Late gadolinium enhancement (MRI) in 12 months



Olme, olmesartan medoxomil; ARNI, angiotensin receptor-neprilysin inhibitor; LGE, late gadolinium enhancement.

patients with signs of diffuse MF, and MRI signs of MF (LGE-) regressed in some patients in 12 months of CHF therapy in accordance with the guidelines. In 12 months, ECV remained 33% or higher in 25 (45%) of 56 patients in the Olme group (mean ECV 31.9 ± 2.0%) and 13 (21%) of 63 patients in the ARNI group (statistically significantly lower mean ECV 31.0 ± 1.7%; p = 0.0091). The proportion of elevated ECV was statistically significantly higher in the Olme group than in the ARNI group (p = 0.0104).

Discussion

The most common cardiac diseases, such as AH, CHF, CAD, can cause a slow but progressive structural remodeling of the heart chambers – this process is characterized by the proliferation and transition of fibroblasts to myofibroblasts, increased formation of connective tissue and fibrosis [2].

We did not verify MF invasively and conducted only modern MRI tests. MRI provides accurate identification and quantification of myocardial scarring/fibrosis [6].

Fibrosis, even diffuse type, is not an irreversible condition. Experience has proven that MF, both local and diffuse types, can regress. Angiotensin-converting enzyme inhibitors/ARNIs, beta-blockers, and mineralocorticoid receptor antagonists are recommended as the cornerstone therapy for patients with chronic HFmrEF, except when drugs are contraindicated or cannot be tolerated [20]. Olmesartan has recently become the focus of myocardial metabolism studies [18]. At the same time, researchers seek to compare it mainly with ARNI [16–19].

In this study, olmesartan was not superior to ARNIs in the effect on diffuse MF regression. Rather, intermediate estimates of LV longitudinal strain showed similar changes of LVGLS in the Olme and ARNI groups in 3 and 6 months, but LVGLS was statistically significantly lower (i.e., better absolute values) in the ARNIE group in 12 months. After 12 months of therapy, the rate of preserved LGE (LGE+) was statistically significantly lower in the ARNI group (35%), that is, almost 2/3 of patients achieved regression of fibrosis (LGE –, and ECV decreased to < 33% in 79% of patients in the ARNI group after 12 months). Olmesartan reduced LGE in only 44% of cases and ECV decreased to < 33% also in 44% of cases. Of course, treatment was comprehensive and included not only olmesartan or ARNI.

The design of the PROBE study was published recently – its compares ARNIs with valsartan in the regression of diffuse interstitial fibrosis in patients with AH [21]. This is a continuation of the search for drugs for MF regression, which began with losartan at the beginning of the 21st century [22].

As for the effect on BP and markers of CHF, olmesartan similarly decreased SBP, DBP and reduced NT-proBNP in the first 3 months, but ARNIs increased the power and were superior to olmesatan in reducing SBP, NT- proBNP,

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and LVGLS by the 6th month. In 12 months, this superiority of ARNI was confirmed by a lower prevalence of persistent diffuse MF.

Limitations

This study was limited by non-randomized design and relatively small number of patients followed up. Therefore, the superiority of ARNIs over olmesartan require further broader evaluation in a large randomized clinical trial.

Conclusion

Olmesartan is able to cause regression of myocardial fibrosis in individual patients with arterial hypertension and dyslipidemia in the complex treatment of chronic heart failure with mid-range left ventricular ejection fraction. It quickly reduces systolic and diastolic blood pressure, reduces the levels of chronic heart failure markers, restores indicators of reduced left ventricular global longitudinal deformation. However, sacubitril/valsartan are superior to olmesartan, which begins to be evident and significant compared to olmesartan in some parameters in 6 months, and a statistically significantly higher prevalence of diffuse myocardial fibrosis regression is seen in 12 months.

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