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Can a Lipophilic Statin Improve the Treatment of Heart Failure With Preserved Ejection Fraction in Patients With Hypertension and Obesity?

Aim	To evaluate the effect of pleiotropic (anti-inflammatory and antifibrotic) effects of a lipophilic statin (atorvastatin) in the treatment of heart failure (HF) with preserved left ventricular (LV) ejection fraction (HFpEF)
Material and methods	This observational study included 80 patients with HFpEF; 40 of them received atorvastatin 20–80 mg/day in addition to a standard treatment. 40 patient who refused of the statin treatment or had intolerance of the drug received only the standard treatment. The follow-up period was 12 months and included 5 visits. At the visits, the general condition of patients was evaluated; electrocardiography and echocardiography were performed at rest and during dosed physical exercise (PE); anthropometry was analyzed; and office blood pressure (BP), heart rate (HR) and parameters of systolic and diastolic LV function were recorded.
Results	Among the patients included into the study, women aged 60–70 years prevailed who had pronounced obesity (n=46; 57.5% with class II–II obesity), severe arterial hypertension (AH) (n=65; 81.2% with grade 3 hypertension), dyslipidemia, type 2 diabetes mellitus, and chronic kidney disease. The administration of atorvastatin in addition to standard therapy was associated with regression of HF symptoms and increased PE tolerance; these effects were more pronounced after 6 months of observation. Furthermore, during a 12-month follow-up, significant multidirectional changes in LV global longitudinal strain were noted; in the main group, the LV global longitudinal strain increased indicating an improvement in the LV systolic function while in the control group, it decreased reflecting early, preclinical manifestations of HF progression. A diastolic stress test in combination with a cardiopulmonary stress test was performed in 64 patients with HFpEF at enrollment and at 6 and 12 months of follow-up. When the load reached 50 W in the atorvastatin treatment group after 12 months, a significant increase in tissue Doppler velocity parameters was revealed, specifically in e' septal and e' lateral. This led to a significant decrease in the E/e' ratio while in the control group, no time-related changes in these parameters were noted. Similar changes were also detected at higher levels of PE.
Conclusion	Long-term use of the lipophilic statin (atorvastatin) in addition to a standard therapy was associated with regression of clinical manifestations of HFpEF, provided preservation of the systolic function, and some improvement in the LV diastolic function both at rest and during dosed PE.

Keywords	Heart failure; preserved left ventricular ejection fraction; lipophilic statin; diastolic stress-test; left ventricular global longitudinal strain
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Introduction

Heart failure with preserved ejection fraction (HFpEF) of the left ventricle (LV) is the most common form of HF and a serious global health concern, since the number of patients with this form of HF is rising annually, there is no effective treatment, and mortality has not changed in decades. This is mostly because of the large variety of cardiac and extracardiac disorders that may cause this type of HF. Since many HFpEF patients are overweight or obese, it is possible to identify the obesity-associated phenotype specific to this disease [1]. Excess adipose tissue with extra vasculature exacerbates the hemodynamic load on the LV, which results in compensatory increased cardiac output, a quick depletion of the physiological reserve, thickening of the heart walls, and enlargement of the heart cavities [2]. Because visceral adipose tissue has an active receptor apparatus, it is the primary source of neurohormones and pro-inflammatory cytokines that are synthesized. These factors contribute to the

development of local and systemic pro-inflammatory status, myocardial fibrosis, adverse cardiac remodeling, diastolic dysfunction (DD), and HFpEF [3, 4].

New approaches to the treatment of HFpEF are being actively sought, since there is no convincing evidence of lower morbidity and mortality during the use of angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), beta-blockers, and mineralocorticoid receptor antagonists (MRAs) for the treatment of this phenotype of the disease. Several studies showed that long-term administration of ACE inhibitors or ARBs (candesartan) only improved symptoms and reduced HF NYHA class [5–8]. The EMPEROR-Preserved study showed that the administration of empagliflozin was associated in patients with HFpEF with a 21 % and 29 % decrease in cardiovascular mortality and hospitalizations for HF, respectively. The administration of sacubitril/valsartan to this category of patients led to a comparable decrease in the number of hospitalizations for HF, but the reduction in cardiovascular mortality did not exceed 13 % [9].

At the same time, systemic inflammation as one of the main mechanisms of HF in obesity justifies the use of statins in patients with HFpEF, which improve the oxidative balance in endothelial cells, restore the bioavailability of nitric oxide, and have antifibrotic and anti-inflammatory effects (Figure 1) [10].

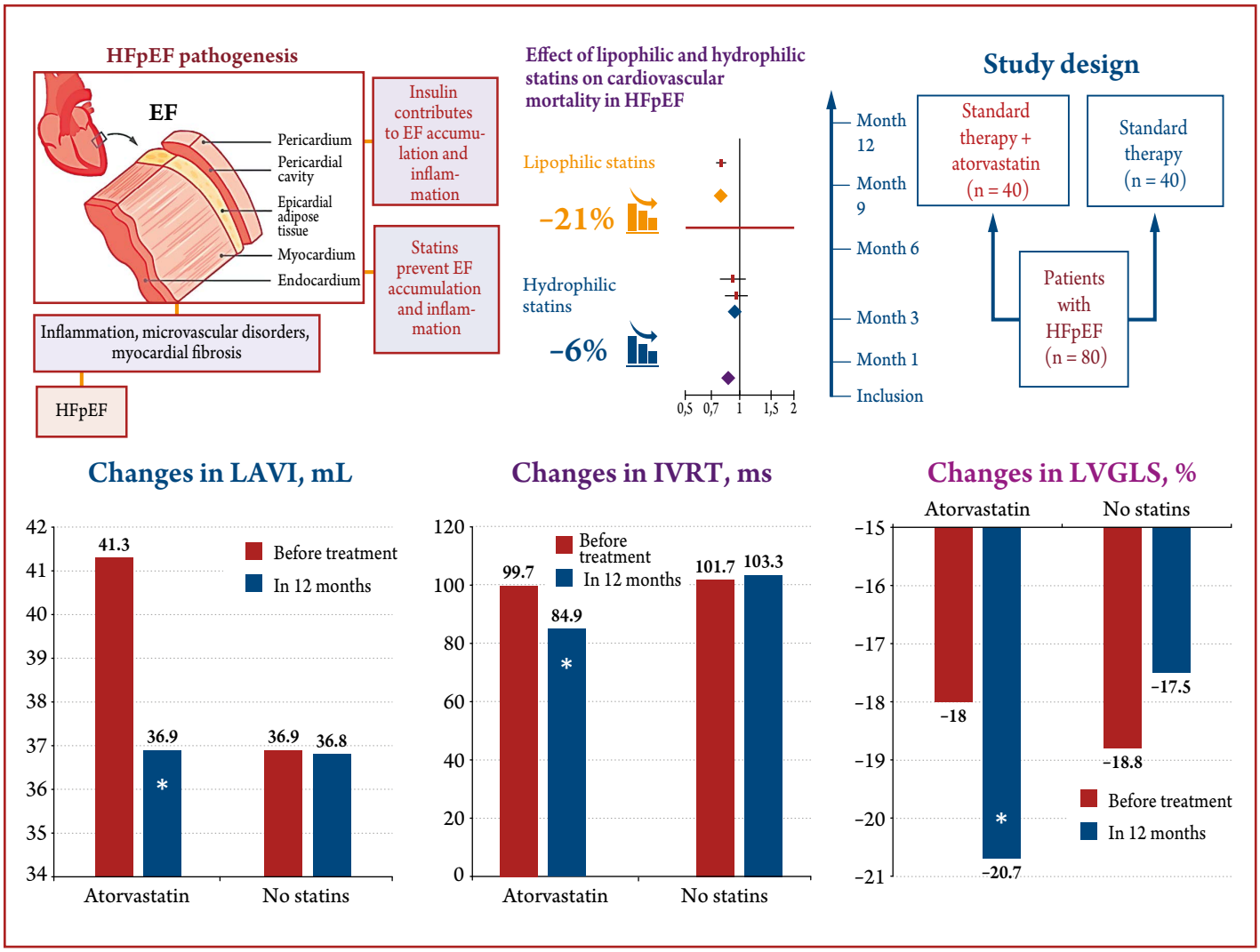
Objective

Evaluate the pleiotropic (anti-inflammatory and antifibrotic) effects of a lipophilic statin (atorvastatin) in the treatment of patients with HFpEF.

Material and Methods

The observational study included 80 patients with HFpEF aged from 50 to 80 years who signed informed consent. They were divided into two comparable groups of 40 patients

Central illustration. Can a Lipophilic Statin Improve the Treatment of Heart Failure With Preserved Ejection Fraction in Patients With Hypertension and Obesity?



EF, epicardial fat; LAVI, left atrial volume index; HFpEF, heart failure with preserved ejection fraction; IVRT, isovolumetric relaxation time; LVGLS, left ventricular global longitudinal strain

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each. Inclusion criteria comprised arterial hypertension (AH) (office blood pressure (BP) ≥140/80 mm Hg), obesity (body mass index (BMI) >30 kg/m^2), and chronic heart failure (CHF) with preserved left ventricular ejection fraction (LVEF). Exclusion criteria were patient's refusal to participate in the study; history of coronary artery disease (CAD), cerebrovascular accident (CVA), atrial fibrillation, severe renal and hepatic failure, any decompensated somatic disease, malignancies, alcohol or drug misuse, mental illness.

All patients completed 5 visits during the 12 month follow-up periods: at baseline, in 3, 6, 9, and 12 months of follow-up. At each visit, patient complaints, clinical manifestations of HF were analyzed using the Symptomatic Hospital and Outpatient Clinical Score (SHOCS), anthropometric measurements were taken, office BP was measured, and the results of 6 minute walk distance (6MWD) test were analyzed. At three visits (baseline, month 6, and month 12), 12-lead electrocardiogram was recorded, transthoracic two-dimensional echocardiography was conducted followed by the analysis of the main LV systolic and diastolic function parameters, left ventricular global longitudinal strain (LVGLS) at rest and during graduated exercise in combination with cardiopulmonary exercise testing (CPET). Biochemical parameters were analyzed at inclusion and in 6 and 12 months of follow-up. Cerebral natriuretic peptide (BNP) levels were determined at baseline using the Triage MeterPro analyzer.

Standard HF therapy was prescribed following the Russian clinical guidelines to all patients at the baseline visit [11]. Subjects received ACE inhibitors or ARBs, beta-blockers, diuretics at the recommended doses, and dose titration was performed if necessary.

Atorvastatin at the dose of 20–80 mg/day was administered in the treatment group in addition to the listed treatments. In the control group, patients who refused to take statins or had manifestations of intolerance received only standard therapy. The study protocol was approved by the intercollegiate ethics committee in 2018.

The data obtained were processed in Statistica 12.0 (Statsoft Inc., USA). The data are expressed as the means with standard deviations and the absolute values with percentages. Non-parametric data are presented as the medians with the 25th and 75th percentiles. Student, Mann-Whitney, Wilcoxon tests were used for statistical processing depending on the nature of the variable distribution. The Bonferroni test was used in multiple comparisons. The differences between the values compared were considered statistically significant at $p < 0.05$.

Results

General characteristics of subjects are presented in Table 1. There were more female patients, the mean age was 66.3 years. All patients had AH and obesity, which met the inclusion criteria. Lipid and carbohydrate metabolism disorders were established in 78 (97.5 %) patients, in 16 (20 %) patients had signs of chronic kidney disease, which manifested by dyslipidemia, hyperglycemia, and decreased glomerular filtration rate.

In accordance with the inclusion criteria, all patients had signs of DD, such as left atrial (LA) enlargement and an increased E/e' ratio. At the same time, LVEF was preserved (50 % or more). All subjects received renin-angiotensin-aldosterone system inhibitors, such as ACE inhibitors or ARBs, and most patients also took diuretics and beta-blockers. Subject of the treatment group received atorvastatin at a mean dose of 36.7 mg/day. The study groups were comparable in all indicators of interest.

Changes in complaints and clinical manifestations of HFpEF were assessed at each visit using the SHOCS questionnaire, exercise tolerance was evaluated using the 6 MWD test (Table 2). All patients showed a decrease in clinical manifestations of HFpEF, including dyspnea during exercise, asthenia, palpitations, during the long-term drug therapy. Regression of symptoms was most pronounced in the treatment group after 6 months of follow-up. After 12 months, significantly fewer patients complained of dyspnea, palpitations, and asthenia in the atorvastatin group compared to the control group. Moreover, all patients showed a statistically significant decrease in the total SHOCS score after 6 months of follow-up.

Regression of HF clinical manifestations during the best possible therapy was accompanied by a longer 6 MWD. It should be noted that an increase in the 6-MWD was comparable in both groups in the first 6 months of follow-up, but a slight decrease in this indicator was noted in the control group by the end of the follow-up, while it remained the same in the atorvastatin group.

According to transthoracic echocardiography at rest (Table 3), all patients had higher left atrial volume index (LAVI) at inclusion in the study, which was a diagnostic criterion for LVDD. In the atorvastatin group, a significant decrease in this indicator was observed after 6 and 12 months of follow-up, while a similar trend was observed in the control group only in the first 6 months of treatment.

During the 12 month follow-up period, a significant multidirectional trend of LVGLS was observed: it increased in the treatment group, which was indicative of an improved LV systolic function, and it decreased in the control group, which reflected early, preclinical manifestations of HF progression despite the administration of the maximal tolerated doses of standard multicomponent therapy. Analysis of changes in LV diastolic function during the long-term treatment for HF showed that there were no significant differences in indicators at inclusion that would reflect the LV myocardial stiffness in diastole. At the same time, the additional use of atorvastatin

Table 1. General characteristics of patients included in the study

Parameter	Treatment group (n = 40)	Control group (n = 40)	p
Female, n (%)	35 (87.5)	36 (90)	0.78
Age, years (M ± SD)	67.1 ± 4.7	65.4 ± 6.9	0.81
BMI, kg/m^2, (M ± m)	35.3 ± 5.7	36.9 ± 5.2	0.73
Office SBP, mm Hg (M ± SD)	136.1 ± 18.6	142.3 ± 16.9	0.62
Office DBP, mm Hg (M ± SD)	82.3 ± 10.4	88.0 ± 10.9	0.68
HR, bpm (M ± SD)	69.8 ± 12.4	71.9 ± 11.1	0.75
Total cholesterol, mmol/L (M ± m)	5.8 ± 1.0	5.4 ± 0.99	0.53
HDL cholesterol, mmol/L (M ± SD)	3.9 ± 1.2	3.5 ± 0.9	0.57
Glucose, mmol/L (M ± SD)	7.1 ± 2.2	6.2 ± 1.5	0.32
Creatinine, μmol/L, (M ± SD)	89.4 ± 14.4	90.2 ± 16.8	0.76
BNP, pg/mL (M ± SD)	59.3 ± 6.9	62.8 ± 6.1	0.64
GFR, mL/min/1.73 m^2 (M ± SD)	58.2 ± 4.7	58.5 ± 5.2	0.89
LVMI, g/m^2 (M ± SD)			
• Male patients	120.6 ± 20.6	114.3 ± 17.2	0.39
• Female patients	95.9 ± 17.2	90.4 ± 13.5	0.46
LAVI, mL/m^2 (M ± SD)	41.3 ± 6.3	36.9 ± 5.3	0.24
E/e' mean (M ± SD)	13.2 ± 2.5	12.2 ± 3.1	0.67
LVEF, % (M ± SD)	65.9 ± 3.1	66.3 ± 2.8	0.78
ACE inhibitors, n (%)	23 (57.5)	19 (47.5)	0.56
ARBs, n (%)	17 (42.5)	21 (52.5)	0.45
Diuretics, n (%)	33 (82.5)	34 (85)	0.75
Beta blockers, n (%)	34 (85)	32 (80)	0.69

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; LDL, low-density lipoprotein; BNP, brain natriuretic peptide; GFR, glomerular filtration rate; LVMI, left ventricular mass index; LAVI, left atrial volume index; E/e', the ratio of peak early mitral inflow velocity to peak mitral annular velocity; LVEF, left ventricular ejection fraction; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker.

was accompanied by more pronounced positive changes in the main and additional criteria of DD compared to the standard HF therapy alone. For example, a significant increase in the E/A ratio was detected in the treatment group revealed, and this indicator did not change in the control group. Tissue Doppler showed that mitral annular velocity significantly increased in the treatment group, the E/e' ratio significantly decreased, which was indicative of improved LV relaxation. The control group also showed positive changes in several tissue Doppler indicators, such as increased e' sept and reduced E/e' mean. Significantly decreased isovolumetric relaxation time (IVRT) in the treatment group, which is an early sign of impaired LV relaxation, was probably caused by relative recovery of diastolic function due to the antifibrotic effect of atorvastatin.

Diastolic stress testing in combination with cardiopulmonary exercise testing was performed in 64 patients with HFpEF at inclusion, in 6 and 12 months of follow-up (Table 4). Diseases of the musculoskeletal system, pain in the calf muscles, severe weakness when pedaling without load were the main reasons why stress testing was abandoned. Diastolic function was assessed at 50 W, when anaerobic threshold and submaximal heart rate (HR) were reached, and during rest.

Table 2. Changes in the clinical condition of patients with HFpEF during the standard treatment and the combined administration of atorvastatin

Parameter	Treatment group (n = 40)			Control group (n = 40)		
	Inclusion	Month 6	Month 12	Inclusion	Month 6	Month 12
Dyspnea during exercise, n (%)	40 (100)	30 (75)	15 (36)*	40 (100)	33 (83)	33 (83)#
Asthenia, n (%)	29 (73)	17 (43)	12 (43)*	34 (81)	23 (58)	19 (48)*#
Palpitations, n (%)	30 (75)	9 (23)*	3 (8)*	29 (73)	14 (35)*	8 (20)*#
SHOCS score (M ± m)	4.4 ± 1.6	2.5 ± 1.4*	2.7 ± 1.3*	3.9 ± 1.7	2.5 ± 1.4*	2.5 ± 0.9*
6 MWD, m Me [25 %;75 %]	350.0 [250.0; 400.0]	400.0 [300.0; 450.0]*	400.0 [200.0; 450.0]*	350.0 [250.0; 350.0]	400.0 [312.5; 450.0]*	300.0 [200.0; 400.0]#

* $p < 0.05$ when compared versus the inclusion visit;
# $p < 0.05$ when compared versus the treatment group at the same stage of follow-up. HFpEF, heart failure with preserved ejection fraction; SHOCS, Symptomatic Hospital and Outpatient Clinical Score; 6 MWD, 6 minute walk distance.

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Table 3. Changes in the echocardiographic indicators of patients with HFpEF at rest during the standard treatment and the combined administration of atorvastatin

Parameter	Treatment group (n = 40)			Control group (n = 40)		
	Inclusion	Month 6	Month 12	Inclusion	Month 6	Month 12
LAVI, mL/m2 (M ± m)	41.3 ± 6.3	37.8 ± 6.9*	36.9 ± 6.1*	36.9 ± 5.3	32.1 ± 4.9*	36.8 ± 6.9
LVEF, % (M ± m)	65.9 ± 3.1	65.3 ± 3.1	65.5 ± 2.9	66.3 ± 2.8	66.3 ± 3.3	65.0 ± 2.2
LVGLS, % (M ± m)	-18.0 ± 3.4	-19.2 ± 2.5	-20.7 ± 2.9*	-18.8 ± 2.4	-18.5 ± 3.4	-17.5 ± 3.7*#
E/A (M ± m)	0.89 ± 0.2	0.92 ± 0.2	0.96 ± 0.2*	0.85 ± 0.2	0.81 ± 0.2	0.85 ± 0.2
e' sept, cm/s(M ± m)	5.2 ± 1.2	6.4 ± 1.3*	6.9 ± 1.2*	5.2 ± 1.0	5.7 ± 1.2	5.9 ± 1.5
e' lat, cm/s(M ± m)	7.1 ± 1.5	8.2 ± 1.4*	8.8 ± 1.1*	7.6 ± 1.1	8.5 ± 1.7	8.4 ± 1.4*
E/e' mean (M ± m)	13.2 ± 2.5	10.9 ± 2.4*	10.8 ± 1.7*	12.2 ± 3.1	10.7 ± 3.5*	10.6 ± 3.2*
IVRT, ms (M ± m)	99.7 ± 19.1	95.3 ± 15.0*	84.9 ± 17.4*	101.7 ± 17.6	99.9 ± 20.1	103.3 ± 25.9#

* p < 0.05 when compared versus the inclusion visit;
# p < 0.05 when compared versus the treatment group at the same stage of follow-up. HFpEF, heart failure with preserved ejection fraction; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; LVGLS, left ventricular global longitudinal strain; E/A, the ratio of peak early to late transmitral filling velocities; e' sept, septal mitral annular velocity; e' lat, lateral mitral annular velocity; E/e', the ratio of peak early mitral inflow velocity to peak mitral annular velocity; IVRT, isovolumetric relaxation time.

Table 4. Changes in the stress echocardiographic indicators of patients with HFpEF at rest during the standard treatment and the combined administration of atorvastatin

Parameter	Treatment group (n = 33)			Control group (n = 31)		
	Inclusion	Month 6	Month 12	Inclusion	Month 6	Month 12
E/A	0.89 ± 0.2	0.92 ± 0.2	0.96 ± 0.2*	0.85 ± 0.2	0.81 ± 0.2	0.85 ± 0.2
e' sept 50 W, cm/s	7.8 ± 1.4	8.4 ± 1.4	8.9 ± 1.5*	8.4 ± 2.1	8.5 ± 1.4	8.6 ± 1.2
e' lat 50 W, cm/s	10.6 ± 2.2	11.3 ± 2.3	12.3 ± 2.6*	10.9 ± 2.3	10.6 ± 1.3	11.2 ± 2.7#
E/e' 50 W mean	11.6 ± 2.9	10.3 ± 2.1	9.6 ± 3.2*	10.6 ± 3.2	10.4 ± 1.3	10.8 ± 1.7#
e' sept AT, cm/s	9.7 ± 1.6	9.7 ± 1.8	9.8 ± 1.7	9.6 ± 1.5	9.4 ± 1.0	9.4 ± 1.1
e' lat AT, cm/s	12.6 ± 2.2	11.9 ± 2.3	12.3 ± 2.8	11.6 ± 2.0	11.4 ± 0.8	11.5 ± 1.6
e' sept Max, cm/s	8.0 ± 1.0	12.0 ± 1.4	12.7 ± 1.3*	10.5 ± 2.1	7.5 ± 0.7	7.3 ± 1.4*#
e' lat Max, cm/s	10.3 ± 2.3	14.5 ± 0.7	14.9 ± 1.2*	13.0 ± 4.2	9.8 ± 1.8	9.3 ± 2.2*#
e' sept, cm/s	6.5 ± 1.2	7.6 ± 1.4	7.9 ± 1.4*	6.9 ± 1.6	6.7 ± 1.0	6.8 ± 1.3
e' lat, cm/s	9.2 ± 1.9	10.0 ± 2.4	10.7 ± 2.1	9.3 ± 1.7	9.1 ± 2.0	9.4 ± 1.6
E/e' mean	12.4 ± 3.4	11.3 ± 3.0	10.8 ± 3.2*	11.7 ± 3.3	11.7 ± 2.3	11.4 ± 2.6

* p < 0.05 when compared versus the inclusion visit; # p < 0.05 when compared versus the treatment group at the same stage of the study.
E/A, the ratio of peak early to late transmitral filling velocity; e' sept, septal mitral annular velocity; W, watt; e' lat, lateral mitral annular velocity; E/e', the ratio of peak early mitral inflow velocity to peak mitral annular velocity; AT, anaerobic threshold.

A significant increase in the tissue Doppler velocity indicators, such as e' sept and e' lat, was observed at 50 W in the treatment group after 12 months of treatment of HFpEF, which led to a significant decrease in the E/e' ratio. There were no changes in these indicators in the control group. In both groups, an increase in exercise until anaerobic threshold was accompanied by a slight compensatory increase in e' sept and e' lat, and long-term standard HF therapy in combination with atorvastatin contributed to a more pronounced increase in e' sept and e' lat at this stage of exercise than the use of standard therapy alone. This trend was significant for changes in e' sept and e' lat at the submaximal heart rate. Standard HF therapy in combination with atorvastatin was accompanied by an increase in velocities in 6 months of follow-up, velocities decreased when anaerobic threshold was reached in the control group. Relative improvement in LV diastolic function during rest was shown in the analysis of tissue Doppler velocity indicators. Thus, there was a significant increase in e' sept and a decrease in E/e' in the treatment group after 12 months of follow-up. There were no significant changes in these indicators in the control group.

Discussion

There are few controversial studies evaluating the efficacy of statins in patients with HFpEF. Nochioka et al. [12] analyzed the data of 3,124 patients with HFpEF included in the CHART-2 registry. The mean age of patients was 69 years and the mean follow-up period 3.4 years. Three-year mortality of patients taking statins (rosuvastatin, atorvastatin, pravastatin, pitavastatin, etc.) was significantly lower than that of patients not taking these drugs (8.7 % vs.14.5 %; hazard

ration (HR) 0.74; 95 % confidence interval (CI) 0.58–0.94; p < 0.001). Statins had the most pronounced positive effect on the risk of sudden cardiac death, which, according to the authors, may be due to improved coronary endothelial function, stabilization of atherosclerotic plaques, recovery of the ventricular conduction system function, which results in lower incidence of acute coronary syndrome and life-threatening ventricular arrhythmias.

The use of statins was accompanied by higher survival among 3,427 patients with HFpEF included in the Swedish registry [13]. The analysis showed that one-year survival of statin-treated patients was 85.1 % versus 80.9 % of statin-naive patients (HR 0.80, 95 % CI 0.72–0.89; p < 0.001). However, in randomized clinical trial GISSI-HF, rosuvastatin at the dose of 10 mg/day did not show a statistically significant benefit for patients with HFpEF in terms of mortality compared to placebo [14]. In our study, lipophilic atorvastatin was prescribed to patients with HFpEF and obesity. It has more pronounced anti-inflammatory properties and a protective effect on the vascular endothelium. In this regard, we revealed during long-term follow-up a positive effect of atorvastatin on the LV diastolic function and some improvement in the LV systolic function, which led to a regression of the disease symptoms and an increase in exercise tolerance. Similar results were obtained in a prospective randomized study [15], in which atorvastatin at the dose of 10 mg/day was added to antihypertensive therapy (n = 167). After 12 months of treatment, the patients' clinical condition improved, and they did better in the 6 MWD test. N-terminal pro-brain natriuretic peptide levels significantly decreased, and the LV diastolic function tended to improve of the LV in patients receiving atorvastatin.

Conclusion

Long-term administration of a lipophilic statin (atorvastatin) in addition to standard therapy leads to regression of clinical manifestations of heart failure with preserved ejection fraction and higher physical activity of patients. Analysis of left ventricular global longitudinal strain showed that the additional use of atorvastatin contributes to the preservation of left ventricular systolic function, whereas it decreases during standard therapy of heart failure with preserved left ventricular ejection fraction by the end of the 12 month follow-up period. The administration of standard therapy for heart failure in combination with atorvastatin improves the left ventricular diastolic function at rest and during graduated exercise, improves the compensatory mechanisms of the left ventricle at peak exercise, which was manifested by a significant increase in the tissue Doppler velocity indicators.

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No conflict of interest is reported.

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