ORIGINAL ARTICLE

Effect of atorvastatin on systolic and diastolic function in patients with heart failure with reduced ejection fraction (HFrEF)

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ABSTRACT

Aim To investigate the benefit of high-dose lipophilic statin therapy on cardiac remodelling, function and progression of heart failure (HF) in patients with ischemic heart disease.

Methods A total of 80 patients with ischemic HF diagnosis were followed during 6 months, and they were divided in two groups. First group (n=40) was treated by high-dose lipophilic statin therapy (atorvastatin 40 mg) and conventional therapy for HF, while the second group (n=40) had no atorvastatin in the therapy.

Results In the beginning of study, from all of the observed parameters, only the ratio of flow rates in early and late diastole (E/A ratio) differed between the test groups (p=0.007). After six months, a statistically significant increase in left ventricular end-diastolic diameter (LVIDD) in patients who had not been treated with atorvastatin was found. In the patients treated with atorvastatin, there was a significant reduction in basal right ventricle diameter in diastole and systole ($p<0.001$ and $p<0.001$, respectively), and in tricuspid annular plane systolic excursion (TAPSE) ($p<0.001$); there was a reduction in LVIDD ($p<0.001$), and an increase of ejection fraction of the left ventricle according to Teicholtz and Simpson ($p<0.001$ and $p<0.001$, respectively). Also, there was an increase of deceleration time of early diastolic velocity (DTE) ($p<0.05$) and a decrease of isovolumic relaxation time (IVRT) ($p<0.001$).

Conclusion The reduction in the right and left ventricle diameters was noted after the six-month atorvastatin therapy. Atorvastatin in the therapy resulted in increased EFLV and better systolic function and should be a part of a therapeutic modality of HF.

Key words: heart failure, hydroxymethylglutaryl-CoA reductase inhibitors, therapeutics

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INTRODUCTION

Heart failure (HF) is a clinical entity characterized by structural and/or functional cardiac abnormalities (1). Based on ejection fraction of the left ventricle (EFLV) it is divided into HF with preserved ejection fraction (HFpEF), where EFLV is ≥ 50%, HF with mid-range ejection fraction (HFmrEF) with EFLV in the range of 40%-49%, and as HF with reduced ejection fraction (HFrEF) and EFLV <40% (1).

The question of the use of statins in patients with HF is raised, and their effect is already well known in the primary and secondary prevention of atherosclerotic cardiovascular disease (2,3). Statins inhibited the activity of 3-hydroxy-3-methylglutaryl coenzyme A reductase, and are primarily used in the treatment of hyperlipidaemia (2). They have a lipid lowering effect, pleiotropic effects, improvement of endothelial function, anti-inflammatory effect, immunomodulatory effect and anti-thrombotic effect (2). It seems natural that the pleiotropic effects of statins may play a useful role in patients with HF (2-4). It is known that in the patients with higher risk for a cardiovascular event, a benefit of statins will be greater. In patients with HF with diabetes and hypertension, statins will be more effective than in those who do not have these risk factors (2-4). Statins have immuno-modulatory and anti-inflammatory effects, and they can induce anti-atherosclerotic effects regardless of their antilipemic action (4). Statins have an effect on endothelial dysfunction, which may contribute to vascular remodelling (5). The benefit of statin therapy in the process of atherosclerosis is well established (6-10).

The use of statins is a part of routine premedication prior to primary percutaneous coronary intervention (pPCI) (11,12). High doses of statins (atorvastatin 80 mg or rosuvastatin 40 mg), when administered prior to pPCI in patients with STEMI are positive predictors of outcome, and they are associated with reduced occurrence of major adverse cardiovascular events (MACE) (12-15) reducing infarct size by increasing myocardial microvascular perfusion (16-18). The statins significantly reduce the level of total cholesterol and LDL, and increase the level of high-density lipoproteins (HDL) (19,20).

Statins are divided into lipophilic (atorvastatin, simvastatin, lovastatin, fluvastatin, cerivastatin and pitavastatin) and hydrophilic (rosuvastatin, pravastatin) in relation to tissue selectivity (21). The question arises about the effect and a choice of statins on the heart muscle in patients diagnosed with HF. Atorvastatin, as a lipophilic statin, shows potential benefit in patients diagnosed with chronic HF (10), but still with a lot of questions in patients who have been verified with ischemic heart disease in addition to HF.

The aim of this study was to investigate the benefit of high-dose lipophilic statin therapy on cardiac remodelling, function and progression of HF in patients with ischemic HF.

PATIENTS AND METHODS

Patients and study design

This prospective, clinical, and controlled study involved 80 patients, who received high-dose lipophilic statin therapy between January and June 2020. According to New York Heart Association (NYHA) heart failure classification (10) all patients belonged to class II, III, and IV. Criteria for inclusion were verified HF of ischemic etiology, ejection fraction of the left ventricle (EFLV) ≤ 40%, and due to the lipid profile, the patients who did not need statin therapy. Exclusion criteria were: lipophilic statins therapy for more than 3 months before the start of the study, heart failure of non-ischemic origin, severe liver or kidney dysfunction, occurrence of statin side effects (increase in transaminases four times more than reference range, muscle pain).

Patients with ischemic heart failure were determined according to the previous clinical findings of myocardial infarction or already by cardiac catheterization, in the period of two years before research, verified coronary artery disease with stenosis over 50%. Patients were divided into two groups: the first group (n=40) was treated by a high-dose lipophilic statin therapy (atorvastatin 40 mg) and conventional therapy (angiotensin converting enzyme inhibitors or angiotensin II receptor blockers, mineralocorticoid receptor antagonists, beta blockers) for HF, while the second (n=40) had no atorvastatin in therapy.

An informed consent was obtained from all patients following an explanation of the purpose of the study. An ethical approval was obtained from the Ethics Committee of Clinical Centre University of Sarajevo.

Methods

All the patients were undergoing transthoracic echocardiographic examination (TTE) at the beginning of the study and after 6 months. Two-dimensional TTE was performed at the beginning and 6 months after the inclusion of the high-dose lipophilic statin therapy. The left and right ventricles were displayed in a parasternal longitudinal section (long axis view), a parasternal short section (short axis view) and in an apical four-chamber section (four chamber view) to measure the ejection fraction. The EFLV was measured in two ways, by Teicholz and by Simpson. The function of the right ventricle (EFRV) was measured by the tricuspid annular plane systolic excursion (TAPSE). The analysis of trans mitral flows was performed in the apical section of four cavities by placing a two-millimetre volume Doppler sample above the peaks of open mitral cusps during diastole. By the Doppler parameters of the mitral flow, the following was measured: flow rates in early and late diastole and their ratio (E, A, E/A, respectively), deceleration time of early diastolic velocity (DTE) and isovolumic relaxation time (IVRT).

Statistical analysis

The Shapiro-Wilk test was used to test the significance of the difference in deviation from the normal distribution. For the comparative analysis of independent numerical variables, a t-test was used for variables that met the conditions for application, i.e. an appropriate non-parametric test (Mann-Whitney U test) for variables in which an incorrect distribution was found. For comparative analysis of dependent numerical variables, a paired t-test, i.e. the corresponding non-parametric test (Wilcoxon test) was used. In the analysis of the dependence between the category variables, χ^2 exact test was used. Statistical level of 95% ($p<0.05$) was taken as significant.

RESULTS

The average age of the patients with HF who were treated with high-dose atorvastatin therapy was 69.07±8.53 years, while the patients with HF who were not treated with atorvastatin therapy were 71.81±7.73 years old (p=0.128). In the group of patients who were treated with atorvastatin, 31 (77.5%) were males, while nine (22.5%) were females. In the group of patients who were not treated with atorvastatin, 32 (80%) were males, while eight (20%) were females.

In the beginning of the study, from all of the observed parameters, only the E/A ratio differed between the groups (p=0.007). After six months, there was a statistically significant increase in the left ventricular end-diastolic diameter (LVIDD) in patients who are not treated with atorvastatin. Other parameters did not differ significantly (Table 1).

In patients treated with atorvastatin, there was a significant reduction in basal right ventricle diameter in both diastole and systole ($p<0.001$ and $p<0.001$, respectively), in TAPSE ($p<0.001$), and a reduction in LVIDd ($p<0.001$), as well as an increase of ejection fraction of the left ventricle according to Teicholtz and Simpson ($p<0.001$ and $p<0.001$,

Table 1. Basal values of echocardiography parameters of patients with heart failure at the beginning and after 6 months without and with the atorvastatin 40 mg treatment

Parameter	**Not treated** (n=40)		p	**Treated** (n=40)		p
	Basal	**After 6 months**		**Basal**	**After 6 months**	
Basal right ventricle diameter (cm)*						
in diastole	3.55 (3.3-3.9)	3.55 (3.3-3.9)	0.166	3.7 (3.3-3.9)	3.4 (3.0-3.5)	<0.001
in systole	3.1 (2.8-3.5)	3.05 (2.8-3.5)	0.166	3.35 (2.9-3.5)	2.9 (2.55-3.0)	<0.001
Right ventricle function*						
TAPSE (mm)	13 (10.75-14)	13 (10-14)	0.286	12 (9.25-14)	16 (14.5-17.5)	<0.001
Basal left ventricle diameter (cm) †						
LVIDD	5.97±0.49	6.01±0.49	0.002	6.02±0.62	5.60±0.61	<0.001
LVIDS	5.23±0.58	5.26±0.60	0.046	5.29±0.63	4.89±0.63	<0.001
Ejection fraction of left ventricle (%)*						
Teicholtz	31 (30-36.75)	31.5 (28-38.5)	0.730	34 (30-36.75)	40.0 (37-44.5)	<0.001
Simpson	34 (30-40)	32 (30-40)	0.017	34 (30-38)	42 (38-47)	<0.001
Other parameters						
E/A ratio*	0.6 (0.6-0.7)	0.6 (0.6-0.7)	1.0	0,73±0.12	0.73±0,12	1.0
DTE (ms)*	290 (280-310)	291 (280-310)	0.082	294 (290-310)	296 (286-310)	0.031
IVRT) (ms)†	113.32±9.22	113.77±9.34	0.261	116.60±7.04	116.39±7.74	<0.001

*median and interquartile range (25-75 percentile); †mean ± standard deviation (± SD); TAPSE, Tricuspid annular plane systolic excursion; LVIDD, left ventricular end-diastolic diameter; E/A ratio - flow rates in early and late diastole and their ratio (E, A, E / A); DTE, deceleration time of early diastolic velocity; IVRT, isovolumic relaxation time

respectively). Also, there was an increase of DTE ($p<0.05$) and decrease of IVRT ($p<0.001$) (Table 1).

DISCUSSION

The results of this study have proved the reduction in the right and left ventricle diameters after a six-month atorvastatin therapy in patients with EFLV ≤40%. Improving systolic and diastolic function leads to a lower rate of re-hospitalization, as well as to the improvement in the quality of life. Kjekshus et al. stated that the use of statins reduces the risk of developing HF, as well as reducing the progression of coronary artery disease (22). Zhang et al. demonstrated an improvement in the left ventricular ejection fraction, reduction of the left ventricular end-diastolic diameter, end-systolic diameter, and in brain natriuretic peptide (BNP is also the New York Heart Association functional class) (23), which was confirmed in this research. Liu et al. analysis of patients with respect to prescribed statin (atorvastatin, simvastatin, or pitavastatin) showed that the use of lipophilic statins in patients with HF reduced overall mortality and the number of hospitalizations, while the use of lipophilic statins alone increased the values of EFLV (24). Also, the rates of hospitalization were lower in the patients with HF who were taking 80 mg of atorvastatin, while no benefit was shown on the reduction of the rate of HF onset (29). In an analysis of 110 patients with EFLV below 30%, Vrtovec et al. indicated that the mortality rate was lower in the patients using atorvastatin therapy during a one-year follow-up (25).

Hobbs et al. indicated that the use of lipophilic statins had an effect on the increase in EFLV, and thus on patient outcome, during a five-year period (26). Wu et al. showed a significant improvement in global strain imaging in patients undergoing peritoneal dialysis in patients on atorvastatin therapy (27). It was shown that the EFLV values of patients with nonischemic HF and EFLV of ≤35% taking atorvastatin increased significantly, and the end-diastolic and end-systolic diameters were reduced (28).

Bielecka-Dabrowa et al. concluded that statin use has benefits regardless of the etiology of HF, and that lipophilic statins are more favourable in patients with HF (29). The Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACLE) clinical trial showed that the use of atorvastatin was beneficial in mortality, cardiac arrest occurrence and re-hospitalizations in the patients with unstable angina or non-Q acute myocardial infarction, who were treated with 80 mg of atorvastatin (18).

The use of high doses of lipophilic statins has benefits in the initial treatment of acute coronary syndrome, but also in the period after that, due to the effect on the heart muscle, especially in patients with reduced EFLV. This research imposes the use of lipophilic statins in this type of patients. Their use should be preferred in patients with HF, and potential side effects should not be the reason not to include them in the therapy (pharmacokinetic interactions are particularly considered).

Despite the small number of patients included in this study, it can be a basis for further research that would include a larger number of patients, and examine the impact of comorbidities (the presence of renal failure, liver disease, or diabetes mellitus) on the effect of statin therapy.

In conclusion, atorvastatin in the therapy resulted in increased EFLV and better systolic function and should be a part of the therapeutic modality of HF.

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Conflicts of interest: None to declare.

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