Effects of atorvastatin treatment in middle-aged patients with advanced idiopathic dilated cardiomyopathy — a randomized prospective single centre study

Efekty leczenia atorwastatyną chorych w średnim wieku z zaawansowaną kardiomiopatią rozstrzeniową — prospektywne randomizowane badanie jednoośrodkowe

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Abstract

Introduction. Idiopathic dilated cardiomyopathy is a disease of unknown aetiology, characterized by left ventricular systolic dysfunction. Despite new diagnostic methods and pharmacological treatment, dilated cardiomyopathy still remains a major cause of morbidity and mortality. The aim of the study was to determine prognostic factors, efficacy of statin use, and clinical adverse events in patients with idiopathic dilated cardiomyopathy.

Material and methods. Ninety-five patients with idiopathic dilated cardiomyopathy (47 in the treated group and 48 in the control group) were randomized to receive add-on therapy with atorvastatin 20 mg daily. All patients underwent thorough clinical, electrocardiographic and echocardiographic evaluation at baseline and after 12 months of follow-up.

Results. During the 12 months of follow-up, 23 patients died (12 in the treated group and 11 in the control group). During the follow-up, the severity of heart failure symptoms (as measured by the NYHA functional class) decreased and the glomerular filtration rate increased in parallel to an improvement seen in several echocardiographic parameters.

Conclusions. Based on our study findings, statin use is not associated with a better prognosis in patients with idiopathic dilated cardiomyopathy. Risk stratification in this group of patients is possible on the basis of clinical, biochemical, and echocardiographic parameters.

Key words: dilated cardiomyopathy, heart failure, New York Heart Association functional class, atorvastatin, echocardiography

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Introduction

Dilated cardiomyopathy (DCM) [1, 2] is a primary chronic myocardial disease manifesting with systolic dysfunction which is not due to pericardial disease, coronary artery disease, hypertension, congenital heart disease, or valvular heart disease [3]. The diagnosis of DCM requires excluding the above listed etiologic factors. In most cases, the cause is difficult to establish, and microscopy shows diffuse interstitial and perivascular myocardial fibrosis with partial involvement of the left ventricular subendocardial layer, with some focal necrosis and cellular infiltrates which usually are not the predominant histological findings [2]. A large variation of the cardiomyocyte size is notable, with atrophy of some cells and hypertrophy of others. No characteristic histologic findings of idiopathic DCM have

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been identified in the research studies. It is known that in addition to a genetic predisposition, a major role is played by inflammatory processes and pathological apoptosis or programmed cell death [2, 4].

The natural history of DCM is varied and incompletely understood. Many patients may remain asymptomatic despite slowly progressing disease [5, 6]. Annual mortality in patients with the typical progression of heart failure resulting from DCM has been estimated at 11–13% [7].

The aim of the present study was to determine the effects of one-year atorvastatin treatment at the dose of 20 mg daily, and in particular the effect on the rate of clinical endpoints (death, readmission, and the need for cardiac transplantation) in patients with idiopathic DCM during one year of follow-up.

The study was a prospective, unblinded clinical trial with random assignment to the active treatment (atorvastatin 20 mg).

Material and methods

Study group

The study included 95 patients (47 in the group receiving active treatment with atorvastatin 20 mg [ATOR(+)] and 48 in the control group [ATOR(–)]) with the diagnosis of DCM who were under the care of the Chair and Department of Cardiology, Medical University of Łódź, and its cardiology clinic. All patients recruited in the study received written information about the study and gave a written informed consent for participation in the study. The study protocol was approved by the Bioethics Committee at the Medical University of Łódź (approval No. RNN/207/06/KE of November 28, 2006). All patients recruited into the study received medications recommended for the treatment of heart failure (according to the current Polish Cardiac Society and the European Society of Cardiology guidelines). In addition to the drugs recommended for the treatment of heart failure, patients who were randomly assigned to the active treatment group also received atorvastatin 20 mg daily for one year. All patients underwent detailed clinical, electrocardiographic, and echocardiographic evaluation (using two-dimensional echocardiography and tissue Doppler imaging) at baseline and at 12 months of follow-up.

Patients who were assigned to the active treatment group (n = 47) and the control group (n = 48) were subjects with the diagnosis of DCM made in accordance to the current recommendations [5]:
— ventricular dilation;
— reduced global left ventricular systolic function as evidenced by the left ventricular ejection fraction (LVEF) below 35%;
— no coronary lesions as evaluated by coronary angiography;

— absence of other causes of ventricular dysfunction including hypertension, valvular disease, and ischemic heart disease.

All patients included into the study fulfilled the following criteria:
— diagnosis of idiopathic DCM according to the World Health Organization (WHO) criteria, with exclusion of secondary cardiomyopathy;
— disease duration of up to 3 months or increase in the severity of heart failure by at least one New York Heart Association (NYHA) functional class;
— full drug therapy according to the current standards of care and recommendations of the Polish Cardiac Society;
— written consent for participation in the study, given after the patients were provided written information and received extensive answers to any questions they might have had;
— age above 18 years.

Study protocol

The study protocol included the following procedures at baseline and at 12 months:
— medical history;
— physical examination with blood pressure measurement;
— blood sampling (10 mL) from an antecubital vein for complete blood count and biochemical testing;
— resting electrocardiogram;
— 6-minute walking test (6MWT) to evaluate exercise tolerance;
— conventional Doppler echocardiography to evaluated global and regional wall motion and diastolic function;
— tissue Doppler imaging to evaluate myocardial velocity and strain.

The patients were followed up for one year (mean 12.6 ± 3.9 months) to identify the occurrence of clinical endpoints (evaluated separately and as a combined endpoint) (Table 1) including:
— all-cause mortality;
— need to implant a pacemaker;
— patient enlisting to the cardiac transplantation program,
— worsening of heart failure symptoms (by at least one NYHA class) or the 6MWT result (walking distance reduction by more than 10%);
— combined clinical endpoint defined as the occurrence of at least one of the above listed endpoints.

Statistical analysis
Descriptive statistics and group comparisons
Quantitative descriptive data were reported as mean values ± standard deviation or median (minimum, maximum) in case of non-normally distributed variables. Normal distribution of the variables was verified using the Kolmogo-

Table 1. Rates of clinical endpoints during one-year follow-up (no significant differences between the groups)

Variable	ATOR(+)	ATOR(−)	P
Pacemaker implantation	13 (27.7%)	15 (31.2%)	0.82
Worsening of NYHA class	6 (12.7%)	10 (20.8%)	0.41
Reduced 6MWT distance	14 (29.8%)	17 (35.4%)	0.66
Cardiac transplantation	3 (6.4%)	4 (8.3%)	1.0
Need for hospital admission	13 (27.7%)	18 (37.5%)	0.38
Death	12 (25.5%)	11 (22.9%)	0.81
Combined endpoint: • death • need for hospital admission • cardiac transplantation	20 (42.5%)	25 (52.1%)	0.41

ATOR(+) — active treatment group; ATOR(−) — control group; NYHA — New York Heart Association; 6MWT — 6-minute walking test

rov-Smirnov test (for large samples) or the Shapiro-Wilk test (for small samples). If a variable was non-normally distributed, median values were compared using the non-parametric Mann-Whitney U test, and the Student t test was used for normally distributed variables. Categorical data were compared using the chi-square Pearson test. Differences were considered significant at P < 0.05.

Treatment outcomes

In univariate analysis, the patients were divided into those with or without an endpoint, and all variables were compared between the two groups. Quantitative variables were compared using the Student t test for paired samples or the nonparametric Mann-Whitney U test. Categorical data were compared using the Fisher exact test. Receiver-operating characteristics (ROC) curves were plotted for quantitative variables and areas under the curve (AUC) were calculated as the measure of the usefulness of a given variable to predict endpoint occurrence. For each ROC curve, cut-off values were determined and the sensitivity and specificity values were calculated for the endpoint prediction. Finally, odds ratios (OR) were calculated as the measure of the increase in the risk of an endpoint.

Multivariate logistic regression analysis included only those variables which were significant in the univariate analysis.

Results

Group characteristics — functional parameters

The study groups did not differ in regard to major clinical and demographic parameters. Comparison of the medical history data is shown in Tables 2 and 3. Trends were noted for more frequent occurrence of familial DCM in the atorvastatin group and of impaired glucose tolerance in

Table 2. Medical history data collected using a questionnaire (a trend for more frequent occurrence of familial DCM in the active group, no significant differences between the groups)

Variable	ATOR(+)	ATOR(−)	P
Age [years]	51.7 ± 12.3 (25–76)	53.7 ± 11.8 (24–76)	0.42
Gender [male/female]	40/7 (85.1/14.9%)	35/13 (72.9/27.1%)	0.21
Mean duration of follow-up [months]	12.9 ± 4.0	12.3 ± 3.9	0.46
Age at DCM diagnosis [years]	47 ± 10.6	49.8 ± 11.1	0.21
Time since DCM diagnosis [years]	4.7 ± 3.1	3.9 ± 2.5	0.17
Body weight [kg]	82.8 ± 9	84.3 ± 7.7	0.38
Body weight index [kg/m^2]	27.8 ± 4.0	27.9 ± 3.6	0.89
6MWT [m]	297.1 ± 81.3	279.6 ± 84.2	0.31
Familial DCM (1st degree relative)	25/47 (53%)	16/48 (33%)	0.06
Beta-blockers [%]	47/47 (100%)	48/48 (100%)	1.0
ACEI/ARB [%]	46/47 (98%)	48/48 (100%)	0.49
Diuretics [%]	31/47 (66%)	30/48 (63%)	0.83
Spironolactone [%]	40/47 (82%)	39/48 (81%)	0.78
Digoxin [%]	32/47 (68%)	27/48 (56%)	0.29
Long-acting nitrate [%]	28/47 (60%)	25/48 (52%)	0.54
Acetylsalicylic acid [%]	35/47 (75%)	36/48 (75%)	1.0
Vitamin K antagonist [%]	12/47 (26%)	11/48 (23%)	0.81

ATOR(+) — active treatment group; ATOR(−) — control group; 6MWT — 6-minute walking test; ACEI — angiotensin-converting enzyme inhibitor; ARB — angiotensin receptor blocker

Table 3. Cardiovascular risk factor rates in the control group [ATOR(–)] and the active treatment group [ATOR(+)]

Variable [%]	ATOR(+)	ATOR(–)	P
A history of cerebrovascular disease (stroke, aneurysm)	13 (28%)	16 (33%)	0.66
Hypertension	25 (53%)	23 (48%)	0.68
Diabetes type 2	5 (11%)	9 (19%)	0.39
Impaired glucose tolerance	1 (2%)	8 (17%)	**0.03**
Atrial fibrillation	16 (34%)	22 (46%)	0.29
Smoking	28 (60%)	20 (42%)	0.1

Table 4. Lipid levels at baseline and at 12 months in both groups. Baseline data available for n = 47 in the ATOR(+) group, n = 48 in the ATOR(–) group, 12-month data available for n = 35 in the ATOR(+) group, n = 37 in the ATOR(–) group. No significant differences (P < 0.05) at 12 months compared to baseline

Variable	ATOR (+)	ATOR(–)	p	P'	P"
Total cholesterol [mg/dL]					
Baseline	176.1 ± 47.6	187.5 ± 43.8	0.22	0.13	0.54
Change at 12 months	–15.9 ± 59.4	6.6 ± 64.6	0.13		
HDL cholesterol [mg/dL]					
Baseline	45.8 ± 15.3	47.8 ± 15.4	0.53	0.04	0.51
Change at 12 months	6.3 ± 17.7*	–2.4 ± 22.0	0.06		
LDL cholesterol [mg/dL]					
Baseline	106.9 ± 42.1	106.6 ± 35.5	0.97	0.51	0.59
Change at 12 months	–9.9 ± 51.5	–3.8 ± 42.7	0.59		
TG [mg/dL]					
Baseline	141.8 ± 75.6	133.2 ± 64.2	0.55	0.18	0.84
Change at 12 months	–24.3 ± 104.1	–2.8 ± 84.5	0.34		

p denotes differences between the ATOR(+) and ATOR(–) group during 12-month follow-up; P' denotes differences between baseline and 12 months in the ATOR(+) group, and P" denotes differences between baseline and 12 months in the ATOR(–) group; *significant (P < 0.05) difference at 12 months compared to baseline; ATOR(+), active treatment group; ATOR(–) — control group; HDL — high-density lipoprotein; LDL — low-density lipoprotein; TG — triglycerides

Table 5. Distribution of the New York Heart Association (NYHA) functional class in the active treatment group [ATOR(+)] and the control group [ATOR(–)] at baseline and at 12 months of follow-up (a significant difference in the NYHA class distribution at 12 months vs. baseline in the ATOR(+) group, P = 0.03)

Group		NYHA class			
		I	II	III	IV
A	ATOR(+) baseline	1/47 (2.1%)	10/47 (21.3%)	29 (61.7%)	7 (14.9%)
B	ATOR(+) 12 months	3/35 (8.6%)	16/35 (45.7%)	15/35 (42.9%)	1/35 (2.9%)
C	ATOR(–) baseline	0/48 (0%)	13/48 (27.1%)	24/48 (50%)	11/48 (22.9%)
D	ATOR(–) 12 months	1/37 (2.7%)	9/37 (24.3%)	24/37 (64.9%)	3/37 (8.1%)

the control group. Lipid levels during the follow-up in both groups are shown in Table 4. The baseline values did not differ between the atorvastatin and control groups, and a significant increase in HDL cholesterol level was found at 12 months in the atorvastatin group compared to baseline which was not seen in the control group.

Table 5 shows the distribution of NYHA class in the atorvastatin and control groups during 12 months of fol-low-up. Atorvastatin treatment was associated with a significant improvement in the severity of heart failure during 12 months of follow-up (P = 0.03). A significant change in the NYHA class was noted during 12 months of follow-up in favour of the atorvastatin group compared to the control group (P = 0.03) (Table 6).

Table 7 shows heart failure parameters during 12 months of follow-up and their changes at 12 months in the atorvas-

Table 6. Change in the New York Heart Association (NYHA) functional class in the active treatment group [ATOR(+)] and the control group [ATOR(–)] at 12 months compared to baseline, a significant difference (P = 0.03)

	Variable	
Group	Improvement in NYHA class NYHA	Worsening or no change in NYHA class
ATOR(+)	21/35 (70.2%)	14/35 (29.8%)
ATOR(–)	12/37 (47.9%)	25/37 (52.1%)

Table 7. Heart failure parameters in the study groups. Baseline data available for n = 47 in the ATOR(+) group, n = 48 in the ATOR(–) group, 12-month data available for n = 35 in the ATOR(+) group, n = 37 in the ATOR(–) group

Variable	ATOR(+)	ATOR(–)	p	P'	P"
NYHA class [I–IV]					
Baseline	3.0	2.9	0.67		
Change at 12 months	0.6*	0.1	**0.02**	**0.01**	0.14
6MWT [m]					
Baseline	297 ± 81	279 ± 84	0.31		
Change at 12 months	11 ± 45.8	1.7 ± 18.4	0.21	0.14	0.37
NT-proBNP [pg/mL]					
Baseline	4741 ± 4531	3925 ± 2354	0.27		
Change at 12 months	–904 ± 4762	–674.6 ± 2480	0.79	0.27	0.19
LA [mm]					
Baseline	50.1 ± 7.1	51.4 ± 7.8	0.43		
Change at 12 months	–0.5 ± 1.5	0.1 ± 1.0	0.06	0.06	0.64
LVESD [mm]					
Baseline	56.8 ± 9.6	61.3 ± 10.7	0.03		
Change at 12 months	–1.7 ± 2.2*	0.1 ± 5.0	**0.05**	**0.0001**	0.92
LVEDD [mm]					
Baseline	66.5 ± 8.9	66.0 ± 11.4	0.79		
Change at 12 months	–1.2 ± 2.2*	–0.6 ± 1.6	0.15	**0.003**	**0.03**
LVESV [cm³]					
Baseline	192.6 ± 51.8	190.9 ± 61.8	0.89		
Change at 12 months	–12.4 ± 14.3*	–3.4 ± 11.9	**0.005**	**0.0001**	0.09
LVEDV [cm³]					
Baseline	253.7 ± 64.5	240.3 ± 68.6	0.33		
Change at 12 months	–11.3 ± 14.8*	–3.7 ± 12.4	**0.02**	**0.0001**	0.07
LVEF [%]					
Baseline	23.9 ± 8.6	21.1 ± 6.5	0.07		
Change at 12 months	1.6 ± 2.4*	–4.4 ± 9.2	**0.002**	**0.0004**	0.93

p denotes differences between the ATOR(+) and ATOR(–) group during 12-month follow-up; P' denotes differences between baseline and 12 months in the ATOR(+) group, and P" denotes differences between baseline and 12 months in the ATOR(–) group; *significant (P < 0.05) difference at 12 months compared to baseline; ATOR(+) — active treatment group; ATOR(–) — control group; NYHA — New York Heart Association; 6MWT — 6-minute walking test; NT-proBNP — N-terminal propeptide of the brain natriuretic peptide; LA — left atrium; LVESD — left ventricular end-systolic diameter; LVEDD — left ventricular end-diastolic diameter; LVESV — left ventricular end-systolic volume; LVEDV — left ventricular end-diastolic volume; LVEF — left ventricular ejection fraction

tatin group compared to the control group. A significant reduction in the severity of heart failure symptoms as measured by the NYHA class was noted in the atorvastatin group which was not seen in the control group. In both study groups, a reduction in the level of N-terminal propeptide of brain natriuretic peptide (NT-proBNP) and an increase in 6MWT distance were noted but these differences were not significant.

Table 8. Significant (P < 0.05) predictors of mortality in the study group during 12 months of follow-up in univariate analysis

Variable	Death (+) n = 12	Death (−) n = 35	P
Atrial fibrillation (yes/no)	1/11 (8.3/91.6%)	15/20 (42.9/57.1%)	0.04
Smoking (yes/no)	11/1 (91.6/8.3%)	17/18 (48.6/51.4%)	0.02
Need for hospital admission (yes/no)	7/5 (58.3/41.6%)	6/29 (25.7/74.3%)	0.01
Family history (yes/no)	1/11 (8.3/91.6%)	20/15 (57.1/42.9%)	0.006
Diuretics (yes/no)	5/7 (41.6/58.3%)	26/9 (74.3/25.7%)	0.04
Heart rate [bpm]	87.3 ± 17.5	73.2 ± 9.3	0.001

Clinical endpoints during the follow-up

The mean duration of follow-up was 12.6 ± 3.9 months. During this time, 23 patients died due to heart failure, including 12 patients in the active treatment group (25.5%) and 11 patients in the control group (22.9%). The mean age of the patients who died vs. those who survived did not differ significantly (50.4 ± 13.5 vs. 53.5 ± 11.5 years, respectively, P = 0.21). Endpoints noted during one-year follow-up are summarized in Table 1.

Another endpoint was the need for hospital admission due to heart failure worsening. During one-year follow-up, this was required in 31 (32.6%) patients, including 14 (29.8%) in the active treatment group and 17 (35.4%) in the control group (P = 0.66), and the mean time to hospital admission in the active treatment group did not differ compared to the control group (11.2 ± 4.7 vs. 9.8 ± 4.6 months, respectively, P = 0.19). A nonsignificant reduction in the readmission rate by 14% was noted in the active treatment group compared to the control group (RR 0.86, 95% CI 0.65–1.14, P = 0.38). During one-year follow-up, atorvastatin treatment was not associated with a significant increase in cardiac transplantation-free survival in the active treatment group compared to the control group (95.6% vs. 91.7%, respectively, P = 0.36).

During 12 months of follow-up, a cardiac resynchronization therapy device was implanted in 28 patients, including 13 (27.7%) in the active treatment group compared to 15 (31.2%) in the control group, a nonsignificant difference (P = 0.82).

Based on the rates of individual endpoints, we also evaluated the rate of a combined endpoint that included death, readmission, and the need for heart transplantation. This endpoint occurred in 20 (42.5%) patients in the active treatment group and in 25 (52.1%) patients in the control group, with a nonsignificant reduction in the rate of the combined endpoint by 17% (RR 0.83, 95% CI 0.57–1.22, P = 0.41).

Echocardiographic parameters

When echocardiographic parameters were evaluated at 12 months, significant reductions in the left ventricular end-systolic dimension (LVESD), left ventricular end-diastolic dimension (LVEDD), left ventricular end-systolic volume (LVESV), and left ventricular end-diastolic volume (LVEDV) were found in the active treatment group. In addition, 12-month atorvastatin treatment was associated with a significant improvement in LVEF. LVEDD was the only parameter which improved significantly at 12 months in the control group.

Prognostic parameters

In our study, we identified several clinical predictors of mortality during 12 months of follow-up which are shown in Table 8. Atorvastatin treatment was not among these predictors.

Discussion

Our study is one of few prospective trials of statin treatment in DCM patients. We have not shown a significant improvement in short-term outcomes based on the rate of clinical endpoints but our data indicate atorvastatin treatment may have an effect on the reduction of the severity of heart failure symptoms and beneficial changes in echocardiographic parameters.

Multiple studies indicate that cardiomyopathy is the end-stage of heart failure developing due to three major mechanisms of cardiac damage [6, 9, 13]:
— genetic — in 20–25% of DCM cases [11], reported by Gienner and Battersby in 1961 [12], mostly autosomal dominant, less frequently autosomal recessive or X-linked [11, 12]. To date, more than 12 gene deletions were identified [11, 12, 26–29]. The proportion of patients with familial DCM in our study was 41.5%;

— immunologic — impaired cellular and humoral immunity manifesting with the presence of specific cardiac autoantibodies and an increase in proinflammatory cytokines such as tumour necrosis factor α (TNFα) which are responsible for systolic dysfunction [26–29];

— metabolic — obesity is an established cardiovascular risk factor. The Framingham Study showed that an increase in body mass index (BMI) by 1 kg/m^2 is associated with an increased risk of heart failure (by 5% in women and 7% in men), and the risk was increased 2-fold in obese subjects compared to those with normal BMI. Another cause of DCM may be longstanding diabetes which results in cardiac microangiopathy, changes in adipocyte metabolism, cardiac hypertrophy, calcium and potassium transport changes, cardiac conduction system abnormalities, and reduced sympathetic innervation. Among subjects with DCM, the risk of incident heart failure is increased 5-fold in women and 2-fold in men.

In our study group, 23 patients (24.2%) died due to heart failure over one year, including 12 patients in the study group and 11 patients in the control group. Available literature data indicate that prognosis in patients with clinically overt DCM is poor, with mortality up to 25% at one year and 50% at 5 years [14, 24–29]. Our study did not show a beneficial effect of atorvastatin on the clinical endpoints although a nonsignificant reduction in the endpoint rate was observed and it cannot be excluded that these differences might become significant with a longer duration of follow-up.

According to the current knowledge, development and progression of heart failure depends on neurohormonal activation, inflammation, and adaptive changes in the myocardium known as left ventricular remodelling [26–29]. These parameters are modulated by the current drug treatment of heart failure. Our patients received standard guideline-based heart failure treatment, with particular attention paid to renin-angiotensin system inhibitors and beta-blockers [1, 14]. Our observations during 12 months of follow-up in the atorvastatin group (20 mg/day) and the control group are consistent with the available literature data.

Of note, literature data do suggest a beneficial effect of statins on the major pathogenetic mechanisms of heart failure [24–29].

In the experimental study by Hayashidani et al. [15], fluvastatin was shown to reduce the risk of adverse post-infarction left ventricular remodelling. Following coronary artery ligation, mice received fluvastatin or placebo for 4 weeks. Administration of fluvastatin increased survival (61% vs. 86%, P < 0.05) but had no effect on the extent of post-infarction scar (52 ± 2% vs. 49 ± 3%, P = NS). Fluvastatin reduced post-infarction left ventricular dilatation, end-diastolic left ventricular pressure, myocyte hypertrophy, and extracellular fibrosis within the non-infarcted area. These data suggest

that benefits of statin following an acute coronary syndrome may be independent from the lipid profile.

Gurgun et al. [16] evaluated the effect of 12-week 80 mg fluvastatin therapy on the levels of inflammatory cytokines and left ventricular function in patients with DCM and heart failure due to coronary artery disease, with 20 patients recruited into each study group. The study showed a significant improvement of left ventricular function in both patients with DCM (LVEF increase from 30 ± 5% to 33 ± 5%, P = 0.001) and those with heart failure due to coronary artery disease (LVEF increase from 29 ± 4% to 31 ± 5%, P = 0.01). In addition, clinical symptoms of heart failure as evaluated by the NYHA class were reduced in both groups. The authors noted that the positive effect of statins was probably related to modulation of the inflammatory response, which might be of importance in our patients. This hypothesis was confirmed in the study by Horwich et al. [17] that showed that statin therapy was associated with an improved cardiac transplantation-free survival during one year of follow-up in patients with both ischemic and non-ischemic cardiomyopathy (91% vs. 72%, P = 0.001, and 81% vs. 63%, P = 0.001, respectively). Improved exercise tolerance measured by NYHA class was found in DCM patients treated with simvastatin for 14 weeks compared to placebo.

The effect of atorvastatin 20 mg daily on vascular inflammation parameters and echocardiographic variables was evaluated by Sola et al. [18]. The study included 89 patients with DCM, NYHA class II–IV, and LVEF < 35%. The authors reported improved LVESD (53.4 ± 5.1 vs. 60.3 ± 5.1, P = 0.01), LVEDD (39.1 ± 3.8 vs. 43.1 ± 4.5, P = 0.01), and LVEF (37 ± 4.1 vs. 31 ± 3.1, P = 0.004) in the atorvastatin group compared to placebo. Of note, atorvastatin treatment was also associated with an improvement in the NYHA class (P = 0.001). The authors concluded that atorvastatin might delay adverse myocardial remodelling. These observations are in agreement with changes in echocardiographic parameters seen in the present study. Of note, this effect was not seen with rosuvastatin 10 mg daily in the GISSI-HF study [34].

In the Heart Protection Study (HPS) population [19], the effect of simvastatin treatment was evaluated in relation to the severity of heart failure measured by NT-proBNP levels during nearly 5 years of follow-up. The authors showed that this treatment reduced the coronary event risk, natriuretic peptide levels, and other vascular events.

In the study by Node et al. [20, 21], beneficial effects of statins were shown in a group of 51 patients with left ventricular systolic dysfunction who were in NYHA class II–III. In patients on chronic statin treatment, a clinical improvement in heart failure by at least one NYHA class was seen, along with an increase in LVEF (from 34 ± 3% to 41 ± 4%, P < 0.05) [22, 23] and reduced levels of inflammatory mediators, interleukin-1 (IL-1), TNFα and brain natriuretic

peptide (BNP) [20, 21, 23], which are responsible for major pathogenetic processes leading to myocardial systolic dysfunction in DCM.

However, these beneficial effects of statins were not confirmed in large randomized trials that evaluated the effect of statins in heart failure due to ischemic (CORONA) or mixed aetiology (GISSI-HF) [35]. Of note, both these trials evaluated rosuvastatin 10 mg daily. The COntrolled ROsuvastatin multiNAtional trial in heart failure (CORONA) study [24] evaluated the hypothesis that benefits of rosuvastatin would outweigh possible harms associated with this therapy, leading to increased survival, reduced symptoms, and reduced mortality in patients with chronic symptomatic non-ischemic heart failure. The study included patients > 60 years of age with symptomatic systolic heart failure (LVEF ≤ 35% if NYHA class II or 40% if NYHA class III/ /IV) who previously did not receive lipid-lowering treatment. The study included 5011 patients (mean age 73 years, 41% patients > 75 years) who were randomly assigned to rosuvastatin 10 mg daily (n = 2514) or placebo (n = 2497). The mean duration of follow-up was 32.8 months. No baseline differences were found between the two groups. Significant reductions in low-density lipoprotein (LDL) cholesterol (by 45%, $P < 0.001$), high-density lipoprotein (HDL) cholesterol (by 5%, $P < 0.001$), and triglyceride levels (by 20.5%, $P < 0.001$) were seen in the rosuvastatin group compared to the placebo group. High-sensitivity C-reactive protein (hsCRP) level was also significantly reduced by 37.1%. The primary endpoint (cardiovascular death, myocardial infarction, or stroke) occurred in 692 patients in the rosuvastatin group and 732 patients in the placebo group (RR 0.92; 95% CI 0.83–1.02, $P = 0.12$). Rosuvastatin had no effect on the NYHA class and the rate of incident diabetes ($P = 0.40$). The authors concluded that no mortality reduction with rosuvastatin was observed in heart failure patients during a 3-year follow-up but the hospital admission rate was significantly reduced by about 10% in the rosuvastatin group. No differences were found in the rates of admissions due to unstable angina and non-cardiac causes. The treatment safety analysis did not identify any significant adverse effects of rosuvastatin across the many evaluated clinical and laboratory parameters.

Of note, significant differences exist between the CORONA study population and our study population. The rates of heart failure medication use in the CORONA study were similar to our study, with 90% patients on diuretics, 42% patients on aldosterone antagonists, 91% patients on ACE/ /ARB, 75% patients on beta-blockers and 32% patients on digoxin but the major difference was the aetiology of heart failure. In our study, we evaluated patients with idiopathic DCM, while the patients in the CORONA study had heart failure of ischemic aetiology which is associated with worse outcomes. Patients in the CORONA study were older, which

makes it much more difficult to show a beneficial treatment effect. Rosuvastatin treatment was not associated with a significant reduction in the rate of the primary endpoint (RR 0.92; 95% CI 0.83–1.02, $P = 0.12$), similarly to our patients treated with atorvastatin (RR 0.83; 95% CI 0.57– –1.22, $P = 0.18$), although numerically the effect was more evident in our study group. Both studies, however, showed a reduced hospitalization rate and improved NYHA class in the active treatment group.

An important study looking into the effect of statins in ischemic heart failure was the analysis of the CORONA study by Cleland et al. [30]. The authors hypothesized that despite a lack of a protective effect of statins in the general heart failure population, an inverse association exists between the effect of rosuvastatin and NT-proBNP level. Data analysis showed a cut-off NT-proBNP level for benefits of rosuvastatin in patients with ischemic heart failure, estimated at 868 pg/mL. Thus, statin treatment had an effect on the cardiovascular event risk. In patients with milder heart failure (NT-proBNP level < 868 pg/mL), rosuvastatin treatment was associated with fewer adverse clinical events and a 35% reduction in the primary endpoint rate (cardiovascular death, myocardial infarction, or stroke, $P = 0.005$), while no such effect was seen in patients with higher NT-proBNP levels (> 868 pg/mL). In summary, the authors concluded that their analysis supported statin use in patients with milder heart failure and coronary artery disease. In our study, the above NT-proBNP level criterion was met by 5.3% patients with non-ischemic heart failure.

Another study that looked for predictors of beneficial effects of statins in heart failure was the study by McMurray et al. [31]. These authors evaluated antiinflammatory properties of statins in the context of potential benefits of these drugs in patients with heart failure. This analysis included the CORONA study participants with ischemic heart failure who received rosuvastatin 10 mg daily or placebo. The patients were divided into two groups depending on their baseline hs-CRP levels, with hs-CRP level < 2.0 mg/L in Group I (placebo: n = 779, rosuvastatin: n = 777), and hs-CRP level ≥ 2.0 mg/L in Group II (placebo: n = 1694, rosuvastatin: n = 1711). The patients were followed up for the occurrence of cardiovascular death, myocardial infarction, and stroke. Median hs-CRP level was higher in Group II compared to Group I (5.6 mg/L vs 1.1 mg/L, respectively) and associated with worse treatment outcomes. During a 3-month follow-up, a nonsignificant 6% reduction in hs-CRP level in Group I (27% in the placebo subgroup) and a significant ($P = 0.024$) 33% reduction in hs-CRP level in Group II (11.1% in the placebo subgroup) was noted. The authors concluded that a beneficial interaction between hs-CRP level and the effect of rosuvastatin on the clinical endpoint rate was identified, particularly in patients with hs-CRP levels ≥ 2.0 mg/L.

Predictors of a good response to statin therapy were also looked for in the study by Gullestad et al. [32] who evaluated the efficacy of statin treatment in patients with chronic ischemic heart failure in relation to plasma galectin-3 level, a marker of myocardial fibrosis. This analysis included 1492 participants of the CORONA study who were randomized to rosuvastatin 10 mg daily or placebo. The primary endpoint which included cardiovascular death, myocardial infarction, and stroke occurred in 411 patients. The mean duration of follow-up was 32.8 months. In this analysis, a cut-off galectin-3 level of ≤ 19.0 ng/mL was identified that was associated with significantly fewer clinical adverse effects (HR 0.65, 95% CI 0.46–0.92, P = 0.014), along with a 30% reduction in all-cause mortality and a 28% reduction in the rate of deaths and readmissions due to exacerbated heart failure. It was also found that a combination of low galectin-3 level and NT-proBNP level < 102.7 pmol/L identified patients with particularly large rosuvastatin treatment benefits. The authors concluded that galectin-3 level of ≤ 19.0 ng/mL was another predictor of a good response to rosuvastatin treatment in patients with ischemic heart failure.

In another important study that was a subanalysis of the CORONA trial data, Rogers et al. [33] evaluated adverse clinical events including readmissions due to heart failure. The follow-up included 5011 patients, of which 1291 were hospitalized at least once due to exacerbated heart failure (including 750 patients with only one readmission). Although the time to the first readmission did not differ between the rosuvastatin and placebo groups (HR 0.91, 95% CI 0.82–1.02, P = 0.105), the risk of readmission was reduced by 20% when multiple hospitalizations were taken into account. Similar findings were obtained in an analysis that included admissions due to all cardiovascular causes and all hospitalizations. The authors concluded that rosuvastatin treatment was associated with a reduction in the annual readmission risk by up to 15–20%, which corresponds to the observed NYHA class improvement in our study.

Based on these analyses of the CORONA trial data, a number of predictors of a good response to statin therapy in patients with chronic ischemic heart failure were identified. Some of them are used in the routine clinical practice (NT-proBNP, hs-CRP) while others require further research, e.g., galectin-3. Any of these parameters might help predict the effect and benefits of statins in these patients.

Study limitations

Our study had a number of limitations. It was a single-centre, unblinded study but these factors arguably had a less important effect on the evaluation of measurable parameters and clinical endpoints. The study sample was small which was related to the uniform aetiology. Study results might have been affected by the fact that the duration of follow-up was limited to one year.

Conclusions

Based on the result of our prospective randomized study, atorvastatin treatment in patients with idiopathic DCM is safe but does not reduce the risk of mortality and major clinical endpoints during one year of follow-up. Our findings indicate that some beneficial effect on subjective functional parameters (NYHA class) and left ventricular remodelling may be expected. It cannot be excluded that more benefits could be obtained in other populations during longer follow-up.

Conflict of interest(s)

None.

Streszczenie

Wstęp. Kardiomiopatia rozstrzeniowa jest chorobą serca charakteryzującą się poszerzeniem i upośledzeniem kurczliwości lewej komory lub obu komór. Częstość jej rozpoznań zwiększa się z powodu starzenia się populacji, stosowania nowych metod diagnostycznych oraz postępów w farmakoterapii niewydolności serca.

Materiał i metody. W przedstawionym badaniu podjęto próbę określania skuteczności atorwastatyny oraz jej wpływu na częstość występowania powikłań klinicznych. Do badania włączono łącznie 95 chorych (47 do grupy badanej i 48 do grupy kontrolnej) z kardiomiopatią rozstrzeniową w 2 klasie według *New York Heart Association* (NYHA). Poza standardowymi lekami zwykle zalecanymi w leczeniu niewydolności serca w badanej grupie (aktywnego leczenia) stosowano dodatkowo atorwastatynę w dawce 20 mg/dobę przez rok. Wszyscy pacjenci zostali poddani szczegółowej ocenie klinicznej, elektrokardiograficznej i echokardiograficznej na początku badania i po 12 miesiącach obserwacji.

Wyniki. W trakcie trwającej 12 miesięcy obserwacji zmarło 23 pacjentów (12 z grupy badanej i 11 z grupy kontrolnej). Ponadto w badanej populacji obserwowano zmniejszenie się nasilenia objawów klinicznych (z III do II klasy czynnościowej wg NYHA), zwiększenie wartości przesączania kłębuszkowego oraz poprawę wielu parametrów echokardiograficznych lewej komory).

Wnioski. U pacjentów z idiopatyczną kardiomiopatią rozstrzeniową stosowanie statyn nie wiąże się z poprawą rokowania, a stratyfikacja średnioterminowego ryzyka jest możliwa na podstawie szczegółowego badania klinicznego, badania echokardiograficznego oraz oceny biochemicznej.

Słowa kluczowe: kardiomiopatia rozstrzeniowa, niewydolność serca, klasyfikacja czynnościowa według NYHA, echokardiografia

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