Atorvastatin Therapy Is Associated with Reduced Levels of N-terminal Prohormone Brain Natriuretic Peptide and Improved Cardiac Function in Patients with Heart Failure

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ABSTRACT

Background: Statins have been suggested to improve cardiac function, but the evidence underlying beneficial effects of statins in heart failure (HF) is insufficient. We analyzed plasma N-terminal prohormone brain natriuretic peptide (NT-proBNP) levels and cardiac function in patients with HF of various etiologies, and who were treated with or without statins.

Hypothesis: Statin treatment is associated with improved cardiac function in HF.

Methods: The study cohort consisted of 139 consecutive male patients receiving atorvastatin ($n = 44$), simvastatin ($n = 29$), pravastatin ($n = 19$), or no statin ($n = 47$). The NT-proBNP levels were measured using electroluminescence immunoassay. Left ventricular end-diastolic diameter (LVEDD), fractional shortening (FS), and ejection fraction (EF) were determined by echocardiography.

Results: Patients receiving atorvastatin presented with reduced NT-proBNP levels (1,552±3,416 versus 3,771±6,763 pg/mL; $p<0.01$), and improved values of LVEDD (65.2±8.9 versus 70.7±10.9 mm; $p<0.05$) and EF (33.2±12.6 versus 28.2±9.6%; $p<0.05$). By contrast, plasma NT-proBNP and cardiac parameters in patients treated with statins other than atorvastatin did not significantly differ from control. Atorvastatin treatment was equally effective in patients with ischemic and nonischemic HF.

Conclusions: Atorvastatin treatment is associated with improved cardiac function in HF, and may represent an additional option for patients with this disease.

Key words: N-terminal prohormone brain natriuretic peptide, atorvastatin, heart failure

Introduction

Recent years witnessed a major progress in the therapy of heart failure (HF), which, in addition to traditional agents such as diuretics or digitalis derivatives, currently includes angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), and β-adrenergic receptor blockers. Despite these therapeutic advances, the incidence and the health burden of HF are on the rise worldwide, and additional options for effective HF treatment are discussed.

In several interventional trials, statins were shown to lower plasma levels of total and low-density lipoprotein (LDL) cholesterol, and thereby to counteract the development of coronary artery disease (CAD), which frequently underlies HF.[1,2] In addition, statins were demonstrated to modulate diverse inflammatory and immune responses.[3,4] As systemic inflammation is intimately involved in the HF pathogenesis, statins may be expected to benefit patients with HF separately, or in addition to the effects on plasma cholesterol and CAD. However, data on the potential therapeutic use of statins in HF are surprisingly sparse. Three recent end-point studies revealed reduced HF-related mortality in subjects undergoing therapy with statins.[5–7] In addition, in 3 small prospective studies, statins were shown to improve cardiac function in patients with dilated cardiomyopathy.[8–10] No case-control studies assessing the relationship between statin therapy and HF have been reported to date. Therefore, the present investigation has been undertaken to obtain further evidence underscoring the potential benefits of statin treatment in patients with HF.

Methods

The study cohort consisted of 139 male patients of our specialized Heart Failure and Transplantation Center, and who were consecutively referred to the center between October 2004 and December 2005 with clinical evidence of HF (New York Heart Association [NYHA] functional class II–IV). All patients were in a stable clinical state. The etiologies of HF included ischemic (48.5%), idiopathic (49.3%), valvular (0.7%), toxic (0.7%), and alcoholic (0.7%). Heart failure was classified as ischemic if patients had a clinical history of CAD or myocardial infarction, and were classified as valvular if patients presented with aortic or mitral insufficiency (III° acc. to the American Society of Echocardiography). Alcoholic or toxic etiologies were diagnosed based on clinical history of alcohol

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abuse or doxorubicin therapy, respectively. In remaining cases, idiopathic HF was diagnosed if ejection fraction (EF) was <40%. Patients after heart transplantation or patients with chronic inflammatory diseases, severe liver disease, or malignancy were excluded from the study. Background medication had an average duration of 3.4 y and included diuretics, ACE inhibitors, digoxin, β-blockers, and aldosterone antagonists. In this study, 44 patients were given atorvastatin (20–40 mg/d), 29 patients were given simvastatin (20–40 mg/d), and 18 patients were given pravastatin (10–30 mg/d) at the discretion of the treating physician. None of the patients received anti-HF therapies for less than 6 mo. In each patient, statin treatment was initiated concurrently with other anti-HF therapies. Patients obtaining pravastatin or simvastatin were categorized as receiving other statin.

Concentrations of N-terminal prohormone brain natriuretic peptide (NT-proBNP) in sera were measured using electrochemoluminescence immunoassay (ECLIA) (Roche Diagnostics, Mannheim, Germany) on the Elecsys 2010 automated analyzer. The intraassay and interassay variability were <2.7% and <3.2%, respectively, and the functional assay sensitivity was 51 pg/mL. During the study period, the assay precision and accuracy were, respectively, 3.04±0.97% and −2.02±2.25% at normal NT-proBNP level, and 3.98±0.82% and −4.11±3.02% at pathological NT-proBNP level. Other analyses were performed in a routine clinical laboratory on a Hitachi747 automated analyzer (Roche Diagnostics, Mannheim, Germany). The HF survival score was calculated as described previously.[11] Measurements of peak VO_2 were performed during maximal treadmill exercise. Ultrasound parameters such as left ventricular end-diastolic diameter (LVEDD), fractional shortening (FS), and EF were determined by echocardiography as recommended by the American Society of Echocardiography.[12,13] All M-mode measurements were performed according to the leading-edge method. The results were expressed as mean±standard deviation (SD). Deviations from normal distribution were assessed with 1 Kolmogorov-Smirnov goodness-of-fit test sample. Student t test and Mann-Whitney U test were employed to show differences in continuous variables with normal and abnormal distributions, respectively. Pearson χ^2 test was used to compare categorical variables.

Results and Discussion

There were no significant differences between groups treated with atorvastatin, other statins, or receiving no statin with regard to body mass index, systolic blood pressure, smoking habit, and occurrence of diabetes mellitus (Table 1). Patients in each group obtained comparable medication. Patients receiving statin treatment were, on average, older than their untreated counterparts. Therefore, *t* results were adjusted for age. Further adjustments were made for the usage of digoxin, ACE inhibitors, and β-blockers appeared not to influence the results of the study. Patients receiving atorvastatin presented with significantly lower NT-proBNP levels and better values of LVEDD, EF, FS, and HF survival scores. The paucity of the significant improvement of VO_2 value may be related to the fact that this parameter reflects aggregated functioning of heart and lungs, which are unlikely to be influenced by statins. In contrast to patients on atorvastatin, no significant differences with respect to plasma NT-proBNP concentrations or cardiac function parameters were noted in patients treated with other statins. With regard to plasma lipids, lower cholesterol levels were noted in patients receiving statins. No statistical significances appeared when NT-proBNP, EF, and HF survival score values were analyzed within separate subgroups treated with simvastatin or pravastatin (not shown). Similar NT-proBNP levels were observed in atorvastatin-treated HF patients with ischemic (n = 28) and nonischemic (n = 16) etiologies (NT-proBNP: 1,509±3,210 versus 2,240±4,731, not significant [ns]).

The influence of statins on cardiac function in HF has been previously addressed in 3 small prospective trials. Laufs et al. randomized 14 patients with dilated cardiomyopathy to cerivastatin or placebo, and followed them for 20 wk.[8] Both standardized life quality and exercise capacity increased significantly in the statin group. Node et al. examined the effect of simvastatin in 23 patients with nonischemic HF, and found improved EF and slightly (approx. 25%) decreased levels of BNP after 3 mo of treatment.[9] Wojnicz treated 34 patients with inflammatory dilated cardiomyopathy for 6 mo with atorvastatin and registered EF improvement, but no effect on NT-proBNP concentrations. The pronounced effects of statins on NT-proBNP levels seen in the present study (a decrease by more than 60%) were likely related to the longer average treatment period.

The mechanism by which statins might improve cardiac function is controversially discussed. The deterioration of left ventricle function in HF is often preceded by the development of vascular atherosclerosis, and statins could be reasonably argued to exert their beneficial effects by reducing plasma cholesterol, and thereby, progression of coronary disease. However, data from end-point studies show that improved survival with statin therapy is observed in both ischemic and nonischemic HF etiologies, and is independent of the plasma total or LDL-cholesterol levels.[5–7] Moreover, statins were shown to improve cardiac function in patients with nonischemic dilated cardiomyopathy.[8,9] As in the present study, total cholesterol was significantly lower in the atorvastatin group and there was a trend towards significance for lower cholesterol in the other statin group. It cannot be entirely excluded that improved plasma lipid profile, at least partially, accounts for better outcomes. However, 2 observations argue against the notion that the improvement of cardiac function in HF is exclusively related to the lipid-lowering effects of statins. First, the beneficial effects of statins on plasma NT-proBNP levels were evident both in patients with ischemic and nonischemic HF. Second, despite comparable reduction of plasma cholesterol in patients receiving atorvastatin or other statins, the enhancement of cardiac function was observed only in the former group. Several other mechanisms, apart from lipid lowering mechanisms, are known that might underlay beneficial effects of statins in HF. These include protection of endothelial function and/or

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TABLE 1: Characteristics of the study cohort: comparison between patients treated with atorvastatin, statin other than atorvastatin, or receiving no statins

				p-value	
	Control (n = 47)	Atorvastatin (n = 44)	Other statin (n = 48)	1 versus 2	1 versus 3
Demographic data					
Age (y)	51±7	57±8	58±8	<0.001	<0.001
Body mass index (kg/m²)	26.7±4.2	27±3.6	26±2.9	ns	ns
Systolic blood pressure (mm Hg)	116±17	113±10	114±13	ns	ns
Diabetes mellitus (%)	23	16	26	ns	ns
Smoking (%)	14	7	6	ns	ns
Medication					
Digoxin (%)	63	66	78	ns	ns
β-blocker (%)	83	93	85	ns	ns
ACE-inhibitor (%)	81	91	85	ns	ns
Loop diuretic (%)	85	93	86	ns	ns
Nitrate (%)	11	23	21	ns	ns
Aldosterone antagonist (%)	41	42	59	ns	ns
Plasma lipids					
Cholesterol (mg/dL)	207.3±49.0	180.8±34.8	190.2±43.3	<0.001	0.07
Triglycerides (mg/dL)	236.4±199.2	233.0±123.8	274.5±194	ns	ns
Heart function parameters					
NYHA Class III + IV (%)	33.9	26.8	39.3	ns	ns
NT-proBNP (pg/mL)	3771±6763	1552±3416	2652±3717	<0.01	ns
LVEDD (cm)	70.7±10.9	65.2±8.9	68.2±7.3	<0.05	ns
Ejection fraction (%)	28.2±9.6	33.2±12.6	27.9±10.3	<0.05	ns
Shortening fraction (%)	18.0±6.4	21.9±7.0	20.4±8.5	<0.05	ns
Heart failure survival score	8.4±1.0	9.1±1.0	8.6±0.8	<0.01	ns
Peak VO_2	15.0±4.4	15.6±4.1	15.9±3.4	ns	ns

Data are presented as mean±standard deviation or percentage of patients. Plasma lipid and heart function parameter data were adjusted for age. *Abbreviations:* ACE = angiotensin converting enzyme; LVEDD = left ventricular end-diastolic diameter; ns = not sgnificant; NYHA = New York Heart Association.

suppression of systemic inflammatory processes that are intimately involved in the pathogenesis of HF. Actually, statins were shown to enhance nitric oxide availability, to increase circulating endothelial progenitor cells, and to reduce secretion of pro-inflammatory cytokines in patient and animal models of HF.[14–18] In addition, statins might directly improve cardiac function by promoting myocardial perfusion or cardiomyocyte survival.

The present study shows that plasma NT-proBNP levels were significantly lower only in patients who were on atorvastatin, but not in those receiving other statin. The reason for this finding is unclear. Various statins exhibit distinct physicochemical and pharmacokinetic properties, and differ in their ability to exert diverse physiologic effects. For instance, atorvastatin was found to be more effective than simvastatin in the reduction of systemic inflammation markers and enhancement of endothelium-dependent vasodilation.[19–21] However, both pravastatin and simvastatin were demonstrated to exert HF-relevant pleiotropic functions and, moreover, treatment with simvastatin improved

cardiac function in patients with dilated cardiomyopathy, irrespective of reduced cholesterol levels.[8] It has to be pointed out that HF patients investigated here received statin treatment at doses commonly administered in clinical practice in Germany. Forty mg simvastatin is equivalent to only 15 mg atorvastatin; at least with respect to lipid-lowering effects. It cannot be entirely ruled out that the more pronounced effect of atorvastatin observed in this study is not related to specific properties of this compound, but rather reflects a more efficacious drug regimen.

There are several further limitations to the present study. For instance, levels of LDL and high-density lipoprotein (HDL) cholesterol were not available. However, it seems unlikely that differences in LDL and HDL levels, after accounting for total cholesterol and triglycerides, would account for the markedly lower NT-proBNP levels seen in the atorvastatin-receiving group. The sample size did not permit the separate assessment of the effect of each statin treatment on parameters reflecting heart function in subgroups with various HF etiologies. Finally, the study had an exploratory character. Clearly, cross-sectional confirmatory or longitudinal prospective studies on larger patient collectives are necessary to fully assess beneficial effects of various statins in HF. In this context, it is worth noting that 2 large prospective studies (the Gruppo Italiano per lo Studio della Soprawivenza nell'Infarto Miocardico-Heart Failure trial [GISSI-HF] and the Controlled Rosuvastatin Multinational Trial in HF [CORONA]) were designed to investigate the impact of rosuvastatin on the mortality and morbidity in patients with symptomatic HF.[22,23]

In conclusion, our findings show that atorvastatin treatment is associated with better cardiac function parameters in HF, and suggest that this drug may represent an advantageous additional treatment option for patients with HF, irrespective of underlying etiology.

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