Statins Do Not Significantly Affect Muscle Sympathetic Nerve Activity in Humans with Non-Ischemic Heart Failure: A Double-Blind Placebo Controlled Trial

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Abstract

Background—HMG-CoA reductase inhibitors (statins) have been shown to reduce sympathetic nervous system (SNS) activation in experimental heart failure (HF). However, this potential mechanism of action of statins in HF has not been well studied in humans.

Methods and Results—Twenty-six patients with non-ischemic, systolic HF (left ventricular ejection fraction [LVEF] ≤ 35%) were randomized to atorvastatin (10mg) vs. placebo for 3 months. Pre- and post- treatment testing included echocardiography, laboratories, quality of life (QOL) questionnaires, and peroneal nerve muscle sympathetic nerve activity (MSNA) via microneurography. Eighteen subjects had technically adequate pre- and post- MSNA tracings. The cohort was 65% male, 81% NYHA II, LVEF $26 \pm 6\%$, and LDL cholesterol 108 ± 26 mg/dl. Baseline MSNA was 41 ± 2 bursts / minute. LDL significantly decreased in the atorvastatin (−36.8%) vs. placebo (−0.1%) group (p<0.0001). However, there was no significant change in MSNA (−16.2% vs. – 2.5%), LVEF, B-type natriuretic peptide, or QOL score in the atorvastatin compared to placebo group.

Conclusions—Short-term statin therapy in patients with non-ischemic HF does not result in a significant decrease in SNS activation as measured by MSNA. These findings are consistent with the neutral outcomes of large clinical trials of statins in HF.

Keywords

heart failure; lipids; nervous system; sympathetic

Introduction

Heart failure (HF) is a national public health problem with an overall prevalence in the United States of approximately 6 million. One out of five patients newly diagnosed with HF will die within one year, despite advances in medical and device therapies for HF over the past decades.[1, 2] Numerous observational, experimental, and small clinical studies of HMG-CoA reductase inhibitor (statin) therapy in HF suggested that statins would have beneficial

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effects on outcomes in HF of both ischemic and non-ischemic etiology;[3–9] however, initial encouraging findings were not translated into survival benefit in two large randomized controlled trials of statins powered for clinical outcomes (Controlled Rosuvastatin Multinational Trial in Heart Failure [CORONA] and the GISSI-HF trial).[10, 11]

Several pleiotrophic effects of statins of theoretic benefit in non-ischemic HF have been demonstrated experimentally, including anti-inflammatory actions, anti-remodeling effects, and improvement in endothelial function.[12] Statins have also been shown in experimental models to substantially decrease the excess sympathetic nervous system (SNS) activation characteristic of HF.[13–15] This study aimed to assess the effect of statin therapy on SNS activation, as measured by muscle sympathetic nerve activity (MSNA) in humans with non-ischemic, systolic dysfunction HF.

Methods

Participants

We studied 26 subjects with non-ischemic cardiomyopathy and HF followed at a single university center. Eligibility criteria included age ≥ 18 years, NYHA II–III HF or NYHA I HF with HF symptoms in past year, and left ventricular ejection fraction (LVEF) ≤ 35%. LVEF was documented by 2D echocardiography within 3 months of study enrollment. Those with coronary artery disease (CAD) – defined as angiographic evidence of ≥ 50% lesion in 1 or more of the 3 major epicardial vessels, history of myocardial infarction, history of revascularization procedure, or evidence of significant perfusion defect in the setting of ischemic symptoms – were excluded from our study. Additional exclusion criteria included other clinical indication for statin treatment such as peripheral vascular disease or cerebrovascular disease, major cardiovascular event or surgical procedure within past 8 weeks (including implantable cardioverter defibrillator placement), low density lipoprotein (LDL) cholesterol < 70 mg/dL, and HF secondary to congenital heart disease or uncorrected valvular disease. Patients were excluded if they were already on treatment with a statin, had been treated with a statin in the prior two months, had statin intolerance, moderate – severe liver disease, liver enzymes > 3× upper limit of normal, or known peripheral or autonomic neuropathy.

Study Protocol

Subjects were randomized in a double-blinded fashion (1:1) to either atorvastatin (10 mg orally per day) or matching placebo for a treatment period of 3 months. This dose and duration of therapy were chosen based on a prior randomized trial in patients with HF which showed a significant effect of atorvastatin 10 mg in improving heart rate variability, an alternative index of autonomic tone [16]. Study visits were conducted at baseline (pre-treatment), 6 weeks (mid-treatment monitoring visit), and 3 months (final study visit). Patients were required to be on stable, optimal doses of standard HF therapy, including stable dose of beta-blocker for 8 weeks, angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) for 4 weeks, and aldosterone antagonist (AA, NYHA III subjects) for 4 weeks. Throughout the study period, patients were maintained on baseline doses of beta-blockers, ACEI / ARB, aldosterone antagonists, and diuretics, with the exception of two patients who needed adjustment in their diuretic doses due to fluid retention. The primary endpoint of the study was change in muscle sympathetic nerve activity (MSNA, bursts/minute). Secondary endpoints included change in LVEF by transthoracic echocardiography, health-related quality of life (QOL), and cardiac biomarkers, including B-type natriuretic peptide (BNP), cardiac troponin I (cTnI), and high sensitivity C-reactive protein (hs-CRP). The study protocol was approved by the UCLA Medical Institutional Review Board (Medical IRB −1), overseen by the UCLA Office for

Human Research Protection Program and accredited by the Association for Accreditation of Human Research Protection Programs, Inc.

MSNA was recorded directly from the peroneal nerve using the technique of microneurography, as previously described [17]. The location of the nerve was first identified with transcutaneous stimulation using a pencil-shaped electrode. A tungsten microelectrode (tip diameter 5–15 um) (Bioengineering, University of Iowa) was then inserted into the nerve, and a reference electrode is inserted subcutaneously 1–2 cm from the recording electrode. The microelectrodes were connected to a preamplifier (gain 1000), and an amplifier (gain 50–100); nerve signals were bandpass filtered (700–2000 Hz)(Nerve Traffic Analyzer, Model 662C-3, University of Iowa, Bioengineering). For recording and analysis, nerve activity was rectified and integrated (time constant 0.1 sec) to obtain a mean voltage display of sympathetic nerve activity that is recorded on paper. Blood pressure was recording during MSNA recording using automated pressure cuff on the upper arm and heart rate was monitored continuously from electrocardiogram patch electrodes. Muscle sympathetic bursts were identified by visual inspection by a single blinded investigator (TBH) and expressed as burst frequency (bursts/min).

2D echocardiography was performed by experienced technicians using Acuson Sequoia Echocardiography System (Siemens Medical, Inc.) at baseline and final study visit. LVEF was quantified by the modified Simpson's biplane method using harmonic imaging. [18] Left ventricular systolic and diastolic dimensions and degree of regurgitation were also assessed. Echoes were interpreted by physician blinded to treatment. Blood was collected and processed by UCLA Clinical Laboratory and Pathology Services; blood samples were sent to the lab immediately after phlebotomy and analyzed within one hour. Biomarkers – BNP, cTnI, and hsCRP – were analyzed by using industry-standard analytical platforms (Stratus CS STAT from Dade Behring for cTnI and Triage, Biosite, for BNP, and nephelometry for hs-CRP).

HRQL was measured using the Minnesota Living with Heart Failure Questionnaire (MLHFQ), a 21-item disease-specific measure of QOL.[19] The MLHFQ was self-administered during the baseline and final study visits. NYHA functional class was also assessed at baseline and final study visits by physician blinded to treatment. A subject global assessment, in which subjects describe their condition as categories of better, unchanged, or worse, was also performed at the final study visit.[20]

Statistical Analysis

Power analysis was based on previous study of MSNA in HF subjects treated with carvedilol vs. placebo; [21] a sample size of 7 / group afforded 95% power to detect a mean difference of 13 bursts / minute in the treatment group with a standard deviation of 8 / group and based on a 2-sided 5% significance level. All data was analyzed on an intention to treat basis. The independent sample t test and Mann-Whitney U tests were used for comparison of parametric and non-parametric continuous variables, respectively. Chi-square test was used to compare categorical variables. Two-way Analyses of Variance (ANOVA were used to compare mean difference of change between active therapy and placebo groups. As a secondary analysis, paired samples t-test were also compare baseline to post-treatment variables within groups. Statistical comparisons were performed using two-sided significance tests, and a p value of < 0.05 was considered statistically significant. Calculations were performed with PASW Statistics version 18.0.1 (IBM, Somers, NY).

Results

Study Population

Twenty-six patients were enrolled in the study, with 14 randomized to atorvastatin and 12 randomized to placebo. The subjects were predominantly male and NYHA II, with a mean age of 48 ±15 years. Mean LVEF at baseline was 26 ± 6 % and mean peak oxygen uptake by cardiopulmonary exercise testing was 16.0 ± 4.5 ml/kg/min. Ninety-six percent (n=25) subjects completed the study; one subject randomized to placebo could not complete the study because he unexpectedly underwent status II heart transplantation. The remainder of the patients had excellent compliance with therapy, as assessed by pill counts (data not shown). There were no significant differences between the active treatment and placebo groups in terms of baseline age, LVEF, lipid levels, or cardiac biomarkers(Table 1). The only significant differences between the groups were slightly more males and a higher mean creatinine value in the placebo group. In the cohort who had baseline and 3-month MSNA recordings (microneurography cohort, n=18), the atorvastatin and placebo groups were also similar in terms of baseline patient characteristics; the only significant difference between the groups was more males in the placebo group (Table 1).

Effect of Atorvastatin on Lipid Parameters

At the end of the 12-week study period, there was a significant difference between atorvastatin and placebo groups in terms of changes in total cholesterol and LDL cholesterol levels. There was a 36.8% reduction in LDL cholesterol in the atorvastatin group and no significant reduction in the placebo group. There were no significant changes in HDL cholesterol or triglycerides in either of the treatment groups (Table 2).

Statin therapy and MSNA

Baseline MSNA in the total cohort was 41 ± 2 (standard error of the mean [SEM]) bursts / minute and 60 ± 4 bursts / 100 heart beats. Systolic blood pressure at time of MSNA recording was higher in the placebo group compared to atorvastatin group at baseline; however, there was no significant difference between the groups in terms of change in systolic blood pressure by the end of the study. Baseline and changes in diastolic blood pressure and heart rate at time of MSNA recording were similar between the groups (Table 3).

Eighteen subjects had baseline and final sympathetic microneurographic tracings technically adequate for analysis. Reasons for inadequate microneurographic tracing were 1) inability of investigators to locate sympathetic nerve on baseline or final study, or 2) inability of patient to tolerate discomfort of the procedure. In the 18 subjects with baseline and final MSNA, There was no significant effect of atorvastatin (n=9) compared to placebo (n=9) on the primary endpoint of change in MSNA in this cohort of non-ischemic systolic HF patients, as shown in Table 3 and Figure 1. Muscle sympathetic nerve activity showed a non-significant 16.2% decrease in the atorvastatin group and 2.5% decrease in the placebo group. There was also no difference in the percentage of patients with a 20% or more decrease in MSNA when treated with atorvastatin compared to placebo.

Cardiac Biomarkers

There was no baseline difference in the cardiac biomarkers BNP, hs-CRP, or cTnI between the atorvastatin and placebo treatment groups. Furthermore, there was no significant change in any biomarkers with statin treatment compared to placebo by the end of the study period (Table 4).

Cardiac Structure and Function, Clinical Assessments and Quality of Life

Statin therapy had no significant effect on changes in cardiac size, systolic, or diastolic function, although there was a trend in terms of change in LVEF in the placebo group (decreased at follow-up) compared to the atorvastatin group (stable at follow-up) (Table 5). At the end of the study, most patients (46%) reported no significant change in their overall health status, while 42% felt better and 12% felt worse; this global assessment at the end of the study was similar between the two groups (Figure 2). There was no significant difference between the atorvastatin and placebo groups in terms of baseline MLHFQ score (41±21 vs. 38±28) or change in MLHFQ score at follow-up (−3±12 vs. −4±20).

Discussion

Statins have been reported and shown experimentally to have a number of mechanisms of action which may be particularly beneficial for HF, including anti-inflammatory actions, prevention of remodeling, and SNS inhibition. The current randomized, controlled, double-blinded study of humans with non-ischemic HF patients optimized on standard HF therapies failed to show a significant effect of atorvastatin 10 mg orally a day on the primary endpoint of MSNA, an index of SNS activation in HF, in addition to the secondary endpoints of LVEF, cardiac biomarkers, or QOL. This is the first study to evaluate the effect of statins on MSNA in humans with non-ischemic HF measured by sympathetic microneurography.

The central role of SNS activation in HF pathophysiology and progression has been recognized for over a quarter century, when plasma norepinephrine levels were found to be strong predictors of mortality risk in HF.[22] More recently, changes in the autonomic nervous system in HF have been characterized by a complex interplay of cardiac, central, and systemic factors; this "new model" of the SNS activation in HF describes mechanisms including impaired vagal regulation of heart rate, an adjusted set-point for central sympathetic outflow, blunted ventricular baroreceptor reflex control of MSNA, and early increase in cardiac norepinephrine spillover. [23] Although SNS activity is difficult to evaluate in the clinical setting, two techniques thought to best quantify SNS activity in humans are radiotracer measurements of regional norepinephrine spillover and sympathetic microneurography, which uses a microelectrode to directly measures post-ganglionic sympathetic nerve activity.[24]

MSNA, at rest and during stress, correlates well with cardiac sympathetic nerve activity in humans, as measured by cardiac norepinephrine spillover.[25] Furthermore, MSNA quantified by sympathetic microneurography at the peroneal nerve has been validated as a tool to study sympathetic nervous system activation in humans with HF,[26, 27] as well as in a variety of other disease processes, including hypertension and obesity.[28] MSNA at rest has consistently been found to be elevated in HF patients when compared to normal controls, and furthermore, life-prolonging therapies for HF patients, including ACEIs, ARBs, and beta-blockers have also been shown to decrease MSNA over time in humans with HF.[21, 29, 30]

Improvements in autonomic nervous system function with statin treatment have been demonstrated in animal models of HF. Pliquett et al. studied autonomic function in rabbits with pacing-induced HF.[14] HF rabbits fed simvastatin for three weeks had higher heart rate variability (HRV) than HF rabbits not treated with simvastatin, indicating an improvement in autonomic function; the HF rabbits fed the highest dose (3mg/kg/day) had HRV similar to non-HF controls. Pliquett et al. also investigated the effects of statin therapy on baroreceptor sensitivity, renal sympathetic nerve activity (RSNA), and plasma norepinephrine levels in rabbits with pacing-induced HF.[13] Norepinephrine levels and RSNA were significantly lower in HF rabbits who received moderate to high dose simvastatin compared to non-statin

treated HF animals. Furthermore, baroreflex responses in terms of heart rate and RSNA were depressed in HF rabbits treated with vehicle but restored to near-normal in HF rabbits treated with simvastatin. Cholesterol levels were unchanged by simvastatin in both studies, suggesting a cholesterol-independent, or pleiotrophic, effect of statins on autonomic function. This group subsequently linked autonomic improvement to an effect of simvastatin on inhibition of central angiotensin II and the superoxide pathway. In this study of pacing-induced HF in rabbits, the heightened blood pressure and RSNA responses to intracerebral angiotensin II injection seen in HF animals was abolished by simvastatin therapy.[15]

This human study, which fails to demonstrate an appreciable effect of atorvastatin for three months on MSNA in subjects with non-ischemic HF, is consistent with neutral findings from larger clinical trials. In the GISSI-HF trial, in which > 50% of patients enrolled had HF of a non-ischemic etiology, rosuvastatin 10 mg orally per day compared to placebo had no significant effect on the co-primary outcomes of death and death / cardiovascular hospitalization in 4631 randomized patients and followed for a median of 3.9 years.[11] Krum et al, in a study of 85 exclusively non-ischemic, systolic HF patients also found rosuvastatin compared to placebo therapy for 6 months had no appreciable effect on LVEF, neurohormonal parameters, or other clinical outcomes.[20]

One recently published study assessed MSNA in 7 patients with prior myocardial infarction and HF at three timepoints: during statin therapy, 8 weeks after discontinuation of statin, and 4 weeks after restarting statin (differing doses of simvastatin and atorvastatin). MSNA was higher (42 ± 3 bursts/min) 8 weeks after discontinuation of statin compared to during statin therapy (32 ± 3 and 28 ± 3 bursts/min, respectively).[31] This study differs from ours significantly in that there is no blinding or placebo control, and that all patients have coronary artery disease and prior myocardial infarction. In the CORONA trial, in which 5011 systolic HF patients with exclusively ischemic heart disease were enrolled, rosuvastatin 10 mg a day compared to placebo had no significant effect on the primary outcome of death from cardiovascular causes, nonfatal myocardial infarction, and nonfatal stroke or the secondary outcome of all cause mortality. However, there was a modest but significantly lower rate of hospitalizations for cardiovascular causes in the statin (n = 2193) vs. placebo (n = 2564) groups.[10]

Although in the general population, higher cholesterol levels are clearly associated with increased risk of cardiovascular events, a reversal of traditional epidemiology has been demonstrated in advanced HF populations; lower cholesterol levels are associated with worsened outcomes in both ischemic and non-ischemic HF.[32–34] Likewise, despite the clear-cut evidence for cholesterol-lowering with statins in patients with coronary artery disease, cholesterol-lowering has not been shown to improve survival in symptomatic HF patients with coronary artery disease.[10, 35] Low cholesterol levels in HF may be associated with poor prognosis in HF because they reflect malnutrition and/or inflammation. It has also been hypothesized that lipoproteins in HF play a cardioprotective role neutralizing excess circulating endotoxin.[36] Thus, lowering cholesterol levels with statins or other agents in HF may activate inflammatory, neurohormonal, and sympathetic pathways, thus diminishing other beneficial mechanisms of action of statins. Additional investigations are needed to help explain why traditional epidemiology and traditional therapeutic targets in the general population cannot be applied to patients with advanced HF.

Limitations

The presence of obstructive or central sleep apnea, which can profoundly affect MSNA, was not assessed as part of this study.[23] We do not have data on cardiac or systemic norepinephrine levels, other indicators of sympathetic status in patients with HF. This study was powered to detect a 13 burst/minute or greater difference in MSNA but based on the

sample size cannot exclude statins may have a smaller magnitude of effect on MSNA. In particular, those patients with low MSNA at baseline (Figure 1), may not have been plausibly expected to have a further decrease MSNA. This cohort was comprised primarily of NYHA II patients with relatively low BNP levels and results cannot be extrapolated to sicker HF populations; however, a post-hoc analysis of the CORONA trial suggested that statin therapy might be beneficial in HF patients who are "less sick", with the lowest levels of natriuretric peptides [37]. Our population was predominantly male; however, one recent study suggests that MSNA and changes in MSNA in response to an intervention (exercise) are similar in men and women [38]. We only tested one dose of atorvastatin and did not compare this dose to a higher dose; a higher dose may have had a significant effect. A different statin, such as simvastatin as was used in animal models, may have had a different effect on MSNA. It is also possible that statins or atorvastatin do have sympathoinhibitory effects in HF, but that these effects are not detectable on top of optimal medical therapy with beta-blockers, ACEIs, and aldosterone antagonists; however, the objective of our study was to investigate whether statins could exert potentially beneficial mechanisms of action in HF patients already on standard, life-prolonging HF therapies.

Conclusions

Short-term atorvastatin treatment in humans with systolic, non-ischemic HF on optimal medical therapy does not significantly lower sympathetic activation, as quantified by MSNA (bursts/min). To date, therapies which definitively improve survival in humans with HF – including ACEIs, ARBs, beta-blockers, aldosterone antagonists, as well as cardiac resynchronization therapy, have also been shown to diminish SNS excitation in translational studies.[21, 29, 30, 39, 40] Thus, our findings are consistent with the results of large randomized controlled trials which showed no mortality benefit in a wide range of HF patients of ischemic and non-ischemic etiology treated with statins.

Acknowledgments

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ATORVASTATIN (n=9)

PLACEBO (n=9)

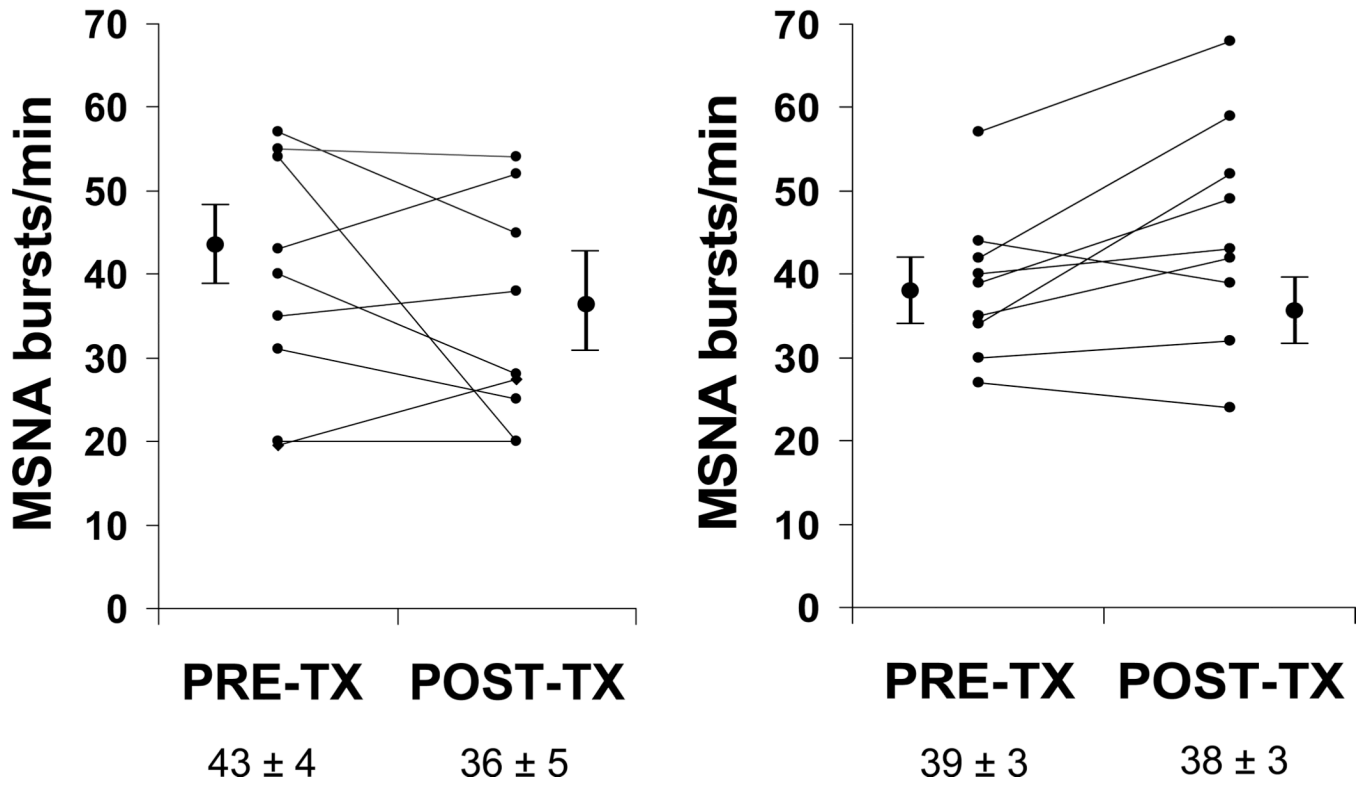| PRE-TX	POST-TX	PRE-TX	POST-TX
43 ± 4	36 ± 5	39 ± 3	38 ± 3

Figure 1.
Graph of MSNA (bursts / minute) at baseline and after three months of therapy in the active treatment (atorvastatin) and placebo groups. Pre-tx = pre-treatment; post-tx = post treatment.
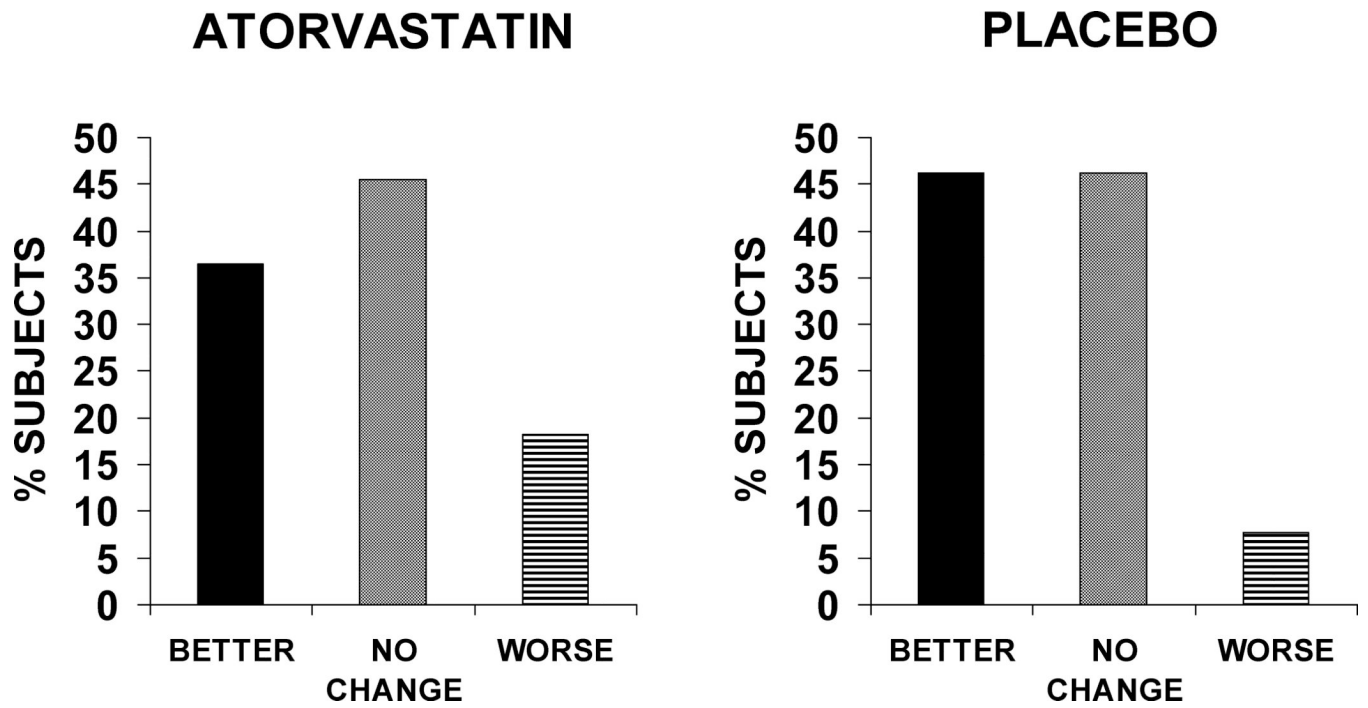
Figure 2.
Subject global assessment for atorvastatin and placebo at end of study.

Table 1

Baseline Characteristics of the Total Study Cohort and the Microneurography Cohort

	Total Cohort (n=26)		Microneurography Cohort (n=18)	
	Atorvastatin Group (n= 14)	Placebo Group (n=12)	Atorvastatin Group (n = 9)	Placebo Group (n = 9)
Age, years	47 ± 14	49 ± 17	47 ± 15	46 ± 19
Male, %	42[*]	86	44[*]	89
Systolic Blood Pressure, mmHg	100 ± 13	101 ± 13	96 ± 11	98 ± 9
Diastolic Blood Pressure, mmHg	65 ± 9	61 ± 8	66 ± 11	60 ± 10
Heart Rate, bpm	74 ± 11	71 ± 8	73 ± 8	71 ± 8
Body Mass Index, kg/m^2	31 ± 7	31 ± 6	29 ± 4	33 ± 6
NYHA I/II/III, %	7/71/21	0/92/8	11/67/22	0/89/11
LVEF, %	24 ± 6	28 ± 7	24 ± 6	29 ± 6
Left ventricular end diastolic dimension, mm	65 ± 12	66 ± 11	65 ± 13	66 ± 8
Peak oxygen uptake, ml/kg/min	15.6 ± 4.1	16.6 ± 5.2	16.0 ± 3.6	15.9 ± 5.8
<u>Laboratory Values</u>				
Total cholesterol, mg/dL	185 ± 34	187 ± 39	182 ± 37	188 ± 44
LDL cholesterol, mg/dL	106 ± 24	110 ± 29	101 ± 23	108 ± 28
HDL cholesterol, mg/dL	49 ± 13	41 ± 10	49 ± 14	42 ± 12
Triglycerides, mg/dL[†]	151 (66 – 235)	177 (87 – 226)	187 (66–245)	193 (89–267)
High sensitivity C-reactive protein, mg/dL[†]	1.6 (0.6 – 4.4)	1.9 (1.0 – 3.0)	1.7 (0.8 – 3.7)	2.1 (0.8 – 4.2)
B-type natriuretic peptide, pg/mL[†]	176 (36 – 472)	55 (29 – 154)	185 (53 – 482)	66 (32–115)
Creatinine, mg/dL	0.9 ± 0.2[*]	1.2 ± 0.4	1.0 ± 0.2	1.1 ± 0.3
Alanine transferase (ALT), U/L	22 ± 10	26 ± 12	24 ± 10	29 ± 13
Aspartate transferase (AST), U/L	22 ± 7	24 ± 7	24 ± 7	24 ± 9
<u>Medications</u>				
Beta-blocker, %	100	100	100	100
Angiotensin Converting Enzyme Inhibitor or Angiotensin Receptor Blocker, %	100	100	100	100
Aldosterone Antagonist, %	83	71	88	88
Loop diuretic, %	66	79	67	88
Digoxin, %	17	43	11	44

[*] p<0.05 atorvastatin vs. placebo groups

[†] Median and interquartile range reported

Table 2

Changes in Serum Cholesterol Levels with Treatment

	Baseline			Final[†]			% Change	
	Statin	Placebo	P value[*]	Statin	Placebo	P value	Statin	Placebo
Total cholesterol, mg/dL	185 ± 34	187 ± 39	0.881	137 ± 7	183 ± 43	0.0001	−25.9%	−2.2%
LDL cholesterol, mg/dL	106 ± 24	110 ± 29	0.710	67 ± 17	110 ± 33	0.001	−36.8%	−0.1%
HDL cholesterol, mg/dL	49 ± 13	41 ± 10	0.130	46 ± 14	40 ± 10	0.638	−6.1%	−2.4%
Triglycerides, mg/dL[‡]	151 (66 − 235)	177 (87 − 226)	0.775	96 (86 − 178)	143 (90 − 224)	0.265	−36.4%	−19.2%

[*] Baseline p values were determined by an unpaired *t* test.

[†] Changes between the two groups from baseline were determined by two-way analysis of variance and non-parametric test for triglycerides.

[‡] Median (interquartile range) reported.

Table 3

Baseline and Follow-up Muscle Sympathetic Nerve Activity (MSNA) and Hemodynamics in Treatment and Placebo Groups

	Baseline (n=18)			Final (n=18)			% Change	
	Statin (n=9)	Placebo (n=9)	P value[*]	Statin (n=9)	Placebo (n=9)	P value[†]	Statin	Placebo
MSNA, bursts/minute	43 ± 3	39 ± 3	0.875	36 ± 5[‡]	38 ± 3	0.269	−16.2%	−2.5%
MSNA, bursts/100 heart beats	62 ± 6	57 ± 5	0.949	52 ± 6	55 ± 5	0.308	−16.1%	−3.5%
Systolic Blood Pressure, mm Hg	107 ± 4	118 ± 3	0.051	102 ± 6	116 ± 4	0.619	−4.6%	−1.6%
Diastolic Blood Pressure, mm Hg	63 ± 5	62 ± 3	0.783	62 ± 5	66 ± 4	0.322	−1.5%	+6.5%
Heart Rate, bpm	70 ± 3	69 ± 3	0.721	69 ± 3	70 ± 4	0.459	−1.4%	+1.4%

Values reported as mean ± S.E.M.

[*] Baseline p values were determined by an unpaired *t* test.

[†] Changes between the two groups from baseline were determined by two-way analysis of variance.

[‡] P values as determined by paired t-test were also not statistically significant (p=0.117 and p=0.443 for atorvastatin and placebo groups, respectively)

Table 4

Changes in Cardiac Biomarker Levels with Treatment

	Baseline			Final			% Change	
	Statin	Placebo	P value[*]	Statin	Placebo	P value[†]	Statin	Placebo
B-type natriuretic peptide, pg/mL	175 (36 – 472)	66 (29 – 154)	0.227	107 (34 – 173)	67 (21 – 299)	0.605	−38.9%	+1.5%
High sensitivity C-reactive protein, mg/L	1.6 (0.6 – 4.4)	1.9 (1.0 – 3.0)	0.700	1.9 (0.5 – 5.7)	3.4 (1.1 – 5.9)	0.307	+18.8%	−78.9%
Troponin I ≥ 0.04 ng/mL, %	8	21	0.356	0	15	0.511	-	-

[*] Baseline p values were determined by Mann-Whitney U test, and chi-square for Troponin I.

[†] Changes between the two groups from baseline were determined by Mann-Whitney U test, and Chi-Square for Troponin I.

Table 5

Echocardiographic Variables in Atorvastatin and Placebo Groups

	Baseline			Final			% Change	
	Statin	Placebo	P value[*]	Statin	Placebo	P value[†]	Statin	Placebo
Left ventricular ejection fraction, %	24 ± 6	28 ± 7	0.173	25 ± 6	24 ± 7[‡]	0.102	+4.2%	−14.3%
Left ventricular end diastolic dimension, mm	65 ± 12	67 ± 11	0.811	65 ± 11	64 ± 11	0.217	0%	−4.5%
E (cm/sec)	75 ± 7	83 ± 10	0.524	84 ± 9	75 ± 11	0.102	+12.0%	−9.6%
E/A ratio	1.2 ± 0.2	1.5 ± 0.3	0.530	1.6 ± 0.3	1.2 ± 0.2	0.199	+33.3%	−20%
E/E' ratio	8 ± 2	6 ± 1	0.680	9 ± 2	7 ± 2	0.994	+12.8%	+16.7%

[*] Baseline p values were determined by an unpaired *t* test.

[†] Changes between the two groups from baseline were determined by two-way analysis of variance.

[‡] P value for change in LVEF at 3 months as determined by paired t-test was significant for the placebo group (p=0.025) but not the atorvastatin group. E, E/A ratio, and E/E' ratio are presented as mean ± standard error of the mean (SEM).