Journal of the American College of Cardiology
© 2006 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 47, No. 2, 2006
ISSN 0735-1097/06/$32.00
doi:10.1016/j.jacc.2005.06.088

Atorvastatin Improves Left Ventricular Systolic Function and Serum Markers of Inflammation in Nonischemic Heart Failure

Srikanth Sola, MD,* Muhammad Q. S. Mir, MD,* Stamatios Lerakis, MD, FACC, Neeraj Tandon, MD, FACC,† Bobby V. Khan, MD, PHD*

Atlanta, Georgia; and Shreveport, Louisiana

OBJECTIVES This study examined the effect of statin therapy on vascular markers of inflammation and echocardiographic findings in patients with nonischemic forms of cardiomyopathy.

BACKGROUND Despite advances in therapy, morbidity and mortality from heart failure (HF) remain high. We wished to determine whether treatment with atorvastatin affects left ventricular (LV) systolic function and markers of inflammation in patients with nonischemic HF.

METHODS A total of 108 patients with nonischemic HF and a left ventricular ejection fraction (LVEF) ≤35% were randomized to either atorvastatin 20 mg/day or placebo in a double-blinded fashion for a 12-month period. The LVEF and LV end-diastolic diameter (LVEDD) and left ventricular end-systolic diameter (LVESD) were determined by echocardiography. Serum markers of inflammation and oxidation were also measured.

RESULTS The LVEF increased from 0.33 ± 0.05 to 0.37 ± 0.04 ($p = 0.01$) in the atorvastatin group over the 12-month follow-up period, whereas those patients in the placebo group experienced a decline in ejection fraction during the same time period. In addition, LVEDD was reduced from 57.1 ± 5.9 mm to 53.4 ± 5.1 mm ($p = 0.007$) and LVESD was reduced from 42.4 ± 3.8 mm to 39.1 ± 3.8 mm ($p = 0.02$) in the cohort of patients treated with atorvastatin; these dimensions increased in the placebo group. There was an increase in erythrocyte superoxide dismutase (E-SOD) activity, and there were significant reductions in serum levels of high sensitivity C-reactive protein, interleukin-6 (IL-6), and tumor necrosis factor-alpha receptor II (TNF-α RII) in the atorvastatin group.

CONCLUSIONS The use of atorvastatin in patients with nonischemic HF improves LVEF and attenuates adverse LV remodeling. The effects on soluble levels of several inflammatory markers with atorvastatin suggest, in part, mechanisms by which statins might exert their beneficial effects in nonischemic HF. (J Am Coll Cardiol 2006;47:332–7) © 2006 by the American College of Cardiology Foundation

Despite advances in pharmacological and interventional therapy, morbidity and mortality due to heart failure (HF) remain high. Patients with HF often have elevated levels of pro-inflammatory cytokines and chemokines, compounds that are involved in adverse left ventricular (LV) remodeling, neurohormonal activation, impaired autonomic and vascular tone, and progression of coronary atherosclerosis (1). Higher levels of these inflammatory markers, including tumor necrosis factor-alpha, interleukin (IL)-6, and C-reactive protein, are also associated with adverse cardiovascular morbidity and mortality (2–4).

See page 342

Hydroxymethylglutaryl CoA reductase inhibitors (statins) have been shown to reduce morbidity and mortality in coronary artery disease (CAD) and other atherosclerosis-related diseases (5–8); however, only limited data are available on the effect of statins in reducing adverse cardiovascular events in patients with HF (9,10). Statins have many effects beyond lipid-lowering that make them of potential benefit in patients with HF of both ischemic and nonischemic etiologies. Statins facilitate nitric oxide (NO) synthesis and improve endothelial function, both of which are typically impaired in patients with HF (11,12). In addition, they inhibit the synthesis of inflammatory cytokines and chemokines, improve autonomic function, and reverse myocardial remodeling (13,14). Moreover, statins might retard the progression of myocardial dysfunction in HF by promoting plaque stabilization and reducing the progress of CAD.

We hypothesized that statin therapy would improve LV function and markers of inflammation in patients with nonischemic etiologies of HF. We undertook the present pilot study to evaluate the effects of therapy with atorvastatin on echocardiographic indexes of LV function and serum markers of inflammation in patients with nonischemic etiologies of HF and systolic dysfunction.

From the *Division of Cardiology, Emory University School of Medicine, Atlanta, Georgia; and the †Division of Cardiology, Louisiana State University Health Sciences Center, Shreveport, Louisiana. Dr. Khan has been an advisory board member for Sanofi-Aventis and Bristol Myers Squibb and on the speakers bureau for Sanofi-Aventis, Bristol Myers Squibb, and Takeda Pharmaceuticals.

Manuscript received March 24, 2005; revised manuscript received June 6, 2005, accepted June 14, 2005.

Abbreviations and Acronyms

CAD	= coronary artery disease
E-SOD	= erythrocyte superoxide dismutase
HDL	= high-density lipoprotein
HF	= heart failure
hsCRP	= high sensitivity C-reactive protein
IL	= interleukin
LDL	= low-density lipoprotein
LV	= left ventricle/ventricular
LVEDD	= left ventricular end-diastolic diameter
LVEF	= left ventricular ejection fraction
LVESD	= left ventricular end-systolic diameter
TNF-α RII	= tumor necrosis factor-alpha receptor II

METHODS

Subjects. Men and women ages 18 years or older were eligible for enrollment if they had: 1) New York Heart Association (NYHA) functional class II to IV HF due to a nonischemic etiology; 2) left ventricular ejection fraction (LVEF) of ≤35%, as documented by echocardiography or ventriculography during the one year before enrollment; and 3) stable doses of HF medications for three months before enrollment. Patients were excluded if they: 1) had been receiving a statin during the six months before enrollment; 2) had had a prior adverse event related to statin use; or 3) had diabetes mellitus. Patients were classified as having nonischemic cardiomyopathy if they had no prior clinical history of a myocardial infarction and no coronary artery stenoses >50% on cardiac catheterization performed during the one year before enrollment. Written informed consent was obtained from all patients.

Study design. Patients (n = 108) were randomized in a double-blinded fashion to either atorvastatin (20 mg/day) or matching placebo for a 12-month period. Study visits took place at 0, 6, and 12 months. Transthoracic echocardiography was performed at each study visit, and LVEF, LV mass/body surface area, and LV systolic and diastolic diameters were determined. Blood was drawn at each study visit to measure several markers of inflammation. The primary end point of the study was change in LVEF, as determined by transthoracic echocardiography. Secondary end points included changes in several markers of inflammation and/or oxidation, including high sensitivity C reactive protein (hsCRP), IL-6, tumor necrosis factor-α receptor II (TNF-α RII), and erythrocyte superoxide dismutase (E-SOD). The study protocol complies with the Declaration of Helsinki and was approved by the institutional review board.

Echocardiographic assessment. Two-dimensional transthoracic echocardiograms were performed at 0, 6, and 12 months. Left ventricular systolic function and cardiac dimensions indexed to body surface area were determined. The heart was imaged in parasternal short axis view to obtain LV wall thickness and parasternal long axis view to measure ejection fraction, which was determined with Simpson's rule. Left ventricular end-diastolic diameter (LVEDD) and left ventricular end-systolic diameter (LVESD) diameters were measured from M-mode tracings. The LV mass index was calculated by the Penn-cube method, as previously described (15). The images were reviewed by two independent echocardiographers who were blinded to the subject's clinical status during the study period, and any discrepancies in interpretations were resolved.

Laboratory measurements. Laboratory samples were collected at each study visit and stored at −80°C after centrifugation. An aliquot was drawn, and E-SOD activity was determined with hemolysates and commercially available kits (Cat. No. SDI 25, Randox Lab. Ltd., Crumlin, County Antrim, Ireland). Briefly, superoxide radicals produced by xanthine and xanthine oxidase reacts with 2-(4-iodophenyl)-3-(4-nitrophenol)-5-phenyltetrazolium chloride to form a red formazan dye (16). The E-SOD activity is then measured by the degree of inhibition of this reaction. The E-SOD activity was expressed as U/g Hb. For analysis of serum IL-6, studies were performed on each sample in triplicate. Sixty microliters of serum were used for analysis, and enzyme-linked immunosorbent assay (ELISA) was performed. The levels of total serum IL-6 were determined on a plate reader at an optical density of 420 nm. High sensitivity CRP was measured with an immunoprecipitation assay. Serum TNF-α RII was measured as an indirect marker of monocyte/macrophage stimulation (17). The interassay variability was <10% and the intra-assay variability was <5% for all four markers. We found no interference by atorvastatin or its metabolites in these assays.

Blood glucose was measured with a glucose dehydrogenase method after precipitation of proteins by trichloroacetic acid. Low-density lipoprotein (LDL) and high-density lipoprotein (HDL) fractions were separated from fresh serum by combined ultracentrifugation and precipitation. Lipoprotein fraction cholesterol and triglycerides were measured enzymatically.

Statistical analysis. All values presented are the mean ± standard deviation for continuous variables and as the percentage of total patients for categorical variables. The independent sample *t* test and chi-square were used for comparison of continuous and categorical variables, respectively. Two-way analysis of variance (ANOVA) was used to compare laboratory and serial echocardiographic data between the groups. Data were analyzed by intention to treat, with a secondary analysis performed with paired samples (patients with complete baseline and follow-up data available). A p value of <0.05 was considered statistically significant, and all p values were two-sided. Calculations were performed with Statistical Package for the Social Sciences (SPSS) software (version 10.0, Chicago, Illinois).

RESULTS

Study population. One hundred and eight patients (67 men and 41 women) were enrolled in the study and followed

Table 1. Baseline Patient Demographics and Characteristics

	Placebo (n = 54)	Atorvastatin (n = 54)
Age (yrs)	54.1 ± 6.9	53.3 ± 6.2
Male (%)	33 (62)	34 (64)
Body mass index (kg/m^2)	24.4 ± 3.8	24.1 ± 4.0
Systolic BP (mm Hg)	119 ± 11	116 ± 11
Diastolic BP (mm Hg)	72 ± 10	75 ± 9
Ejection fraction	0.33 ± 0.04	0.33 ± 0.05
NYHA functional class II (%)	26	30
NYHA functional class III (%)	70	64
NYHA functional class IV (%)	4	6
Baseline laboratory values		
LDL cholesterol (mg/dl)	124 ± 20	118 ± 15
HDL cholesterol (mg/dl)	42 ± 8	44 ± 7
Triglycerides (mg/dl)	144 ± 23	149 ± 19
Fasting glucose (mg/dl)	93 ± 15	91 ± 19
Hemoglobin A1C (%)	5.0 ± 0.7	4.9 ± 0.6
Baseline medications		
ACE inhibitor or ARB (%)	49 (91)	46 (85)
Beta-blocker (%)	39 (72)	36 (67)
Aldosterone blocker (%)	6 (11)	5 (9)
Diuretics (%)	35 (65)	35 (65)

p = NS for difference in baseline characteristics between the study cohorts. Values are n (%) or mean ± SD.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BP = blood pressure; HDL = high-density lipoprotein; LDL = low-density lipoprotein; NYHA = New York Heart Association.

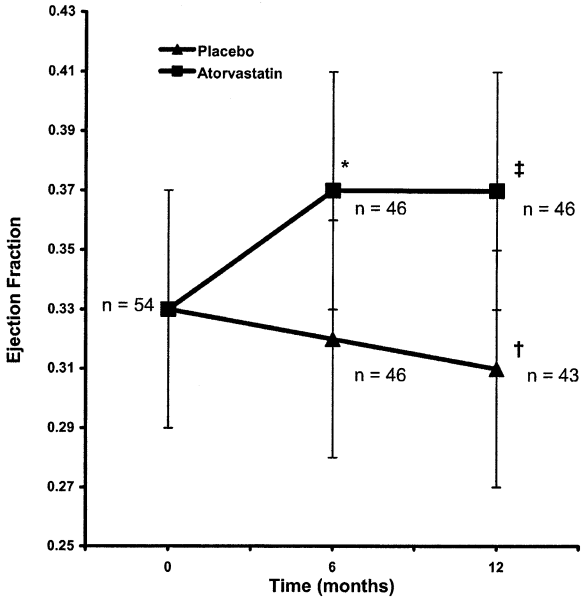

Figure 1. Change in ejection fraction in the placebo and atorvastatin groups during the 12-month study follow up. *p = 0.01 for the difference in ejection fraction between baseline and 6 or 12 months within the atorvastatin group; †p = 0.04 for the difference in ejection fraction between baseline and 12 months within the placebo group; ‡p = 0.004 for the difference in ejection fraction at 12 months between the placebo and the atorvastatin groups.

for 12 ± 2 months. Of these patients, 54 each were randomized to the placebo and atorvastatin groups. At baseline, there was no significant difference in NYHA functional class, baseline LVEF, LDL cholesterol, HDL cholesterol, or triglyceride levels between the two groups, as shown in Table 1.

A total of 89 patients (placebo = 43, atorvastatin = 46) completed the 12-month treatment period. The remaining 19 subjects dropped out of the study by their choice or the decision of the patient's attending physician. Data are presented for those subjects who completed the study. At the end of the 12-month study period, there was a significant reduction in both LDL cholesterol level (2.4 ± 0.4 mmol/l for atorvastatin vs. 2.9 ± 0.4 mmol/l for placebo; $p < 0.0001$) and serum triglyceride levels (1.5 ± 0.2 mmol/l for atorvastatin vs. 1.7 ± 0.2 mmol/l for placebo; p = 0.003) in the atorvastatin versus the placebo groups. There was no change in serum HDL cholesterol levels in either group (Table 2).

Atorvastatin improves LV systolic function. In the group randomized to atorvastatin, there was an increase in LVEF from 0.33 ± 0.05 to 0.37 ± 0.05 (p = 0.01), whereas LVEF decreased from 0.33 ± 0.04 to 0.31 ± 0.03 (p = 0.04) in those patients randomized to placebo (Fig. 1). At the end of the 12-month study period, patients in the atorvastatin group had a statistically significant higher ejection fraction than patients randomized to placebo (0.37 ± 0.05 vs. 0.31 ± 0.03, respectively; ANOVA, p = 0.004). In addition, there were statistically significant decreases in both LVEDD and LVESD in the atorvastatin group after treatment, whereas these dimensions actually increased for patients randomized to placebo (Table 3). Between the placebo and atorvastatin groups, the differences in both LVEDD (ANOVA, p = 0.01) and LVESD (ANOVA, p = 0.01) were statistically significant. The LV mass/body surface area did not change significantly in either group. Statistical comparisons were similar with analysis using intention to treat and by paired samples.

Atorvastatin reduces soluble levels of IL-6, TNF-α RII, and hsCRP and increases E-SOD activity. In patients treated with atorvastatin, serum soluble levels of IL-6

Table 2. Changes in Serum Cholesterol Levels With Treatment

	Baseline			Follow-Up		
	Placebo (n = 54)	Atorvastatin (n = 54)	p Value	Placebo (n = 43)	Atorvastatin (n = 46)	p Value
LDL cholesterol (mg/dl)	124 ± 20	118 ± 15	NS	124 ± 17	93 ± 9	<0.0001
HDL cholesterol (mg/dl)	42 ± 8	44 ± 7	NS	43 ± 8	46 ± 8	NS
Triglycerides (mg/dl)	144 ± 23	149 ± 19	NS	149 ± 22	138 ± 20	0.003

Values are mean ± SD. 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. Abbreviations as in Table 1.

Table 3. Effects of Atorvastatin on Left Ventricular Dimensions

	Baseline			Follow-Up		
	Placebo (n = 54)	Atorvastatin (n = 54)	p Value	Placebo (n = 43)	Atorvastatin (n = 46)	p Value
LV mass/body surface area (g/m^2)	117 ± 22	115 ± 18	NS	118 ± 14	113 ± 13	0.1
LVEDD (mm)	56.1 ± 5.9	57.1 ± 5.9	NS	60.3 ± 5.1	53.4 ± 5.1	0.01
LVESD (mm)	40.9 ± 4.7	42.4 ± 3.8	NS	43.1 ± 4.5	39.1 ± 3.8	0.01
Ejection fraction	0.33 ± 0.04	0.33 ± 0.05	NS	0.31 ± 0.03	0.37 ± 0.04	0.004

Values are mean ± SD. 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. LVEDD = left ventricle end-diastolic diameter; LVESD = left ventricle end systolic diameter.

decreased from 17.1 ± 1.4 ng/dl to 13.3 ± 0.8 ng/dl over the 12-month study period, with no significant change in the placebo group (Table 4). Similar reductions in serum levels of TNF-α RII and hsCRP were noted in the atorvastatin group, with no significant change in the placebo group. Activity of E-SOD, an anti-oxidative marker, was lower in the atorvastatin group at baseline when compared with placebo (550 ± 58 U/g Hb for atorvastatin vs. 580 ± 60 U/g Hb for placebo; p = 0.009) but increased significantly in the atorvastatin group at the end of the follow-up period (649 ± 43 U/g Hb for atorvastatin vs. 577 ± 38 U/g Hb for placebo; p < 0.0001).

Atorvastatin therapy and clinical events. At the end of the 12-month study period, the mean NYHA functional class was 2.9 ± 0.3 in the placebo group vs. 2.2 ± 0.3 in the atorvastatin group (p = 0.001). There were 13 hospital stays for HF among those subjects in the placebo group vs. 8 hospital stays for HF in the atorvastatin group (p = NS). There was no difference in total mortality between the two study groups (four in each group).

DISCUSSION

This study shows a substantial benefit with atorvastatin therapy in patients with systolic HF due to a nonischemic etiology. The LV systolic function improved significantly in the cohort of patients treated with atorvastatin, compared with a decline in systolic function in patients treated with placebo over the 12-month study period. In addition, there were reductions in both LV end-diastolic and end-systolic dimensions in the atorvastatin group when compared with placebo. These findings suggest that atorvastatin might retard the progression of adverse myocardial remodeling in patients with nonischemic HF. Finally, atorvastatin therapy was associated with reductions in levels of hsCRP, TNF-α RII, and IL-6 as well as an increase in E-SOD activity, suggesting an association between changes in pro-inflammatory and pro-oxidative markers and LV systolic function.

The patients in our study were largely either NYHA functional class II or III in symptoms. Baseline medical therapy was good, with 88% of the study population receiving either an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker and 69% receiving a beta-blocker at the time of enrollment. Mean baseline LDL and HDL cholesterol values were 3.2 ± 0.5 mmol/l and 1.1 ± 0.2 mmol/l, respectively, suggesting that the benefits of atorvastatin therapy in patients with nonischemic HF occur at cholesterol values that are below the current National Cholesterol Education Program III guidelines for the initiation of lipid-lowering therapy.

Currently, few data are available on the effects of statins in patients with nonischemic etiologies of HF. The major statin trials have generally excluded patients with HF, although subanalyses of data from several of these studies have found that statin therapy reduces the risk of developing ischemic HF in patients with prior CAD (18,19). Several non-randomized comparisons, such as the Prospective Randomized Amlodipine Survival Evaluation (PRAISE) and the Antiarrhythmics Versus Implantable Defibrillators (AVID) trials, demonstrated a mortality benefit in patients with ischemic and/or nonischemic HF who were treated with statins (20–24).

The data from our study also confirm the results of a randomized trial by Node et al. (25), in which 53 subjects

Table 4. Changes in Markers of Inflammation and Oxidation

	Baseline			Follow-Up		
	Placebo (n = 54)	Atorvastatin (n = 54)	p Value	Placebo (n = 43)	Atorvastatin (n = 46)	p Value
hsCRP (mg/dl)	1.9 ± 0.4	2.0 ± 0.4	NS	1.9 ± 0.3	1.7 ± 0.2	0.002
IL-6 (ng/dl)	17.1 ± 1.4	16.7 ± 1.3	NS	17.3 ± 1.4	13.3 ± 0.8	0.001
TNF-α RII (ng/dl)	33.4 ± 4.2	33.3 ± 3.2	NS	34.5 ± 3.0	24.3 ± 2.3	0.001
Erythrocyte superoxide dismutase (U/g Hb)	580 ± 60	550 ± 58	0.009	577 ± 38	649 ± 43	<0.0001

Values are mean ± SD. 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. hsCRP = high sensitivity C-reactive protein; IL-6 = interleukin-6; TNF-α RII = tumor necrosis factor-alpha receptor II.

JACC Vol. 47, No. 2, 2006
January 17, 2006:332–7

with nonischemic dilated cardiomyopathy were randomized to simvastatin 10 mg/day versus matching placebo for 14 weeks. The authors found that patients treated with simvastatin had a lower NYHA functional class compared with patients receiving placebo (2.04 ± 0.06 vs. 2.32 ± 0.05, $p < 0.01$), which corresponded to an improved LVEF in the simvastatin group (34 ± 3% to 41 ± 4%, $p < 0.05$) but not in the placebo group. In addition, plasma concentrations of TNF-α, IL-6, and B-type natriuretic peptide were significantly lower in the simvastatin group compared with the placebo group. Taken together, the results of these two randomized trials suggest that statins might have a role in improving symptoms and blunting the pro-inflammatory state in patients with nonischemic HF.

Inflammation in HF. Inflammatory mediators play an important role in the development and progression of HF. These mediators, or cytokines, are generally pharmacologically active proteins that are secreted by a variety of cell types in response to a variety of stimuli. Among the cytokines, TNF-α plays an important role in the progression of HF. Tumor necrosis factor-alpha has been implicated in the development of LV dysfunction, pathologic LV remodeling, endothelial dysfunction, increased cardiac myocyte apoptosis, and the development of anorexia and cachexia, among other effects (26,27) The reproducibility of plasma concentrations of soluble TNF receptors, however, are much higher than that of TNF-α itself and might explain why soluble TNF receptors such as TNF-α RII predict both short-term (28) and long-term (29) prognosis better than TNF-α in HF patients. Other cytokines, such as IL-6, are involved in myocyte hypertrophy, myocardial dysfunction, and muscle wasting. Higher levels of IL-6, as well as the inflammatory marker CRP, are associated with a poorer prognosis in HF patients (2–4).

Statins have important anti-inflammatory effects and downregulate CRP and inflammatory cytokines, which are activated in HF of any etiology (13) Our data showed a reduction in serum levels of hsCRP as well as TNF-α RII and IL-6 in patients with HF treated with statins. In addition, statin treatment was associated with an increase in E-SOD activity, suggesting that statins also have antioxidant activity in this patient population. Erythrocyte superoxide dismutase catalyzes the reaction of superoxide anions (O_2-) to hydrogen peroxide (H_2O_2), making it a central element in the maintenance of the vascular redox balance. As such, superoxide dismutase is indirectly involved in regulating levels of nitric oxide bioavailability. Other investigators have found that statin therapy lowers systemic levels of protein-bound nitrotyrosine (NO_2Tyr), a marker for oxidant stress mediated via pathways involving NO-derived oxidants (30,31).

In addition to their anti-inflammatory and antioxidant effects, there are a number of other potential mechanisms that might account for the beneficial effects of statin therapy observed in this study. These include the inhibition of atherosclerosis as well as the direct effects of lipid lowering and plaque stabilization, attenuation of pathological myocardial remodeling, improvement of endothelial dysfunction, and inhibition of neurohormonal activation (13,14,32,33).

Study limitations. Our study has several limitations that must be noted. As a pilot study that focused on mechanisms of action, the number of subjects was small (n = 108) and follow-up was limited to 12 months. Thus, the study was not powered to evaluate the effect of atorvastatin on clinical outcomes in this patient population. Similarly, data on the effects of atorvastatin in patients with both nonischemic HF and diabetes are not available, because many patients with known diabetes are already on a statin, which was an exclusion criterion in our study. Nevertheless, the results of this study suggest that therapy with atorvastatin might be of benefit in patients with nonischemic HF and systolic dysfunction. A large-scale randomized trial of statins in this patient population is warranted.

Conclusions. Currently, only 20% to 30% of patients with nonischemic HF receive statin therapy, compared with approximately 50% to 55% of those with an ischemic etiology of HF and 80% to 85% of patients with CAD (34,35). Our findings suggest that the use of atorvastatin in patients with nonischemic HF and systolic dysfunction is associated with an improvement in LV dysfunction, an attenuation of adverse LV remodeling, and an improvement in HF symptoms (NYHA functional class). The anti-inflammatory and antioxidative effects of statins might play a role in these findings, but their relationship to changes in clinical outcomes is not known.

Acknowledgment

The authors wish to thank Michelle Norman for her assistance with the preparation of the manuscript.

Reprint requests and correspondence to: Dr. Bobby V. Khan, Division of Cardiology, Department of Medicine, Emory University School of Medicine, 69 Jesse Hill Drive SE, C233, Atlanta, Georgia 30303. E-mail: bkhan@emory.edu.

REFERENCES

1. Deswal A, Petersen NJ, Feldman AM, et al. Cytokines and cytokine receptors in advanced heart failure: an analysis of the cytokine database from the VESnarinone Trial (VEST). Circulation 2001;103:2055–9.
2. Rauchhaus M, Doehner W, Francis DP, et al. Plasma cytokine parameters and mortality in patients with heart failure. Circulation 2000;102:3060–7.
3. Deswal A, Petersen NJ, Feldman AM, et al. Cytokines and cytokine receptors in advanced heart failure: an analysis of the cytokine database from the VESnarinone Trial (VEST). Circulation 2001;103:2055–9.
4. Kaneko K, Kanda T, Yamauchi Y, et al. C-reactive protein in dilated cardiomyopathy. Cardiology 1999;91:215–9.
5. Randomized trial of cholesterol lowering in 4,444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994;344:1383–9.
6. Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. N Engl J Med 1996;335:1001–9.
7. The Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. N Engl J Med 1998;339:1349–57.

8. The Heart Protection Study Collaborative Group. The MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomized placebo controlled trial. Lancet 2002;360:7–22.
9. Kjekshus JK, Pedersen TR, Olsson AG, et al. The effects of simvastatin on the incidence of heart failure in patients with coronary heart disease. J Card Fail 1997;3:249–54.
10. Horwich TB, MacLellan WR, Fonarow GC. Statin therapy is associated with improved survival in ischemic and nonischemic heart failure. J Am Coll Cardiol 2004;43:642–8.
11. Drexler H, Horning BD. Endothelial dysfunction in human disease. J Mol Cell Cardiol 1999;31:51–60.
12. Koh KK. Effects of statins on vascular wall: vasomotor function, inflammation, and plaque stability. Cardiovasc Res 2000;47:648–57.
13. Lefer DJ. Statins as potent anti-inflammatory drugs. Circulation 2002;106:2041–2.
14. Hayashidani S, Tsutsui H, Shiomi T, et al. Fluvastatin, a 3-hyroxy-3-methylglutaryl coenzyme A reductase inhibitor, attenuates left ventricular remodeling and failure after experimental myocardial infarction. Circulation 2002;105:868–73.
15. Devereaux RB, Reichek N. Echocardiographic determination of left ventricular mass in man. Circulation 1977;55:613–8.
16. Erel O, Kocyigit A, Bulut V, Gurel MS. Reactive nitrogen and oxygen intermediates in patients with cutaneous leishmaniasis. Mem Inst Oswaldo Cruz 1999;94:179–83.
17. Porsch-Oezcueruemez M, Kunz D, Kloer H, et al. Evaluation of serum levels of solubilized adhesion molecules and cytokine receptors in coronary heart disease. J Am Coll Cardiol 1999;34:1995–2001.
18. Kjekshus JK, Pedersen TR, Olsson AG, et al. The effects of simvastatin on the incidence of heart failure in patients with coronary heart disease. J Card Fail 1997;3:249–54.
19. Aronow WS, Ahn C. Frequency of congestive heart failure in older persons with prior myocardial infarction and serum low-density lipoprotein cholesterol ≥125 mg/dl treated with statins versus no lipid lowering drug. Am J Cardiol 2002;90:147–9.
20. Mozaffarian D, Nye R, Levy WC. Statin therapy is associated with lower mortality among patients with severe heart failure. Am J Cardiol 2004;93:1124–9.
21. Mitchell LB, Powell JL, Gillis AM, et al. Are lipid-lowering drugs also antiarrhythmic drugs? An analysis of the Antiarrhythmics Versus Implantable Defibrillators (AVID) trial. J Am Coll Cardiol 2003;42:81–7.
22. Hognestad A, Dickstein K, Myhre E, et al. Effect of combined statin and beta-blocker treatment on one-year morbidity and mortality after acute myocardial infarction associated with heart failure. Am J Cardiol 2004;93:603–6.
23. Horwich TB, MacLellan WR, Fonarow GC. Statin therapy is associated with improved survival in ischemic and nonischemic heart failure. J Am Coll Cardiol 2004;43:642–8.
24. Ray JG, Gong Y, Sykora K, Tu JV. Statin use and survival outcomes in elderly patients with heart failure. Arch Intern Med 2005;165:62–7.
25. Node K, Fujita M, Kitakaze M, et al. Short-term statin therapy improves cardiac function and symptoms in patients with idiopathic dilated cardiomyopathy. Circulation 2003;108:839–43.
26. Mann DL. Inflammatory mediators and the failing heart: past, present, and the foreseeable future. Circ Res 2002;91:988–98.
27. von Haehling S, Jankowska EA, Anker SD. Tumour necrosis factor-alpha and the failing heart: pathophysiology and therapeutic implications. Basic Res Cardiol 2004;99:18–28.
28. Anker SD, Ponikowski P, Varney S, et al. Wasting as independent risk factor for mortality in chronic heart failure. Lancet 1997;349:1050–3.
29. Anker SD, Rauchhaus M. Insights into the pathogenesis of chronic heart failure: immune activation and cachexia. Curr Opin Cardiol 1999;14:211–6.
30. Shishehbor MH, Aviles RJ, Brennan ML, et al. Association of nitrotyrosine levels with cardiovascular disease and modulation by statin therapy. JAMA 2003;289:1675–80.
31. Shishehbor MH, Brennan M, Aviles RJ, et al. Statins promote potent systemic antioxidant effects through specific inflammatory pathways. Circulation 2003;29:426–31.
32. Bauersachs J, Galuppo P, Fraccarollo D, et al. Improvement of left ventricular remodeling and function by hydroxymethylglutaryl coenzyme A reductase inhibition with cerivastatin in rats with heart failure. Circulation 2001;104:982–5.
33. Pliquett RU, Cornish KG, Peuler JD, et al. Simvastatin normalizes autonomic neural control in experimental heart failure. Circulation 2003;107:2493–8.
34. MERIT-HF Study Group. Effect of Metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet 1999;353:2001–7.
35. Dickstein K, Kjekshus JK. Comparison of baseline data, initial course, and management: Losartan versus Captopril following acute myocardial infarction (the OPTIMAAL trial). Am J Cardiol 2001;97:766–71.