Heart Failure

Statin Therapy May Be Associated With Lower Mortality in Patients With Diastolic Heart Failure
A Preliminary Report

Hidekatsu Fukuta, MD; David C. Sane, MD; Steffen Brucks, MD; William C. Little, MD

Background—No therapy has been shown to improve survival in heart failure (HF) with a normal ejection fraction (EF). There are plausible reasons to hypothesize that statins may be of benefit in HF with a normal EF.

Methods and Results—We evaluated 137 patients with HF and an EF ≥0.50. The effect of treatment received at study entry on survival was determined. During a follow-up of 21±12 months, 20 deaths were observed. Treatment with an ACE inhibitor or receptor blocker, β-blocker, or calcium blocker had no significant effect on survival. In contrast, treatment with a statin was associated with a substantial improvement in survival (relative risk of death [95% CI] 0.22 [0.07 to 0.64]; P=0.006). Patients receiving statins had higher baseline LDL cholesterol than those not receiving statins (153±45 versus 98±33 mg/dL, P<0.01). After statin therapy, LDL cholesterol levels fell to a similar level (101±32 mg/dL) as in patients not receiving statins (98±33 mg/dL). After adjustment for differences in baseline clinical variables between groups (hypertension, diabetes, coronary artery disease, and serum creatinine), statin therapy was associated with lower mortality (adjusted relative risk of death [95% CI] 0.20 [0.06 to 0.62]; P=0.005). Similarly, after propensity matching, statin therapy was associated with improved survival (log-rank 6.12; P=0.013) and a trend toward improved survival without cardiovascular hospitalization (log-rank 3.02; P=0.082).

Conclusions—Statin therapy may be associated with improved survival in patients with HF and a normal EF. (Circulation. 2005;112:357-363.)

Key Words: heart failure • diastole • statins • survival

A substantial proportion (40% or more) of patients with heart failure (HF) have a normal ejection fraction and have been labeled as having diastolic HF.1–4 The mortality and morbidity of these patients are high.5 However, there are few data available to guide the therapy of these patients, and no treatment has been shown to improve survival in diastolic HF.2–4

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Because β-blockers and ACE inhibitors improve survival in patients with HF and a reduced ejection fraction, they might also be of benefit in diastolic HF.1–3,6 Calcium blockers have also been suggested for therapy of patients with diastolic HF.1–3 Recent studies have reported that hydroxyymethylglutarate inhibitor (statin) therapy is associated with lower long-term mortality in patients with HF and a reduced ejection fraction.7,8 It is unknown, however, whether this finding also applies to patients with diastolic HF. Accordingly, we examined the association of therapy with statins and ACE inhibitors or angiotensin receptor blockers, β-blockers, and calcium blockers with 2-year survival in a well-characterized group of patients with diastolic HF.

Methods

Patients
We studied the patients who were evaluated for the presence of HF at Wake Forest University Baptist Medical Center between November 2001 and August 2002. HF was diagnosed as described previously.9 Patients were excluded from the present study if they had a left ventricular (LV) ejection fraction <0.50, hemodynamically significant valvular disease, prosthetic valve replacement, active myocardial ischemia, myocardial infarction, malignancy, or dialysis-dependent renal failure. The resulting study population consisted of 137 consecutive patients with HF and an ejection fraction ≥0.50. Other data and earlier follow-up of these patients have been reported previously.10,11

Data Collection
Medication status was determined on the basis of the initial management after the cardiac evaluation. All treatment decisions were made by the patients’ physicians. The Doppler echocardiographic examination was performed as described previously.12 Briefly, LV volumes were measured from the apical 4-chamber view by the area-length method and used to calculate the ejection fraction. Tissue Doppler imaging was obtained from the lateral mitral annulus and used to determine peak systolic annular velocity and peak early diastolic annular velocity (Ea peak). Peak early diastolic mitral inflow velocity (E peak), peak late diastolic mitral inflow velocity,
and E-wave deceleration time were used to classify the diastolic function as normal, mild (impaired relaxation pattern), or severe (pseudonormalized or restrictive pattern). This classification was performed by consensus of 2 observers who were blinded to baseline clinical features.

Follow-Up
Follow-up was determined in February 2005 with the medical record, the death registry, and direct telephone contact to determine the patients’ vital status and any cardiovascular hospitalizations. All hospitalizations were considered cardiovascular related unless due to a clear noncardiac cause (trauma, scheduled admission for a noncardiovascular procedure, or malignancy).

Statistical Analysis
We used the SAS program package (SAS Institute) for statistical analyses. Differences in quantitative and categorical data at baseline between groups were compared by the Student t test and the Fisher exact probability test. Differences in lipid levels before and after treatment with statins were compared by a paired t test. Because B-type natriuretic peptide (BNP) values were not normally distributed, a logarithmic transformation was used. Survival curves of patients grouped by medication status were calculated by the Kaplan-Meier method and compared with the log-rank test. Relative risk of clinical variables for death was determined with Cox proportional hazards regression analysis. To assess the independent association of treatment with mortality, the Cox hazards regression analysis was performed including the 4 baseline clinical variables that showed the most significant univariate predictive value for death and the 4 variables with the most significant difference between groups.

To further adjust for the nonrandomized assignment of patients to treatment, propensity analysis was performed. Propensity score was calculated as the likelihood of assignment to treatment with a statin by use of a logistic regression model that included the clinical variables that showed significant difference between groups and the 2 strongest univariate predictors for death. The patients in treatment group were matched with those in the no-treatment group with a propensity score within 2%.

Data are presented as mean±SD. Risk for death is presented as relative risk (RR) with 95% CI. P<0.05 was considered significant.

Results

Baseline Clinical Characteristics
Baseline clinical characteristics of all patients and patients grouped by statin therapy are shown in Table 1. Compared with patients not receiving statins, those receiving statins were more likely to be males with hypertension, diabetes, and coronary artery disease and to have higher serum creatinine values and lower BNP levels.

The indications for statin therapy included the following (values shown as number of patients [percent of patients]): (1) LDL cholesterol >100 mg/dL and the presence of coronary artery disease (12 [18%]), (2) LDL cholesterol >130 mg/dL and the presence of multiple risk factors (5 [7%]), (3) LDL cholesterol >160 mg/dL and the presence of 0 to 1 risk factors (4 [6%]), and (4) HDL cholesterol <40 mg/dL and triglyceride >150 mg/dL (2 [3%]).13 Forty-five patients who had been previously diagnosed with hyperlipidemia and had received statins before the study entry continued to receive statins. Prescribed statins included atorvastatin (46 [68%]; dose 22±18 mg/d), simvastatin (14 [21%]; 37±26 mg/d), pravastatin (7 [10%]; 30±11 mg/d), and fluvastatin (1 [1%]; 80 mg/d).

Lipid data before and after treatment with statins were available in 21 patients receiving statins, and baseline lipid data were available in 47 patients not receiving statins (Table 2). Treatment with statins significantly reduced total and LDL cholesterol levels (P<0.01). After treatment, total and LDL cholesterol levels of patients receiving statins were similar to those of patients not receiving statins. Of the 47 patients who did not receive statins, only 6 patients had LDL cholesterol >130 mg/dL.

Survival Analysis
Follow-up was available in 132 of the 137 patients. During a mean follow-up of 21±12 months, 20 deaths and 43 cardiovascular hospitalizations were observed. Survival curves of patients grouped by medication status are shown in Figure 1. Treatment with ACE inhibitors or angiotensin receptor blockers, β-blockers, or calcium blockers had no discernible effect on survival. In contrast, patients receiving statins had significantly higher survival rates than those not receiving statins (RR of death [95% CI] 0.22 [0.07 to 0.64], P=0.006).

Among clinical variables, significant predictors for all-cause death included age (RR [95% CI] 1.60 [1.10 to 2.34] per 10-year increment, P=0.016), New York Heart Association functional class >II (3.21 [1.16 to 8.85], P=0.024), serum hemoglobin (1.75 [1.12 to 2.74] per 1-SD decrement, P=0.014), BNP (2.40 [1.58 to 2.65] per 1-SD increment in logarithmic transformation, P<0.001), pseudonormal or restrictive mitral inflow pattern (2.94 [1.20 to 7.21], P=0.018), E peak (1.61 [1.09 to 2.38] per 1-SD increment, P=0.017), and ratio of E peak to E0 peak (E/E0; 1.67 [1.18 to 2.35] per 1-SD increment, P=0.004). After adjustment for the strongest univariate predictors (BNP, E/E0, serum hemoglobin, and age), the association of statin therapy with lower mortality remained significant (RR [95% CI] 0.32 [0.10 to 0.99], P=0.048; Table 3, model 1). Similarly, after adjustment for differences in baseline clinical variables (hypertension, diabetes, coronary artery disease, and serum creatinine), the association of statin therapy with lower mortality remained significant (RR [95% CI] 0.20 [0.06 to 0.62], P=0.005; Table 3, model 2). Similar adjustments did not alter the lack of effect of treatment with ACE inhibitors or angiotensin receptor blockers, β-blockers, or calcium blockers on survival (Table 3).

Hospitalization-free survival curves of patients grouped by medication status are shown in Figure 2. Treatment with statins, ACE inhibitors or angiotensin receptor blockers, β-blockers, or calcium blockers had no significant effect on survival without cardiovascular hospitalization.

The propensity analysis produced 42 pairs of patients (receiving and not receiving statins) with matched propensity scores. These patients were similar to the original 137 patients in clinical characteristics and medication status. In the propensity-matched patients, 12 deaths and 26 cardiovascular hospitalizations were observed during a follow-up of 21±12 months. In these matched patients, statin therapy was significantly associated with improved survival (log-rank 6.12, P=0.013) and a trend toward improved survival without cardiovascular hospitalization (log-rank 3.02, P=0.082; Figure 3).
Major Finding
HF with a normal ejection fraction (diastolic HF) is common and is associated with a substantial mortality.\textsuperscript{1–5} However, no therapy has been demonstrated to improve mortality. Accordingly, we investigated the effect of treatment with a statin and the use of an ACE inhibitor or angiotensin receptor blocker, β-blocker, or calcium blocker on 2-year survival in 137 patients with diastolic HF. Treatment with an ACE inhibitor or angiotensin receptor blocker, β-blocker, or calcium blocker had no significant effect on survival. In contrast, treatment with a statin was associated with a substantial

Discussion

TABLE 1. Baseline Clinical Characteristics of All Patients and Patients Grouped by Statin Therapy

<table>
<thead>
<tr>
<th></th>
<th>All Patients (n=137)</th>
<th>No Statin (n=69)</th>
<th>Statin Use (n=68)</th>
<th>P, Statin vs No Statin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>65±14</td>
<td>65±16</td>
<td>65±12</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Female gender</td>
<td>78 (57)</td>
<td>45 (65)</td>
<td>33 (49)</td>
<td>0.049</td>
</tr>
<tr>
<td>Hypertension</td>
<td>109 (80)</td>
<td>50 (72)</td>
<td>59 (87)</td>
<td>0.038</td>
</tr>
<tr>
<td>Diabetics</td>
<td>31 (23)</td>
<td>8 (12)</td>
<td>23 (34)</td>
<td>0.002</td>
</tr>
<tr>
<td>New York Heart Association functional class &gt;II</td>
<td>14 (10)</td>
<td>8 (12)</td>
<td>6 (9)</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>80 (58)</td>
<td>34 (49)</td>
<td>46 (68)</td>
<td>0.029</td>
</tr>
<tr>
<td>Left bundle-branch block</td>
<td>6 (4)</td>
<td>1 (1)</td>
<td>5 (7)</td>
<td>0.088</td>
</tr>
<tr>
<td>BNP, pg/mL</td>
<td>233±295</td>
<td>286±353</td>
<td>180±211</td>
<td>0.034</td>
</tr>
<tr>
<td>Serum creatinine, mg/dL</td>
<td>1.4±0.6</td>
<td>1.3±0.4</td>
<td>1.5±0.6</td>
<td>0.029</td>
</tr>
<tr>
<td>Serum hemoglobin, g/dL</td>
<td>12.4±2.0</td>
<td>12.2±1.9</td>
<td>12.7±2.0</td>
<td>&gt;0.1</td>
</tr>
</tbody>
</table>

Medications
ACEI or ARB | 75 (55) | 33 (48) | 42 (62) | >0.1  |
β-Blocker     | 68 (50) | 29 (42) | 39 (57) | 0.073 |
Calcium blocker | 37 (27) | 19 (28) | 26 (39) | >0.1  |
Diuretics     | 69 (50) | 30 (43) | 39 (57) | >0.1  |

Doppler echocardiographic indexes
Ejection fraction, % | 62±7 | 61±7 | 62±7 | >0.1  |
LV mass index, g/m² | 108±44 | 105±45 | 110±42 | >0.1  |
Pseudonormal or restrictive mitral inflow pattern
Left atrial dimension >45 mm | 29 (21) | 13 (19) | 16 (24) | >0.1  |
E peak, cm/s | 75±27 | 78±28 | 73±26 | >0.1  |
A peak, cm/s | 78±26 | 80±29 | 77±23 | >0.1  |
E-wave deceleration time, ms | 231±55 | 228±59 | 234±51 | >0.1  |
Peak systolic mitral annular velocity, cm/s | 6.8±1.8 | 6.8±1.7 | 6.9±1.8 | >0.1  |
E\textsubscript{a} peak, cm/s | 7.4±2.6 | 7.7±3.0 | 7.2±2.2 | >0.1  |
A\textsubscript{a} peak, cm/s | 9.3±3.2 | 9.1±3.0 | 9.5±3.2 | >0.1  |
E/Em | 11±6 | 11±6 | 11±6 | >0.1  |

ACEI indicates ACE inhibitor; ARB, angiotensin receptor blocker; A peak, late diastolic mitral inflow velocity; and A\textsubscript{a} peak, late diastolic mitral annular velocity.
Values are mean±SD or n (within-group percentage).

TABLE 2. Lipid Profile

<table>
<thead>
<tr>
<th></th>
<th>Pretreatment</th>
<th>Posttreatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total Cholesterol</td>
<td>TG</td>
</tr>
<tr>
<td>Statin, yes (n=21)</td>
<td>243±89</td>
<td>213±201</td>
</tr>
<tr>
<td>Statin, no (n=47)</td>
<td>178±40</td>
<td>149±90</td>
</tr>
<tr>
<td>P, Statin yes vs no</td>
<td>&lt;0.01</td>
<td>&gt;0.1</td>
</tr>
</tbody>
</table>

TG indicates triglyceride.
Values are mean±SD, mg/dL.
*P<0.01 vs pretreatment.
improvement in survival. The association was independent of other univariate predictors for death and differences in baseline clinical features. After propensity matching, statin therapy was associated with improved survival and a trend toward improved survival without cardiovascular hospitalization. Thus, the present study suggests that statin therapy may be associated with lower mortality in patients with diastolic HF.

TABLE 3. Univariate and Adjusted RR of Medications for All-Cause Death by Cox Proportional Hazards Regression Analysis

<table>
<thead>
<tr>
<th>Medication</th>
<th>Unadjusted RR (95% CI)</th>
<th>Adjusted* (Model 1) RR (95% CI)</th>
<th>Adjusted† (Model 2) RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statin</td>
<td>0.22 (0.07–0.64)‡</td>
<td>0.32 (0.10–0.99)§</td>
<td>0.20 (0.06–0.62)‡</td>
</tr>
<tr>
<td>ACE-I or ARB</td>
<td>0.92 (0.38–2.22)</td>
<td>0.66 (0.27–1.65)</td>
<td>0.69 (0.24–2.05)</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>0.76 (0.32–1.83)</td>
<td>0.78 (0.32–1.93)</td>
<td>0.76 (0.31–1.87)</td>
</tr>
<tr>
<td>Calcium blocker</td>
<td>1.91 (0.79–4.62)</td>
<td>1.08 (0.39–3.01)</td>
<td>1.86 (0.71–4.93)</td>
</tr>
</tbody>
</table>

ACE-I indicates ACE inhibitor; ARB, angiotensin receptor blocker.
Data are represented as RR of death (95% CI).
*Adjusted for other univariate predictors including age, serum hemoglobin, BNP, and ratio of mitral to annular E waves.
†Adjusted for baseline clinical variables that showed significant difference between patients who did and did not receive each medication.
‡P<0.01; §P<0.05.
Comparison With Earlier Studies

The large randomized trials of statins did not include patients with HF. However, 3 recent observational studies have reported a significant association of statin therapy with lower mortality in patients with HF and a reduced ejection fraction. Specifically, Horwich et al reported that statin therapy was associated with lower mortality or need for urgent transplantation in patients with HF and an ejection fraction <35%.
fraction ≤0.40 during 1-year follow-up. Similarly, Mozaffarian et al⁸ reported that statin therapy was associated with lower mortality in patients with HF and an ejection fraction <0.30 during a mean follow-up of 1.3 years. Finally, Ray et al¹⁹ reported that statin therapy was associated with lower mortality but not reduced risk of nonfatal myocardial infarction or stroke in elderly patients with HF during 7-year follow-up. The present study demonstrates the reduced mortality with statins previously reported in HF with a reduced ejection fraction may also be present in diastolic HF.

Although statin therapy was clearly associated with reduced mortality, we did not observe a clear reduction in cardiovascular hospitalizations. This may be due to the limited power of our study or to the observation that the patients receiving statins were more likely to have coronary artery disease, diabetes, and hypertension and thus may have had a higher risk for events that require hospitalization. The latter possibility is supported by the finding of the association of statins with a stronger trend toward reduced hospitalization in the propensity-matched cohort.

Possible Mechanisms
Patients with diastolic HF are typically elderly; thus, coronary artery disease, whether recognized or unrecognized, is quite common. The improved survival we observed might be due to the known beneficial effects of statins in patients with coronary artery disease.¹⁴–¹⁸ Furthermore, both diabetes and impaired renal function are common in patients with diastolic HF. Because statins may improve outcome in these conditions,²⁰,²¹ this might explain some of the benefit we observed with statins in diastolic HF.

As expected, the patients who were started on statins had higher baseline total and LDL cholesterol than the patients who did not receive statins. Only a few of the patients who did not receive statins had a clear indication for these agents. After therapy, patients who did and did not receive statins had nearly identical total and LDL cholesterol levels (Table 2). Thus, it appears that the possible beneficial effect of statins in diastolic HF may be due to effects other than reduction in LDL cholesterol. Similarly, other studies have reported that the survival benefit of statins is independent of baseline cholesterol level in patients with HF and a reduced ejection fraction and that the benefit is observed even in the subset of patients with lower cholesterol levels.⁷,⁸

Statins have a variety of potential benefits in addition to lipid reduction that may more directly impact diastolic HF. First, statins may exert beneficial effects on LV hypertrophy and fibrosis in experimental animal models and patients.²²–²⁴ Because LV hypertrophy and fibrosis may contribute to diastolic HF, the beneficial effect of statins on LV hypertrophy and fibrosis may directly impact diastolic HF.²–⁴

Second, a mild antihypertensive effect of statins has been observed in hypertensive patients.²⁵–²⁷ Such an antihypertensive effect may contribute to reducing LV mass and improving diastolic function.

Third, statins may increase arterial distensibility.²⁷,²⁸ Potential mechanisms by which statins increase arterial distensibility include the beneficial effect on endothelial function²⁹,³⁰ and regression of aortic atherosclerosis.³¹,³² A statin-induced increase in arterial distensibility may decrease LV afterload and increase coronary perfusion, thereby improving LV relaxation and diastolic function.³³,³⁴

A fourth beneficial effect of statins that could impact diastolic HF may be a protective effect on LV remodeling. Animal studies have reported that statins prevent LV dilation after myocardial infarction.³⁵,³⁶

Other potential beneficial actions of statins that are not limited to diastolic HF include antiinflammatory and antioxidant effects.²⁹ Elevated inflammatory markers are associated with worse symptoms and poor survival in HF.³⁷,³⁸ Myocardial oxidative stress due to increased production of reactive oxygen free radicals also plays an important role in the development of HF.³⁹

Study Limitations
There are several limitations of this study. Because of these limitations, the results of the present study must be considered to be preliminary. Most importantly, statin therapy was not randomly assigned. Despite adjustment for differences in baseline clinical features and other predictors for death and the use of propensity analysis, the benefits of statin therapy might reflect other unmeasured factors that are related to improved survival.

A second limitation is that the study population here consisted of only 137 patients, and the number of events was limited. Thus, the present study is not adequately powered to detect the potential mortality benefits of treatments or the effects on hospitalization. It is important to recognize that the CIs for the relative risk of death associated with treatment with ACE inhibitors or angiotensin receptor blockers, β-blockers, or calcium blockers are wide and include the possibility of substantial benefit (Table 3).

A third limitation is that the lipid profile at baseline or during follow-up was not available for all patients. Furthermore, we do not have complete data on compliance with statins or subsequent initiation of statins. Other studies have reported that low serum cholesterol level is associated with higher mortality in patients with HF and a reduced ejection fraction.⁴⁰,⁴¹ Because of limited power, we could not determine whether the benefit of statins was independent of baseline cholesterol level or the change in cholesterol level.

Clinical Implications
The present study suggests that statins may be a new therapeutic option to improve survival in diastolic HF. Statin therapy in HF is being evaluated in several randomized controlled trials.⁴² However, these trials are designed to evaluate the effect of statin therapy in patients with HF and a reduced ejection fraction. The present study emphasizes the need for a randomized study of the effect of statins in diastolic HF.

Acknowledgment
We gratefully acknowledge the secretarial assistance of Amanda Burnette.

Disclosure
Research support for other studies has been received from manufacturers of statins: Pfizer, Inc (Dr Sane) and Merck Pharmaceuticals (Dr Little). Dr Little has received a speaking honorarium from AstraZeneca.
References

1. Zile MR, Brutsaert DL. New concepts in diastolic dysfunction and dia-

2. Zile MR, Brutsaert DL. New concepts in diastolic dysfunction and dia-


20. O’Rourke MF. Diastolic heart failure, diastolic left ventricular dys-


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Circulation. 2005;112:357-363; originally published online July 11, 2005;
doi: 10.1161/CIRCULATIONAHA.104.519876

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