Statin Therapy in Patients with Diastolic Heart Failure

Address for correspondence:
Ernst R. Schwarz, MD, PhD
Cedars-Sinai Medical Center
8700 Beverly Blvd, Suite 6215
Los Angeles, CA, 90048
Ernst.schwarz@cshs.org

Faramarz Tehrani, MD; Ryan Morrissey, MD; Anita Phan, MD; Christopher Chien MD; Ernst R. Schwarz, MD, PhD

Cedars-Sinai Heart Institute, Cedars-Sinai Medical Center, Los Angeles, California

ABSTRACT

Background: There is controversy regarding the potential effects of statin therapy on mortality in patients with heart failure. The present study analyzed the possible effects of statin therapy on morbidity and mortality in patients with diastolic heart failure over long-term follow-up.

Hypothesis: To evaluate potential effect of statin therapy on hospitalization rate and mortality in patients with diastolic heart failure.

Methods: Patients with preserved left ventricular ejection fraction (≥50%), hospitalized for clinical symptoms of heart failure were evaluated. Patients on statin therapy started at or prior to their first heart failure admission represented group 1 and patients without statin therapy represented group 2. The effects of statins on hospitalization rates and mortality were assessed during a 5 year follow-up.

Results: A total of 270 patients (group 1 n = 81; group 2 n = 189) were followed over 5 years. Patients on statins demonstrated improved survival compared to patients without statin therapy (hazard ratio [HR] = 0.65, 95% confidence interval [CI]: 0.45–0.95, $P = .029$). The survival benefit was maintained after adjusting for differences in baseline characteristics, comorbidities, and other medications. There was no significant difference in the mean cardiovascular hospitalization rate (3.0 ± 3.2 vs 3.8 ± 4.7, $P = .23$) and in overall hospitalization rate (7.1 ± 6.3 vs 7.8 ± 7.7, $P = .52$) between groups 1 and 2, respectively.

Conclusion: Statin therapy appears to be associated with improved survival in patients with diastolic heart failure.

Introduction

Diastolic heart failure is a prevalent form of heart disease, yet to date no form of medical therapy has shown clear mortality benefit in randomized control trials. Recent data have suggested potential benefit of statin therapy in heart failure patients with preserved systolic function. Current study attempted to further evaluate potential effect of statin therapy on hospitalization rate and long term mortality in diastolic heart failure patients.

Methods

The study was approved by the institutional review board of Cedars-Sinai Medical Center. Admission records over a 3 year period were reviewed for patients admitted with the primary diagnosis of heart failure. Inclusion criteria were echocardiographic evidence of an ejection fraction (EF) ≥50% on admission and a clinical diagnosis of heart failure. Patients were excluded if there was severe valvular dysfunction, history of valve replacement, primary pulmonary hypertension, acute pulmonary infection or diagnosed pulmonary embolism, severe chronic obstructive pulmonary disease, acute myocardial infarction or unstable angina within 6 months, end-stage renal disease requiring hemodialysis, cirrhosis, history of heart transplantation, or active malignancy.

Medication status was based on medication lists at discharge from the first admission for heart failure. Patients with documented obesity (body mass index >30) were excluded from the study. The presence of hypertension, diabetes mellitus, and coronary artery disease were recorded for each patient. Hemoglobin, creatinine, and lipid data were recorded from the first admission and at 5 year follow-up. Echocardiographic data including EF, left ventricular function, and valvular function were recorded at admission. The primary end point was mortality and hospitalizations during 5 year follow-up. Mortality data was obtained through clinical charts and the social security death registry.

For baseline data, categorical variables were compared between groups using the Fisher exact test. Between-group comparisons of numerical variables were assessed using the independent samples *t* test or the Wilcoxon rank sum test. Within group comparisons of numerical variables across times were made using the paired *t* test or the Wilcoxon signed rank test. Factors associated with the risk of death were assessed by Cox proportional hazard models. Risk ratios were estimated using Cox proportional hazards models. Survival estimates were calculated using the Kaplan-Meier method. The log rank test was used to compare survival across the 2 groups. Statistical calculations were performed with SAS version 9.1 (SAS Institute, Cary,

Received: November 15, 2008
Accepted: December 18, 2008

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20615 © 2010 Wiley Periodicals, Inc.

NC). All data are presented as mean ± standard deviation (SD). Risk for death is presented as a relative risk (RR) with a 95% confidence interval (CI). A P value $<.05$ was considered statistically significant.

Results

Of the 3487 patients that were screened, 270 patients fulfilled the inclusion and exclusion criteria. Patients on statins at baseline were more likely to be slightly younger and more likely to have hypertension, coronary artery disease, and a worse baseline renal function (Table 1). Patients on statins had a significantly higher baseline creatinine in comparison to patients not on statins, while baseline lipid profiles were similar between the 2 groups. Patients in group 1 had a higher rate of angiotensin-converting enzyme inhibitor/angiotensin receptor blockers (ACEI/ARB) and calcium blocker therapy; there were no other significant differences in heart failure medications at baseline.

Comparisons were made regarding changes in lipid levels in a subgroup of patients with lipid profile data available on 5 year follow-up (Table 2). Patients without statins did not show significant changes in lipid levels at follow-up. Within the statin group a significant decrease in low-density lipoprotein (LDL) and total cholesterol was observed, while triglycerides and high-density lipoprotein (HDL) levels were not significantly different.

In a univariate Cox analysis lower age, female gender, hypertension, increasing hemoglobin concentration, and statin therapy were associated with significantly reduced mortality (Table 3). Statins therapy did not have a significant effect on cardiac or overall rehospitalization rates (Table 4). Patients in the statin therapy group had a lower mortality over the 5 year follow-up (Figure). Statin therapy appears to

Table 1. Comparison of Baseline Characteristics of Patients on Statin Therapy (Group 1) vs Patients Without Statins (Group 2)

Characteristic	All Patients (n = 270)	Statin (Group 1, n = 81)	No Statins (Group 2 n = 189)	P Value
Age (years)	78.96 ± 10.77	76 ± 10	80 ± 11	.004
Female (%)	177 (65.6)	51 (63.0)	126 (66.7)	.58
Hypertension (%)	216 (80.0)	74 (91.4)	142 (75.1)	.003
Diabetes mellitus (%)	98 (36.3)	31 (38.3)	67 (35.5)	.68
Coronary artery disease (%)	120 (44.4)	51 (63.0)	69 (36.5)	<.0001
Hemoglobin, g/dL	12.09 ± 1.71	11.9 ± 1.7	12.2 ± 1.7	.24
Creatinine, mg/dL	1.26 ± 0.72	1.5 ± 1.0	1.2 ± 0.5	.0008
LDL (n = 127)	98.4 ± 38.4	95.8 ± 39.1	100.4 ± 38.0	.43
HDL (n = 128)	49.6 ± 17.5	47.8 ± 14.2	51.0 ± 19.5	.29
TRIG (n = 130)	134.8 ± 90.4	154.7 ± 84.7	120.6 ± 92.1	.003
Total cholesterol (n = 131)	175.4 ± 51.6	174.4 ± 46.4	176.1 ± 55.3	.85
Ejection fraction (%)	62 ± 9	61 ± 10	61 ± 9	.87
Medications				
ACEI/ARBs (%)	148 (54.8)	52 (64.2)	96 (50.8)	.046
β-Blockers (%)	97 (35.9)	35 (43.2)	62 (32.8)	.128
Calcium channel blockers (%)	87 (32.2)	35 (43.2)	52 (27.5)	.015
Diuretics (%)	194 (71.9)	60 (74.0)	134 (70.9)	.41/.63
Hydralazine (%)	1 (0.4)	0 (0.0)	1 (0.5)	<.9
Digoxin (%)	76 (28.2)	23 (28.4)	53 (28.)	<.9
α-Blockers (%)	31 (11.5)	9 (11.1)	22 (11.62)	<.9

LDL = Low-density-lipoprotein; HDL = High-density-lipoprotein; TRIG = Triglycerides; ACEI/ARBs = Angiotensin-converting enzyme inhibitor/angiotensin receptor blockers.

DOI:10.1002/clc.20615 © 2010 Wiley Periodicals, Inc.

Table 2. Lipid Data at Baseline and Observed Changes Over 5 Years for Patients on Statin Therapy (Group 1) vs Those Patients Without Statins (Group 2)

Measure	Patients on Statins (Group 1)				Patients Without Statins (Group 2)				
	Pre	Post	Change	P^a	Pre	Post	Change	P^a	P^b
LDL-C	102.3 ± 37.8	79.7 ± 29.0	−22.7 ± 41.8	.016	99.5 ± 34.2	91.9 ± 27.7	−7.7 ± 32.0	.253	.173
HDL-C	48.5 ± 14.8	48.2 ± 13.1	−0.3 ± 15.6	.92	59.8 ± 21.7	58.3 ± 18.4	−1.6 ± 12.9	.553	.768
Triglycerides	145.5 ± 77.6	158.0 ± 75.9	12.5 ± 69.2	.395	97.7 ± 61.0	105.8 ± 49.7	8.1 ± 51.5	.450	.804
Total Cholesterol	179.4 ± 43.1	159.4 ± 34.3	−20.0 ± 40.7	.028	179.0 ± 42.9	171.3 ± 35.1	−7.8 ± 31.9	.250	.260

LDL-C = Low-density-lipoprotein cholesterol; HDL-C = High-density-lipoprotein cholesterol.
[a] Changes within group.
[b] Changes between groups.

Table 3. Adjusted Relative Risk of Mortality by Cox Proportional Hazards Regression Analysis of Clinical Characteristics and Medications

	RR	95% CI	*P* Value
Clinical Variables			
Age	1.056	1.036–1.076	<.0001
Male Gender	1.579	1.117–2.233	.0097
Diabetes mellitus	1.29	0.905–1.839	.1589
Hemoglobin (Hg ≥10.0 g/dL)	0.86	0.860–0.954	.0043
Serum creatinine (Cr ≥1.5 mg/dL)	1.066	0.705–1.613	.762
Statin therapy	0.646	0.438–0.953	.0277
Medications			
ACEI/ARBs	0.841	0.606–1.166	.2981
β-Blockers	0.802	0.566–1.137	.2153
Calcium channel blockers	0.977	0.685–1.393	.8972
Diuretics	0.984	0.696–1.391	.9265
Statins	0.639	0.436–0.935	.0212

ACEI/ARBs = Angiotensin-converting enzyme inhibitor/angiotensin receptor blockers.

have a beneficial effect on reducing mortality observed on a multivariate model adjusting for clinical factors and other medications (Table 5).

Discussion

Clinical trials regarding the effects of statin therapy on outcome in patients with heart failure have had varied findings. Several studies have shown beneficial effects of statin therapy in heart failure such as improved cardiac function in patients with mild to moderate chronic heart failure or decreased hospitalization rates for heart failure.[1,2] There

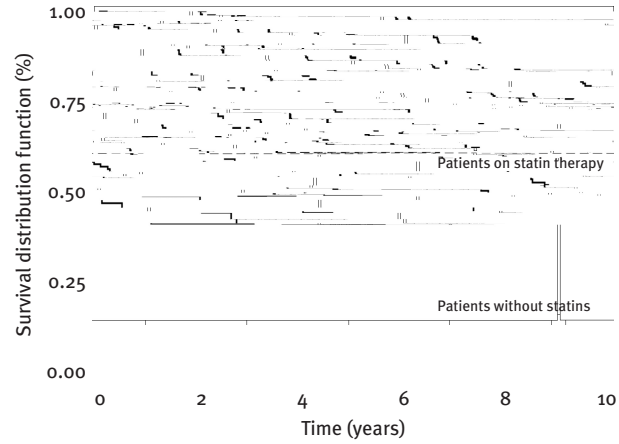

Figure 1. Kaplan-Meier survival curve throughout the entire follow-up period comparing patients on statin therapy (group 1) vs patients without statins (group 2). (RR = 0.646 [0.438–0.953], *P* = .0277).

has also been some evidence that the benefit of statin therapy extends to patients with nonischemic cardiomyopathy. Domanski et al analyzed patients with systolic heart failure enrolled in the β-Blocker Evaluation of Survival Trial (BEST), reporting a survival benefit for statin therapy in patients with moderate to severe heart failure secondary to nonischemic dilated cardiomyopathy.[3] However, results from the randomized controlled rosuvastatin multinational trial in heart failure (CORONA) did not show any improvement in cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke over a median of 32 months in patients over the age of 60 years with systolic heart failure on rosuvastatin therapy, although there were fewer cardiovascular hospitalizations for patients on statin therapy.[4]

Current data on statin therapy in diastolic heart failure has also provided mixed results. Fukuta et al were the first to assess the potential effects, reporting that statins were associated with reduced mortality and a trend towards fewer hospitalizations in patients with pure diastolic heart

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20615 © 2010 Wiley Periodicals, Inc.

Table 4. Total and Cardiac Related Hospitalizations Over a 5 Year Follow-up Period for Patients on Statin Therapy (Group 1) vs Patients Without Statins (Group 2)

5-Year Hospitalization Rate	Total (n = 270)		Statin (Group 1, n = 81)		No Statins (Group 2, n = 189)		*P* Value: Group 1 vs Group 2
	Mean ± SD	Median	Mean ± SD	Median	Mean ± SD	Median	
All-cause	7.3 ± 6.7	5	7.8 ± 7.7	5	7.1 ± 6.3	5	.52
Cardiac related	3.3 ± 3.7	2	3.8 ± 4.7	3	3.0 ± 3.2	2	.23

Table 5. Comparison of Relative Risk of Mortality Associated With Statin Therapy Among Several Multivariate Models

	Model 1	Model 2	Model 3
Statins	0.639 (0.436–0.935), $P = 0.0212$	0.639 (0.435–0.938), $P = 0.0224$	0.646 (0.438–0.953), $P = 0.0277$

Abbreviations: Model 1 = adjusted for other medications; Model 2 = adjusted for age, hemoglobin concentration, and gender; Model 3 = adjusted for age, gender, diabetes, hemoglobin concentration, and serum creatinine concentration.

failure.[5] Shah et al demonstrated improved survival with statin therapy in patients ≥65 years of age with heart failure and preserved EF.[6] A recent prospective trial did not show a difference in the survival benefit of daily rosuvastatin therapy in comparison to placebo in patients with chronic heart failure, including in those patients with preserved systolic function.[7]

The present study appears to show that statin therapy maybe associated with a protective effect on survival in patients with diastolic heart failure, with the survival benefits being noticeable throughout a 5 year follow-up period. These effects are maintained after statistical adjustments for differences in baseline characteristics, comorbidities, and other medications. There are multiple potential mechanisms that can possibly be attributed to these observed beneficial effects.

Statin therapy has been shown to decrease mortality in both patients with known coronary artery disease, as well as those with a high risk for coronary artery disease primarily due to lipid lowering effects.[8,9] In the present cohort of patients, the prevalence of coexistent coronary artery disease was noticeable in both groups. It is certainly possible that the benefit of lipid lowering on atherosclerotic heart disease contributed to the observed mortality benefit. Still, the degree of survival benefit observed is out of proportion to the effect that would be anticipated by the degree of LDL lowering. The PROVE IT-TIMI 22 trial, which compared moderate vs intensive lipid lowering in the highest risk patients with acute coronary syndrome showed only a 3.9% absolute reduction in mortality (16% hazard ratio [HR]) in patients treated with intensive statin therapy (to a median LDL = 62 mg/dL) compared to moderate statin therapy (median LDL = 95 mg/dL).[10] Meanwhile, the present study demonstrated a decrease in mortality of 36.1% in the statin group compared to the non-statin group, although the difference in LDL was not as robust. Furthermore, a mortality benefit due exclusively to lipid lowering effects on atherosclerotic heart disease would be extremely unlikely to be statistically significant in the present study due to the relatively lower sample size and power. Although the known benefit of statins on coronary artery disease may be a contributory factor, it is unlikely to be the sole mechanism responsible for the mortality benefit observed in this study.

Statin therapy has also been shown to be beneficial in patients with renal disease. A meta-analysis of 50 randomized trials assessing effects of statin therapy in patients with chronic kidney disease demonstrated statin therapy to be associated with reduction in the risk of cardiovascular events and cardiovascular mortality, although all-cause mortality did not appear to be affected.[11] Statin therapy in patients with renal insufficiency has been associated with a reduction in cardiovascular morbidity and mortality.[12]

The pleiotropic effects of statins emphasize possible beneficial effects of statins independent of its LDL lowering abilities,[13] and may provide insight into other potential mechanisms involved in improved survival of diastolic heart failure patients. Such pleiotropic effects include improved microvascular circulation and endothelial function through upregulated nitric oxide synthase, attenuation of cardiac remodeling by reducing ventricular hypertrophy secondary to hypertension and angiotensin II, as well as the down-regulation of angiotensin I receptors and decreased secretion of matrix metalloproteinases.[14–18]

Limitations of the present study include a relatively small sample size and an inability to ascertain the thought process behind the decision for statin therapy in the observed subgroup of patients. The accuracy of data and diagnosis were mainly based on information acquired from medical records. Different statins or different dose regimens of statins were not distinguished within the study population. Compliance with medications could not be completely assessed since data relied on documentation in medical records. Although

statin effects were adjusted for all covariables, given the observational nature of the study additional uncounted factors may have contributed to the observed survival benefit.

Conclusion

Statin therapy appears to have the potential to be associated with improved survival in patients with diastolic heart failure. Given the lack of proven effective therapy in this patient population, further investigation of possible beneficial medical therapy is warranted.

Acknowledgments

The authors did not have a source of financial support or funding to report in regards to this project.

References

1. Yamada T, Node K, Mine T, et al. Long-term effect of atorvastatin on neurohumoral activation and cardiac function in patients with chronic heart failure: a prospective randomized controlled study. *Am Heart J*. 2007;153:1055e1–8.
2. Khush KK, Waters DD, Bittner V, et al. Effect of high-dose atorvastatin on hospitalizations for heart failure: subgroup analysis of the Treating to New Targets (TNT) study. *Circulation*. 2007;115:576–583.
3. Domanski M, Coady S, Fleg J, Tian X, Sachdev V. Effect of statin therapy on survival in patients with nonischemic dilated cardiomyopathy (from the β-Blocker Evaluation of Survival Trail [BEST]). *Am J Cardiol*. 2007;99:1448–1450.
4. Kjekshus J, Apetrei E, Barrios V, et al. Rosuvastatin in older patients with systolic heart failure. *N Engl J Med*. 2007;357: 2248–2261.
5. Fukuta H, Sane DC, Brucks S, Little WC. Statin therapy may be associated with lower mortality in patients with diastolic heart failure: a preliminary report. *Circulation*. 2005;112:357–363.
6. Shah R, Wang Y, Foody JM. Effects of statins, angiotensin-converting enzyme inhibitors, and β-blockers on survival in patients ≥65 years of age with heart failure and preserved left ventricular systolic function. *Am J Cardiol*. 2008;2:217–222.
7. GISSI-HF Investigators. Effect of rosuvastatin in patients with chronic heart failure (the GISSI-HF trial): a randomised, double blind, placebo-controlled trial. *Lancet*. 2008;Aug 29. [Epub ahead of print].
8. Randomized trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet*. 1994;344:1383–1389.
9. Collins R, Armitage J, Parish S, Sleight P, Peto R; on behalf of the MRC/BHF Heart Protection Study Collaborative Group. MRC/BHF heart protection study of cholesterol lowering with simvastatin in 20 536 high-risk individuals: a randomised placebo-controlled trial. *Lancet*. 2002;360:7–22.
10. Cannon CP, Braunwald E, McCade CH, et al. Intensive versus moderate lipid-lowering with statins after acute coronary syndrome. *N Engl J Med*. 2004;350:1495–1504.
11. Strippoli GFM, Navaneethan SD, Johnson DW, et al. Effects of statins in patients with chronic kidney disease: meta-analysis and meta-regression of randomized controlled trials. *BMJ*. 2008; 336:645–651.
12. Tonelli M, Moye L, Sacks FM, Kiberd B, Curhan G. Pravastatin for secondary prevention of cardiovascular events in persons with mild chronic renal insufficiency. *Ann Intern Med*. 2003;138: 98–104.
13. Wisniacki N, Taylor W, Lye M, Wilding JP. Insulin resistance and inflammatory activation in older patients with systolic and diastolic heart failure. *Heart*. 2005;91(1):32–37.
14. Mason JM, Freemantle N. Coronary events with lipid-lowering therapy: the AFCAPS/TexCAPS trial. Air Force/Texas Coronary Atherosclerosis Prevention Study. *JAMA*. 199;281:415–419.
15. Okura H, Asawa K, Kubo T, et al. Impact of statin therapy on systemic inflammation, left ventricular systolic and diastolic function and prognosis in low risk ischemic heart disease patients without history of congestive heart failure. *Intern Med*. 2007;46: 1337–1343.
16. Almuti K, Rimawi R, Spevack D, Ostfeld RJ. Effects of statins beyond lipid lowering: potential for clinical benefits. *Int J Cardiol*. 2006;109:7–15.
17. Xu Z, Okamoto H, Akino M, Onozuka H, Matsui Y, Tsutsui H. Pravastatin attenuates left ventricular remodeling and diastolic dysfunction in angiotensin II-induced hypertensive mice. *J Cardiovasc Pharmacol*. 2008;51:62–70.
18. Laufs U, La Fata V, Plutzky J, et al. Upregulation of endothelial nitric oxide synthase by HMG CoA reductase inhibitors. *Circulation*. 1998;97:1129–1135.

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20615

© 2010 Wiley Periodicals, Inc.