

# Statin Therapy and Clinical Outcomes in Heart Failure: A Propensity-Matched Analysis

MARAL OUZOUNIAN, MD,<sup>1,2</sup> JACK V. TU, MD, PhD,<sup>1,2,3</sup> PETER C. AUSTIN, PhD,<sup>2,4</sup> ALICE CHONG, BSc,<sup>2</sup>  
PETER P. LIU, MD,<sup>1,5</sup> AND DOUGLAS S. LEE, MD, PhD<sup>1,2</sup>

Toronto and Ottawa, Ontario, Canada

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## ABSTRACT

**Background:** The influence of statin therapy in heart failure (HF) has been of considerable interest. The objective of this study was to determine if statins are associated with improved outcomes in patients discharged after hospitalization for HF.

**Methods:** Patients admitted to Ontario hospitals between 1999 and 2001 with HF were identified in the Enhanced Feedback For Effective Cardiac Treatment study. Propensity score methods were used to assess 5-year outcomes in the overall cohort as well as in 4 subgroups: those with coronary artery disease (CAD) or without (NoCAD), and those with preserved ejection fraction (HFPEF) or with reduced ejection fraction (HFREF). Of the 6451 HF patients, 1121 were discharged with a prescription for a statin.

**Results:** In propensity analysis stratified on matched pairs in a Cox proportional hazards model, statins were associated with improved mortality at 5 years overall (hazard ratio [HR] 0.85,  $P = .05$ ) and in those with CAD (HR 0.79,  $P = .008$ ). Similarly, statins were associated with lower risk of the combined end point in the CAD group (HR 0.85,  $P = .045$ ).

**Conclusions:** Among patients with HF discharged from hospital, statin therapy was associated with improved outcomes, particularly in patients with CAD. Stratification by ejection fraction did not differentially impact the effect of statins in patients with HF. (*J Cardiac Fail* 2009;15:241–248)

**Key Words:** Health outcomes, heart failure, statins, therapy.

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The 3-hydroxyl-3-methylglutaryl-coenzyme A reductase inhibitors, or statins, have proven efficacy in reducing mortality and cardiovascular morbidity in diverse populations, including patients with dyslipidemia, coronary artery disease (CAD), cerebrovascular disease, and diabetes.<sup>1–4</sup>

The safety and efficacy of statin therapy in patients with established heart failure (HF) has been a matter of considerable interest. Two randomized trials have been published that showed a lack of mortality benefit for rosuvastatin in patients with HF.<sup>5,6</sup> Examination of the real-world effect

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From the <sup>1</sup>Heart & Stroke/Richard Lewar Centre for Excellence, University of Toronto, and Division of Cardiology, Toronto General Hospital, University Health Network, Toronto, Ontario, Canada; <sup>2</sup>Institute for Clinical Evaluative Sciences, Toronto, Ontario, Canada; <sup>3</sup>Divisions of General Internal Medicine and Cardiology, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Ontario, Canada; <sup>4</sup>Departments of Public Health Sciences and Health Policy, Management and Evaluation, University of Toronto, Toronto, Canada and <sup>5</sup>the Canadian Institutes of Health Research, Ottawa, Ontario, Canada.

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Reprint requests: Douglas S. Lee, MD, PhD, Institute for Clinical Evaluative Sciences, 2075 Bayview Ave Rm G-106, Toronto, Ontario, M4N 3M5 Canada.

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of statin therapy in the community may provide further insights that could complement the insights emanating from the randomized trials of statins in HF.

Clinical end points in trials of statin therapy are driven by myocardial infarction, unstable angina, and revascularization, whereas individuals who have HF are at increased risk for hospitalizations for acute decompensated HF or mortality from progressive pump failure, or sudden death.<sup>7,8</sup> The potential benefits of statin therapy in HF range from direct, lipid-lowering effects on atherothrombotic events to multiple pleiotropic effects on inflammation, endothelial function, and cardiac remodeling.<sup>9,10</sup> The risks of unnecessary polypharmacy, however, must be considered carefully, particularly in light of the association of lower cholesterol with increased mortality in HF patients.<sup>11</sup>

Despite recent therapeutic advances in HF, clinical outcomes in this population remain poor.<sup>12</sup> The morbidity and mortality for patients with HF and reduced ejection fraction (HFREF) or preserved ejection fraction (HFPEF) are substantial,<sup>13,14</sup> and there is a growing need to define new therapeutic targets for this population. The paucity of HF patients in existing large statin trials has led to uncertainty regarding the role of statins in this patient population. Data on the differential effects of statin therapy on nonischemic versus ischemic cardiomyopathy or diastolic versus systolic HF are particularly scant.

The objective of this study was to determine if statin therapy was associated with improved clinical outcomes in patients with HF discharged after hospitalization. We hypothesized that statin therapy would be associated with improved outcomes in patients with HF and CAD, regardless of ejection fraction.

## Methods

### Study Sample

The patients included in our analyses were those identified as part of the Enhanced Feedback for Effective Cardiac Treatment (EFFECT) study, a clinical study of acute HF patients for which details have been previously described.<sup>7</sup> The EFFECT study included patients admitted to 103 acute care hospitals in Ontario, Canada, with a primary diagnosis of HF (*International Classification of Diseases, Ninth Revision, Clinical Modification*<sup>15</sup> code 428) in the Canadian Institute for Health Information discharge abstract database from April 1999 to March 2001. Approval from the ethics review board was obtained from all participating institutions before the study.

We examined all patients who were discharged from hospitals alive. Patients with life-limiting noncardiac comorbidities (cancer, dialysis-dependent renal failure, cor pulmonale, or dementia) or obvious contraindications to statin therapy (hepatitis, hepatic cirrhosis) were excluded from this analysis. We also excluded patients with severe left-sided valvular or pericardial disease. Patients who developed HF after admission, died during the index hospitalization, or were transferred from another acute care facility were excluded. To identify patients at a similar inception point or uniform point of disease, the EFFECT study excluded patients who had a previous HF admission within the past 3 years.

### Data Collection and Variable Definitions

Patients who met the Framingham criteria for HF<sup>16</sup> were identified for detailed chart abstraction of demographic, clinical, laboratory, and imaging data as part of the EFFECT study. Data on drugs prescribed at hospital discharge were collected. Information on left ventricular ejection fraction (LVEF) was abstracted from available echocardiographic, cardiac catheterization, or radionuclide angiography studies.

We planned a priori to analyze 4 subgroups of interest. CAD was defined as the presence of a prior history of myocardial infarction (MI), angina, unstable angina, coronary artery bypass graft surgery, or percutaneous coronary intervention. Those with an LVEF of greater than 50% or a qualitative description of "normal" systolic function were defined as having HFPEF, and those with an LVEF of less than 45% or a qualitative description of "moderate" or "severe" systolic dysfunction were defined as having HFREF. In order to clearly distinguish the 2 groups, patients with a borderline LVEF between 45% and 50% were excluded from analyses where stratification was based on left ventricular systolic function.

### Statistical Analysis

Patients who were discharged from hospital on statin therapy (including those who were on therapy at the time of admission) were compared with those who were not by using *t* tests for continuous variables and  $\chi^2$  tests for categorical variables. The primary outcome of interest was the rate of all-cause death at 5 years after the index HF discharge. We also examined the 5-year rates of the combined end point, which included death, readmission for HF, and admission for coronary events or ischemic stroke. Rates of mortality and cardiovascular morbidity were determined by linking the clinical EFFECT data with the Registered Persons Database, which contains information on the vital status of all Ontario residents covered under the Ontario health insurance plan, and the Canadian Institute for Health Information discharge abstract database, which contains data on hospital admissions throughout Canada. Prior studies have validated cardiovascular disease diagnosis coding in the Canadian Institute for Health Information discharge abstract database with high predictive values when compared with clinical criteria.<sup>17–19</sup>

Time to death or the combined end point of all participants following discharge from hospital was analyzed using Cox proportional hazards regression, with statin therapy as the predictor variable and the nonstatin group as the referent category. Participants were followed until death occurred, and surviving patients were censored at 5 years of follow-up after HF hospital discharge. The Cox proportional hazards assumption was confirmed. Adjusted survival curves<sup>20</sup> were examined comparing patients who were discharged with and without a prescription for statin therapy. In sensitivity analyses, we linked HF patient data to the Ontario Drug Benefit database (which contains information on outpatient drug use for those aged  $\geq 65$  years), to account for preadmission and postdischarge statin use.

### Propensity Score Methods

To ensure comparable risk between groups, a propensity score model was created to balance measured potentially confounding variables between patients discharged on statin therapy and those who were not.<sup>21</sup> The propensity score is the conditional probability of receiving a treatment (ie, statin therapy) given a set of

measured covariates.<sup>22–26</sup> We estimated propensity scores for statin therapy for each of the 6451 subjects by using a nonparsimonious multivariable regression model (C statistic 0.88). The variables used in deriving the propensity score included all measured baseline patient characteristics—specifically, age, sex, CAD, hypertension, hyperlipidemia, diabetes, cerebrovascular disease, smoking history (current or previous), peripheral vascular disease, atrial fibrillation, chronic obstructive pulmonary disease, prior MI, prior coronary artery bypass graft surgery, prior percutaneous coronary intervention, gastrointestinal ulcer disease, and laboratory values at the time of admission (hemoglobin, urea, creatinine, sodium, white blood cell count).

A propensity-matched analysis was performed for the overall cohort and separately within the CAD, no CAD (NoCAD), HFPEF, and HFREF subgroups. Patients discharged with and without statin therapy were matched using a greedy matching algorithm on the logit of the propensity score with a caliper width of 0.2 of the standard deviation of the logit of the propensity score.<sup>23</sup> Balances in the distribution of baseline covariates between the 2 groups were assessed by calculating standardized differences, expressed as percentages of the pooled standard deviations.<sup>24,25</sup> Standardized differences represent residual biases in covariates across groups, and an absolute standardized difference of less than 10% suggests adequate balance.<sup>23</sup> Time to death or the combined end point for the propensity-matched sample following discharge from hospital was analyzed using a Cox proportional hazards regression model that stratified on matched pairs.

Statistical significance was indicated by a 2-tailed  $P < .05$ . All analyses were performed using SAS version 8.2 (SAS Institute Inc, Cary, North Carolina).

## Results

A total of 6451 patients were admitted for HF and met criteria for inclusion. The average age of patients in the study was  $74.8 \pm 11.5$  (SD) years, and 49% were female. Of these, 1121 were discharged with a prescription for a statin (17%). Of the 6451 patients identified, 4721 (73%) had CAD and 1730 (27%) did not (NoCAD). Less than 2% of patients were categorized as having CAD based on angina alone. Among those patients with an LVEF assessment ( $n = 2789$ ), 706 (25%) had HFPEF and 1473 (53%) had HFREF. Median follow-up time for patients discharged alive from hospital was 3.2 years, and a total of 21,323 person years of follow-up were available for analysis. There were no losses to follow-up for morbid events or death, since all hospital admissions and deaths were identified.

### Clinical Characteristics

The baseline characteristics of patients discharged alive with and without statin therapy are shown in Table 1. Patients discharged on statins were younger, but had greater cardiovascular disease and risk factor burden than those not discharged on a statin. The distribution of baseline characteristics of the CAD, NoCAD, HFPEF and HFREF subgroups were similar, apart from those variables which defined the subgroups. In each subgroup, patients discharged on statin therapy were younger, but were more likely to have

hypertension, dyslipidemia, diabetes, and peripheral vascular disease than those not discharged on statin therapy.

### Clinical Outcomes

Of the study cohort, 5171 (80%) experienced at least one of the clinical outcomes during the 5-year observation period, which were distributed as follows: 4070 deaths (63%), 2684 HF hospitalizations (42%), 1215 acute coronary syndrome events (19%), and 318 ischemic strokes (5%). Patients who were discharged on statin therapy had lower unadjusted 5-year mortality rates than those who were not (54% vs 65%,  $P < .001$ ). The unadjusted 5-year rates of the combined end point (mortality, readmission for HF, admission for acute coronary syndromes, or ischemic stroke) were also lower for those discharged on statin therapy (77% vs 81%,  $P < .003$ ). When 5-year mortality was examined, patients on statin therapy in the CAD (statin vs no statin: 55% vs 68%,  $P < .001$ ) and NoCAD (statin vs no statin: 43% vs 58%,  $P = .001$ ) groups had improved outcomes (Figure 1, left panel). Unadjusted rates of the 5-year combined end point including death, readmission for HF, and admission for coronary events or ischemic stroke were also lower for patients on statin therapy in the CAD group (statin vs no statin: 78% vs 84%,  $P < .001$ ) but not significantly in those without CAD (statin vs no statin: 68% vs 73%,  $P = .24$ ; Figure 1, right panel). In those with HFPEF, there was no significant difference in 5-year mortality (statin vs no statin: 49% vs 55%,  $P = .20$ ) or the composite outcome (74% vs 73%,  $P = .72$ ). Similarly, in those with HFREF, there was no difference in mortality (statin vs no statin: 58% vs 61%,  $P = .31$ ) or the composite outcome (77% vs 78%,  $P = .68$ ).

### Association of Statins With Death in Cox Models

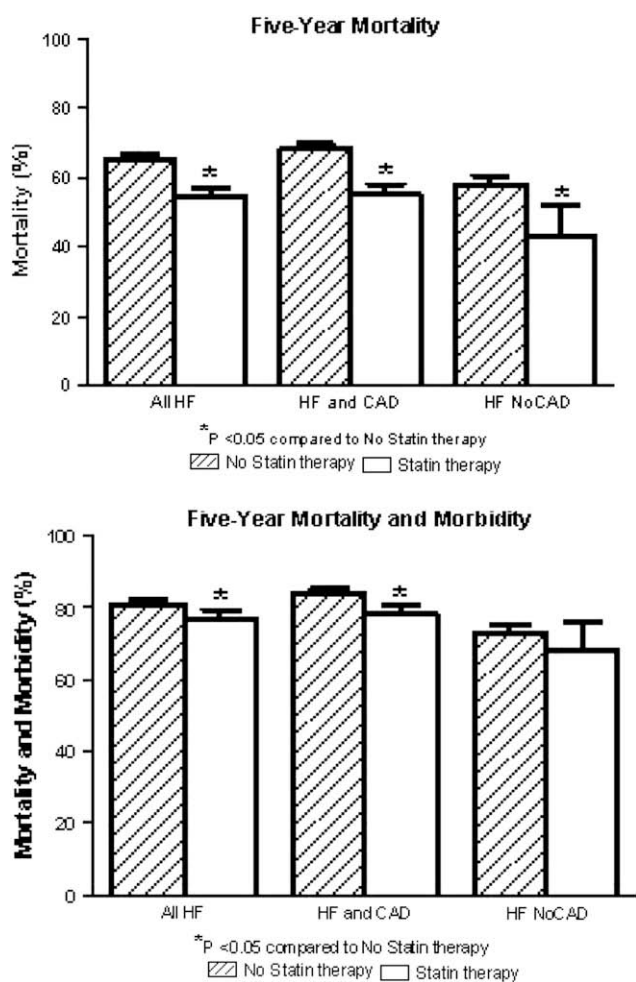
Statin prescription at discharge was associated with a decreased risk of death with a hazard ratio (HR) of 0.72 (95% CI, 0.66–0.78) in unadjusted analysis ( $P < .001$ ). After adjustment for age and sex, the risk reduction with statin prescription remained with a HR of 0.86 (95% CI, 0.79–0.94,  $P < .001$ ). The results of multivariable analyses, adjusted for age, sex, CAD, hypertension, diabetes, smoking history, cerebrovascular disease, peripheral vascular disease, chronic obstructive pulmonary disease, and atrial fibrillation are shown in Table 2. Despite multivariable adjustment, those discharged with statin therapy remained significantly more likely to survive, with an HR in the overall HF cohort of 0.81 (95% CI, 0.74–0.89,  $P < .001$ ).

In analyses of clinical HF subgroups of those with CAD, NoCAD, HFREF, and HFPEF, statin therapy remained significantly associated with improved survival after adjustment for clinical covariates in the CAD group (HR 0.86, 95% CI, 0.77–0.96,  $P = .008$ ). However, survival was not improved with statins in the NoCAD group (HR 0.85, 95% CI, 0.60–1.19,  $P = .34$ ). Adjusted HRs for death in the HFPEF and HFREF groups were 1.16 (95% CI, 0.76–1.76,  $P = .50$ ) and 0.84 (95% CI, 0.70–1.02,  $P = .07$ ), respectively. Adjusted survival curves for the overall

**Table 1. Baseline Characteristics**

Variable	No Statin (n = 5330)	Statin (n = 1121)	P Value
Age, y*	78 (70–84)	71 (64–77)	<.001
Sex, male	2624 (49)	648 (58)	<.001
Coronary artery disease	3719 (70)	1002 (89)	<.001
Hypertension	2542 (48)	683 (61)	<.001
Hyperlipidemia	550 (10)	822 (73)	<.001
Diabetes	1851 (35)	545 (49)	<.001
Smoking history	1987 (37)	522 (47)	<.001
Prior myocardial infarction	1867 (35)	626 (56)	<.001
Prior coronary artery bypass grafting	511 (10)	284 (25)	<.001
Prior percutaneous coronary intervention	120 (2)	89 (8)	<.001
Cerebrovascular disease	751 (14)	202 (18)	<.001
Peripheral vascular disease	635 (12)	207 (18)	<.001
Atrial fibrillation	1530 (29)	264 (24)	<.001
Chronic obstructive pulmonary disease	905 (17)	144 (13)	<.001
Total cholesterol, mg/dL, mean (SD) [mmol/L], mean (SD)	170 (42) [4.41 (1.10)]	175 (53) [4.54 (1.38)]	.15
Hemoglobin, g/dL, mean (SD)	12.5 (2.1)	12.6 (2.0)	.61
Sodium, mEq/L, mean (SD)	138.4 (4.7)	138.7 (4.2)	.07
Blood urea nitrogen, mg/dL, mean (SD) [mmol/L], mean (SD)	27.5 (17.6) [9.8 (6.3)]	28.0 (17.1) [10.0 (6.1)]	.43

HF, heart failure.  
 Values are No. (%) unless otherwise indicated.  
 \*Median age (interquartile range).



**Fig. 1.** Five-year mortality and composite end point for patients discharged alive with heart failure. HF, heart failure; CAD, coronary artery disease.

cohort are shown in Figure 2. In sensitivity analyses, we accounted for statin use and the duration of statin use prior to the HF hospitalization in a multivariable analysis, with a resultant adjusted HR of 0.78 (95% CI, 0.68–0.90, *P* < 0.001). Similar effects were observed when statin use was accounted for after hospital discharge as a time-varying covariate.

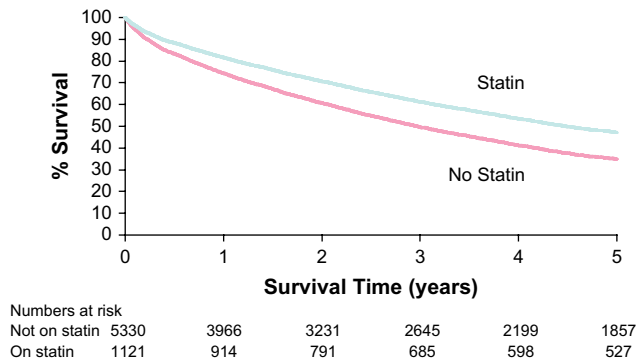
**Propensity-Matched Analysis**

In the propensity-matched analysis, there were 721 matched pairs composed of 1 patient who was discharged on statin therapy and 1 who was not (see Table 3). In the propensity-matched Cox proportional hazards model that stratified on matched pairs, statin prescription at discharge was associated with improved survival in the overall cohort, with an HR of 0.85 (95% CI, 0.72–1.00, *P* = .05). However, statin prescription was more strongly associated

**Table 2. Cox Proportional Hazards Model for 5-Year Mortality for All HF Patients**

Variable	Hazard Ratio, (95% CI)	P Value
Statin therapy	0.81 (0.74–0.89)	<.001
Age, y	1.04 (1.04–1.05)	<.001
Male	1.15 (1.07–1.22)	<.001
Coronary artery disease	1.19 (1.11–1.28)	<.001
Hypertension	0.87 (0.82–0.93)	<.001
Diabetes	1.28 (1.20–1.37)	<.001
Smoking history	1.01 (0.95–1.09)	.72
Cerebrovascular disease	1.22 (1.12–1.33)	<.001
Peripheral vascular disease	1.34 (1.22–1.46)	<.001
Atrial fibrillation	1.03 (0.96–1.10)	.43
Chronic obstructive pulmonary disease	1.31 (1.21–1.42)	<.001

HF, heart failure; CI, confidence interval.



**Fig. 2.** Adjusted survival curves for patients with heart failure who were or were not prescribed statin drug.

with mortality reduction in those with HF and CAD, with an HR of 0.79 (95% CI, 0.67–0.94,  $P = .008$ ). There was no significant effect of statin prescription at discharge in HF patients without CAD, with reduced ejection fraction, or preserved ejection fraction (Figure 3). Statins were also associated with reduced risk of the combined end point of hospitalization for HF or acute coronary events, ischemic stroke, and death only in the CAD group (HR 0.85, 95% CI, 0.72–1.00,  $P = .045$ ) but not in the overall, NoCAD, HFPEF, or HFREF groups (Figure 3).

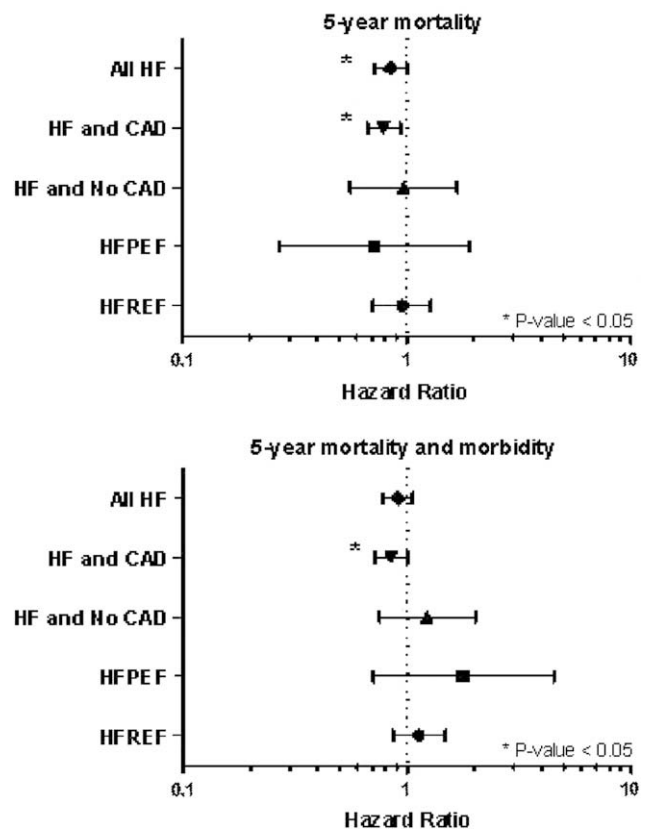
**Discussion**

There has been marked interest in the use of statin therapy in established HF. In this report, we used information

**Table 3.** Balance of Clinical Characteristics After Propensity Matching for the Overall HF Cohort

Variable	No Statin (n = 721)	Statin (n = 721)	Standardized differences
Age, y*	73 (64–79)	72 (65–78)	0.01
Sex, male	408 (57)	417 (58)	0.03
Coronary artery disease	613 (85)	631 (88)	0.07
Hypertension	437 (61)	433 (60)	0.01
Hyperlipidemia	470 (65)	470 (65)	0.00
Diabetes	340 (47)	337 (47)	0.01
Smoking history	314 (44)	332 (46)	0.05
Prior myocardial infarction	385 (53)	382 (53)	0.01
Prior coronary artery bypass grafting	160 (22)	172 (24)	0.04
Prior percutaneous coronary intervention	45 (6)	49 (7)	0.02
Cerebrovascular disease	117 (16)	122 (17)	0.02
Peripheral vascular disease	126 (18)	134 (19)	0.03
Atrial fibrillation	186 (26)	184 (26)	0.01
Chronic obstructive pulmonary disease	100 (14)	104 (14)	0.02

HF, heart failure. Values are No. (%) unless otherwise indicated. \*Median age (interquartile range).



**Fig. 3.** Estimates of the hazards of statin therapy in propensity-matched patients discharged alive with heart failure. HF, heart failure; CAD, coronary artery disease; HFPEF, heart failure with preserved ejection fraction; HFREF, heart failure with reduced ejection fraction.

from a large population-based clinical study to examine the association between statins and fatal and nonfatal outcomes in community-based patients with HF. In this study, we found that statin therapy was associated with a reduction in mortality in those who were prescribed the drug, and these effects remained after accounting for the propensity to be treated with a statin upon HF hospital discharge. In addition to a reduction in overall mortality with statins, there was a 15% reduction in combined mortality and cardiovascular morbidity, which included subsequent hospitalizations for HF, acute coronary syndromes, and ischemic stroke, particularly in those who had concomitant CAD and HF, which was also observed in propensity-matched analysis. The beneficial effects of statins were robust when prior statin use and postdischarge statin use were also taken into account.

To date, the evidence for the benefit of statin therapy on established HF in community-based patient samples has not been definitive. The Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA) study investigated the efficacy of 10 mg daily of rosuvastatin in patients who were at least 60 years of age and had HF of ischemic etiology with reduced ejection fraction.<sup>5</sup> There were no significant differences between the 2 groups in the primary composite outcome of

death from any cause, nonfatal MI, or nonfatal stroke (HR 0.92, 95% CI, 0.83–1.02,  $P = .12$ ), although patients on rosuvastatin had fewer hospitalizations. The Gruppo Italiano per lo Studio della Sopravvivenza nell' Insufficienza cardiaca-Heart Failure trial enrolled patients with symptomatic HF, irrespective of etiology or LVEF, and randomized trial enrollees to rosuvastatin 10 mg daily or placebo.<sup>6</sup> After a median follow-up period of 3.9 years, there were no significant differences between the 2 groups in all-cause death and in the combined end point of death or cardiovascular hospitalization.

Our findings of reduced hospitalizations for cardiovascular causes and HF were consistent with CORONA. However, the discordance in mortality between the aforementioned randomized trials and observational studies such as ours may be related to the enrollment of patients with New York Heart Association class III or IV HF, for whom enrollees' physicians felt it was justifiable to potentially withhold statin therapy if subjects were randomized to placebo. Thus, patients undergoing coronary revascularization procedures and those already on statins were often excluded.<sup>27</sup> As a result of competing risks, enrollees in CORONA and GISSI-HF may have been at lesser relative risk of nonischemic death and at greater risk of events that would largely not be countered by statin use. In the present study, we examined a broad community-based population, which included those with less severe HF and those with concomitant CAD, who may not have been fully represented in the randomized trials.

Several observational studies have examined the association between statin therapy and clinical outcomes, most finding significant benefit for statin therapy in patients with established HF.<sup>28–31</sup> A population-based study in older Medicare beneficiaries hospitalized with HF showed a significant reduction in 1- and 3-year mortality.<sup>29</sup> However, data were not published regarding hospitalizations, nor was stratification by LVEF considered. Furthermore, the majority of observational studies<sup>28–30</sup> did not account for the propensity to treatment with a statin for HF. Using administrative data sources, Go and colleagues<sup>31</sup> performed a propensity score analysis and reported that statin therapy benefited HF patients, with adjusted HR for mortality of 0.76 (95% CI, 0.72–0.80) and 0.79 (95% CI, 0.74–0.85) for HF hospitalization. Our study adds significantly to the current literature on statins because we examined a large cohort of HF patients with detailed clinical data. The availability of clinical data is important in studies with propensity-matched designs since prior statistical studies have demonstrated that propensity adjustment using clinical data may be superior to that performed with administrative data.<sup>32</sup> Furthermore, we were able to examine HF patients categorized by left ventricular systolic function to explore the effect of statins in those with reduced or preserved ejection fraction. Finally, we evaluated a number of additional outcomes, specifically those of ischemic disease where one may anticipate the greatest benefit of statin therapy in patients with HF.

The effects of statin therapy on normocholesterolemic patients with nonischemic cardiomyopathy has been

investigated in a few small randomized trials limited to patients with systolic dysfunction.<sup>33–36</sup> These prospective clinical trials were small (sample size between 15 and 108 patients), follow-up duration was relatively short (ranging from 4 weeks to 12 months), and they were not powered to detect differences in clinical end points such as mortality or hospitalizations. Despite the above, these studies found that statin therapy resulted in an improvement of various biomarkers, including LVEF, cardiac chamber size, endothelial function, and serum levels of inflammatory markers such as C-reactive protein, interleukin-6, and tumor necrosis factor  $\alpha$ .<sup>33–36</sup>

The effects of statin therapy on patients with HFPEF remain largely unexplored. Although the GISSI-HF trial did not restrict patients by LVEF, only 10% of enrollees had an LVEF greater than 40%. This subgroup was too small to draw conclusions about the efficacy of statin therapy in patients with HFPEF. A small prospective study measured diastolic function by echocardiography prior to and following initiation of statin therapy. Atorvastatin initiation was associated with worsening indices of diastolic function, which were reversed by supplementation with coenzyme Q<sub>10</sub>.<sup>37</sup> To date, only 1 prospective cohort study of statin therapy in HFPEF has been published. Fukuta and colleagues<sup>38</sup> evaluated 137 consecutive patients with HF and an LVEF of  $\geq 50\%$ , with a mean follow-up of 21 months. They found that statin therapy was associated with significantly improved survival with an adjusted risk of death of 0.20 (0.06–0.62). These results are in contrast to our study results, which found no significant improvement in survival in those with HFPEF in a larger study sample with longer duration of follow-up.

It is likely that the efficacy of statin therapy observed in our study relates primarily to plaque stabilization and prevention of antithrombotic events. Autopsy findings in patients with HF and sudden death revealed a significant number of acute coronary syndromes precipitated by plaque rupture,<sup>39</sup> leading to the hypothesis that coronary events may be responsible for a greater proportion of adverse outcomes in HF than previously suspected. It has been suggested that patients with nonischemic cardiomyopathy may benefit from the pleiotropic effects of statin therapy, including improved endothelial and autonomic function, left ventricular remodeling, and anti-inflammatory properties. However, there is as of yet limited evidence that these pleiotropic effects will translate into improved outcomes in patients with nonischemic cardiomyopathy with low or normal cholesterol levels.<sup>10</sup>

Concern has been raised regarding the possible harmful effects of statins in patients with HF. Low serum lipid levels have been associated with increased mortality in HF patients, a phenomenon termed *reverse epidemiology* that has also been observed with body weight and blood pressure in this population.<sup>11,40–42</sup> One proposed explanation for these adverse events is the endotoxin-lipoprotein hypothesis, which suggests that lipoproteins may protect the myocardium against inflammation by acting as scavengers

of endotoxins.<sup>43</sup> Additionally, through inhibition of mevalonate synthesis, statins reduce levels of the micronutrient ubiquinone (coenzyme Q), an essential component of mitochondrial oxidative phosphorylation and an endogenous antioxidant.<sup>44,45</sup>

This study has limitations that require comment. Although our study suggests a relationship between statin therapy and improved clinical outcomes, it was observational in nature, and therefore we cannot definitively infer a causal relationship as might be anticipated from a randomized controlled trial of statin efficacy. Additionally, we were unable to determine how physicians chose the patients to be discharged home with statin therapy during a time when guidelines for lipid therapy were more restrictive than currently recommended. However, disparities often exist between randomized trials and findings in the real world, underscoring the importance of community-based observational studies.<sup>46–49</sup> Despite reducing bias through propensity score methods, there may have been confounding from unmeasured variables. However, we examined an array of important clinical predictors of statin use and were able to identify the important discriminative predictors of statin prescription at discharge in our propensity-matched analyses. Although our analyses found a significant effect of statins in those with CAD, the number of HF patients without CAD treated with statins was small ( $n = 119$ ) and the magnitude of the HRs similar between groups, with the attendant potential that we may have been underpowered to detect an effect in the non-CAD group. In addition, we may have been underpowered to detect a difference in the subgroup analyses exploring the effect of statins in patients with HF and preserved or reduced ejection fraction.

In conclusion, statin therapy was associated with significantly improved 5-year mortality and morbidity in patients with HF discharged alive from hospital. After both traditional risk adjustment and propensity score methods, the observed improved outcomes were predominantly in HF patients with evidence of concomitant CAD. In light of available data from recent large randomized trials, our study suggests that statins may be beneficial in HF patients if specific indications such as prior MI or coronary disease coexist. In subgroups of patients with HF of ischemic origin, the benefits of treatment with a statin may be sufficient to outweigh the risk of competing causes of death that are nonischemic in nature.

## References

1. Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, Brown L, Warnica JW, Arnold JM, Wun CC, Davis BR, Braunwald E. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels Cholesterol and Recurrent Events Trial investigators. *N Engl J Med* 1996; 335:1001–9.
2. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;344:1383–9.
3. MRC/BHF. Heart Protection Study of antioxidant vitamin supplementation in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002;360:23–33.
4. Sever PS, Dahlof B, Poulter NR, Wedel H, Beevers G, Caulfield M, Collins R, Kjeldsen SE, Kristinsson A, McInnes GT, Melsen J, Nieminen M, O'Brien E, Ostergren J; ASCOT Investigators. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet* 2003;361:1149–58.
5. Kjekshus J, Apetrei E, Barrios V, Bohm M, Cleland JG, Cornel JH, Dunselman P, Fonseca C, Goudev A, Grande P, Gullestad L, Hjalmarson A, Hradec J, Jánosi A, Kamenský G, Komajda M, Korewicki J, Kuusi T, Mach F, Mareev V, McMurray JJ, Ranjith N, Schaufelberger M, Vanhaecke J, van Veldhuisen DJ, Waagstein F, Wedel H, Wikstrand; JCORONA Group. Rosuvastatin in older patients with systolic heart failure. *N Engl J Med* 2007;357:2248–61.
6. Investigators GISSI-HF. Effect of rosuvastatin in patients with chronic heart failure (the GISSI-HF trial): a randomized, double-blind, placebo-controlled trial. *Lancet* 2008;372:1231–9.
7. Lee DS, Austin PC, Rouleau JL, Liu PP, Naimark D, Tu JV. Predicting mortality among patients hospitalized for heart failure: derivation and validation of a clinical model. *JAMA* 2003;290:2581–7.
8. Ho KK, Pinsky JL, Kannel WB, Levy D. The epidemiology of heart failure: the Framingham Study. *J Am Coll Cardiol* 1993;22(4 suppl A):6A–13A.
9. Lipinski MJ, Abbate A, Fuster V, Vetrovec GW. Drug insight: statins for nonischemic heart failure—evidence and potential mechanisms. *Nat Clin Pract Cardiovasc Med* 2007;4:196–205.
10. Raina A, Pickering T, Shimbo D. Statin use in heart failure: a cause for concern? *Am Heart J* 2006;152:39–49.
11. Kalantar-Zadeh K, Block G, Horwich T, Fonarow GC. Reverse epidemiology of conventional cardiovascular risk factors in patients with chronic heart failure. *J Am Coll Cardiol* 2004;43:1439–44.
12. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG. Force on Practice Guidelines, American College of Chest Physicians, International Society for Heart and Lung Transplantation, Heart Rhythm Society. Altered thyroid hormone metabolism in advanced heart failure. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). *Circulation* 2005;112:e154–235.
13. Bhatia RS, Tu JV, Lee DS, Austin PC, Fang J, Haouzi A, Gong Y, Liu PP. Outcome of heart failure with preserved ejection fraction in a population-based study. *N Engl J Med* 2006;355:260–9.
14. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. *N Engl J Med* 2006;355:251–9.
15. International Classification of Diseases, Ninth Revision, Clinical Modification. Washington, DC: Public Health Services, US Department of Health and Human Services; 1988.
16. McKee PA, Castelli WP, McNamara PM, Kannel WB. The natural history of congestive heart failure: the Framingham study. *N Engl J Med* 1971;285:1441–6.
17. Juurlink D, Preyra C, Croxford R, Chong A, Austin P, Tu J, Laupacis A. Canadian Institute for Health Information Discharge Abstract Database: a Validation Study. Toronto, Ontario: Institute for Clinical Evaluative Sciences 2006.
18. Austin PC, Daly PA, Tu JV. A multicenter study of the coding accuracy of hospital discharge administrative data for patients admitted to cardiac care units in Ontario. *Am Heart J* 2002;144:290–6.
19. Lee DS, Donovan L, Austin PC, Gong Y, Liu PP, Rouleau JL, Tu JV. Comparison of coding of heart failure and comorbidities in administrative and clinical data for use in outcomes research. *Med Care* 2005;43:182–8.

20. Ghali WR, Quan H, Brant R, van Melle G, Norris CM, Faris PD, Galbraith PD, Knudtson ML; APPROACH (Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease) Investigators. Comparison of 2 methods for calculating adjusted survival curves from proportional hazards models. *JAMA* 2001;286:1494–7.
21. Austin PC, Grootendorst P, Anderson GM. A comparison of the ability of different propensity score models to balance measured variables between treated and untreated subjects: a Monte Carlo study. *Stat Med* 2007;26:734–53.
22. Rosenbaum PR, Rubin DB. Difficulties with regression analyses of age-adjusted rates. *Biometrics* 1984;40:437–43.
23. Austin PC. The performance of different propensity score methods for estimating marginal odds ratios. *Stat Med* 2007;26:3078–94.
24. Austin PC, Mamdani MM. A comparison of propensity score methods: a case-study estimating the effectiveness of post-AMI statin use. *Stat Med* 2006;25:2084–106.
25. Normand ST, Landrum MB, Guadagnoli E, Ayanian JZ, Ryan TJ, Cleary PD, McNeil BJ. Validating recommendations for coronary angiography following acute myocardial infarction in the elderly: a matched analysis using propensity scores. *J Clin Epidemiol* 2001;54:387–98.
26. D'Agostino RB Jr. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. *Stat Med* 1998;17:2265–81.
27. Tavazzi L, Tognoni G, Franzosi MG, Latini R, Maggioni AP, Marchioli R, Nicolosi GL, Porcu M; GISSI-HF Investigators. Rationale and design of the GISSI heart failure trial: a large trial to assess the effects of n-3 polyunsaturated fatty acids and rosuvastatin in symptomatic congestive heart failure. *Eur J Heart Fail* 2004;6:635–41.
28. 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.
29. Foody JM, Shah R, Galusha D, Masoudi FA, Havranek EP, Krumholz HM. Statins and mortality among elderly patients hospitalized with heart failure. *Circulation* 2006;113:1086–92.
30. Folkeringa RJ, Van Kraaij DJ, Tieleman RG, Nieman FH, Pinto YM, Crijns HJ. Statins associated with reduced mortality in patients admitted for congestive heart failure. *J Card Fail* 2006;12:134–8.
31. Go AS, Lee WY, Yang J, Lo JC, Gurwitz JH. Statin therapy and risks for death and hospitalization in chronic heart failure. *JAMA* 2006;296:2105–11.
32. Austin PC, Mamdani MM, Stukel TA, Anderson GM, Tu JV. The use of the propensity score for estimating treatment effects: administrative versus clinical data. *Stat Med* 2005;24:1563–78.
33. Wojnicz R, Wilczek K, Nowalany-Kozielska E, Szygula-Jurkiewicz B, Nowak J, Polonski L, Dyrbus K, Badziński A, Mercik G, Zembala M, Wodniecki J, Rozek MM. Usefulness of atorvastatin in patients with heart failure due to inflammatory dilated cardiomyopathy and elevated cholesterol levels. *Am J Cardiol* 2006;97:899–904.
34. Sola S, Mir MQ, Lerakis S, Tandon N, Khan BV. Atorvastatin improves left ventricular systolic function and serum markers of inflammation in nonischemic heart failure. *J Am Coll Cardiol* 2006;47:332–7.
35. Laufs U, Wassmann S, Schackmann S, Heeschen C, Bohm M, Nickenig G. Beneficial effects of statins in patients with non-ischemic heart failure. *Z Kardiol* 2004;93:103–8.
36. Node K, Fujita M, Kitakaze M, Hori M, Liao JK. Short-term statin therapy improves cardiac function and symptoms in patients with idiopathic dilated cardiomyopathy. *Circulation* 2003;108:839–43.
37. Silver MA, Langsjoen PH, Szabo S, Patil H, Zelinger A. Effect of atorvastatin on left ventricular diastolic function and ability of coenzyme Q10 to reverse that dysfunction. *Am J Cardiol* 2004;94:1306–10.
38. 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;112:357–63.
39. Uretsky BF, Thygesen K, Armstrong PW, Cleland JG, Horowitz JD, Massie BM, Packer M, Poole-Wilson PA, Ryden L. Acute coronary findings at autopsy in heart failure patients with sudden death: results from the assessment of treatment with lisinopril and survival (ATLAS) trial. *Circulation* 2000;102:611–6.
40. Rauchhaus M, Clark AL, Doehner W, Davos C, Bolger A, Sharma R, Coats AJ, Anker SD. The relationship between cholesterol and survival in patients with chronic heart failure. *J Am Coll Cardiol* 2003;42:1933–40.
41. Horwich TB, Hamilton MA, Maclellan WR, Fonarow GC. Low serum total cholesterol is associated with marked increase in mortality in advanced heart failure. *J Card Fail* 2002;8:216–24.
42. Anker SD, Negassa A, Coats AJ, Afzal R, Poole-Wilson PA, Cohn JN, Yusuf S. Prognostic importance of weight loss in chronic heart failure and the effect of treatment with angiotensin-converting-enzyme inhibitors: an observational study. *Lancet* 2003;361:1077–83.
43. Rauchhaus M, Coats AJ, Anker SD. The endotoxin-lipoprotein hypothesis. *Lancet* 2000;356:930–3.
44. Mortensen SA, Leth A, Agner E, Rohde M. Dose-related decrease of serum coenzyme Q10 during treatment with HMG-CoA reductase inhibitors. *Mol Aspects Med* 1997;18(suppl):S137–44.
45. Krum H, McMurray JJ. Statins and chronic heart failure: do we need a large-scale outcome trial? *J Am Coll Cardiol* 2002;39:1567–73.
46. Lloyd-Williams F, Mair F, Shiels C, Hanratty B, Goldstein P, Beaton S, Capewell S, Lye M, McDonald R, Roberts C, Connelly D. Why are patients in clinical trials of heart failure not like those we see in everyday practice? *J Clin Epidemiol* 2003;56:1157–62.
47. McMurray J. Heart failure: we need more trials in typical patients. *Eur Heart J* 2000;21:699–700.
48. Jong P, Vowinckel E, Liu PP, Gong Y, Tu JV. Prognosis and determinants of survival in patients newly hospitalized for heart failure: a population-based study. *Arch Intern Med* 2002;162:1689–94.
49. Coca SG, Krumholz HM, Garg AX, Parikh CR. Underrepresentation of renal disease in randomized controlled trials of cardiovascular disease. *JAMA* 2006;296:1377–84.