Statins and Mortality Among Elderly Patients Hospitalized With Heart Failure

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Background—Small studies suggest that statins may improve mortality in patients with heart failure (HF). Whether these results are generalizable to a broader group of patients with HF remains unclear. Our objective was to evaluate the association between statin use and survival among a national sample of elderly patients hospitalized with HF.

Methods and Results—A nationwide sample of 61 939 eligible Medicare beneficiaries ≥65 years of age who were hospitalized with a primary discharge diagnosis of HF between April 1998 and March 1999 or July 2000 and June 2001 was evaluated. The analysis was restricted to patients with no contraindications to statins (n=54 960). Of these patients, only 16.7% received statins on discharge. Older patients were less likely to receive a statin at discharge. Patients with hyperlipidemia and those cared for by a cardiologist or cared for in a teaching hospital were more likely to receive a statin at discharge. In a Cox proportional hazards model that took into account demographic, clinical characteristics, treatments, physician specialty, and hospital characteristics, discharge statin therapy was associated with significant improvements in 1- and 3-year mortality (hazard ratio, 0.80; 95% CI, 0.76 to 0.84; and hazard ratio, 0.82; 95% CI, 0.79 to 0.85, respectively). Regardless of total cholesterol level or coronary artery disease status, statin therapy was associated with significant differences in mortality.

Conclusions—Our data demonstrate that statin therapy is associated with better long-term mortality in older patients with HF. This study suggests a potential role for statins as an adjunct to current HF therapy. Randomized clinical trials are required to determine the role of these agents in improving outcomes in the large and growing group of patients with HF. (***Circulation*. 2006;113:1086-1092.**)

Key Words: heart failure ■ mortality ■ elderly ■ statins ■ survival

Hydroxymethylglutaryl coenzyme A (HMG Co-A) reductase inhibitor (statin) therapy lowers morbidity and mortality in a broad range of patient populations with and without cardiovascular disease. In these trials, statin therapy may also reduce the risk of heart failure (HF), although patients with symptomatic or severe HF generally have been excluded from these studies.[1,2] A few small studies[3–5] have suggested that statin therapy is associated with improved survival in patients with ischemic and nonischemic HF, but the generalizability of these findings remains unclear. No large national study has investigated this issue. Accordingly, we evaluated statin therapy and outcomes in 54 960 Medicare beneficiaries admitted to acute care hospitals in the United States from 1998 through 2001 with a principal diagnosis of HF as part of the Centers for Medicare and Medicaid Services' National Heart Care (NHC) Project.

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Methods

NHC Project

We used data obtained from the NHC Project, a Centers for Medicare and Medicaid Services undertaking designed to improve the quality of care for Medicare beneficiaries with HF.[6] Two samples of Medicare fee-for-service beneficiaries hospitalized with a principal discharge diagnosis of HF (*International Classification of Diseases*, 9th revision, clinical modification codes 402.01, 402.11, 402.91, 404.01, 404.91, or 428) between April 1998 and March 1999 or July 2000 and June 2001 were identified. For each sampling period, a systematic sample of 800 discharges was obtained from each state and sorted by patient age, sex, race, and hospital. States with fewer than 800 discharges (Alaska, Hawaii, Idaho, Utah, Vermont, and Wyoming) were sampled in their entirety over 2 sampling periods. Combining these 2 samples resulted in a cohort of

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TABLE 1. Study Sample Inclusion and Exclusion Criteria

Description	n	%
Total cases abstracted	78 882	100.0
Exclusions criteria		
Age <65 y or unknown	6553	8.31
Repeated admissions	3726	4.72
Transferred out, AMA, or discharge disposition unknown	1506	1.91
In-hospital death from abstraction or discharge date ≥DOD	4223	5.35
No DOD information	915	1.16
Outside US (Puerto Rico, Virgin Islands)	1417	1.80
Discharged to hospice or terminal care	1299	1.65
Contraindications to statin therapy	4655	5.90
No medication documented at discharge	1227	1.55
Met ≥1 of the above exclusion criteria	23 922	30.32
Study sample	54 960	69.67

AMA indicates left against medical advice; DOD, date of death.

78 882 discharges. The NHC abstraction process and data quality monitoring were similar to that detailed previously for the Cooperative Cardiovascular Project.[7]

Of the 78 882 initially abstracted cases, we excluded patients who met the following criteria: were <65 years of age (n=6553); had HF readmissions (n=3726); were transferred out of the hospital, left against medical advice, or had unknown discharge disposition (n=1506); died during hospitalization (n=4223); had no date of death information available (n=915); were hospitalized outside the United States (n=1417); were discharged to hospice (n=1299); had contraindications to statin therapy, including statin allergy or liver dysfunction (n=4655); or had no medications recorded on discharge (n=1227). In total, 23 922 patients met ≥1 of the above exclusion criteria, leaving a final analysis cohort of 54 960 patients (Table 1).

Additional Data Sources

Patient vital status within 1 year and 3 years after discharge was determined with the Medicare Enrollment Database.[8] In addition, patient data were linked to attending physician characteristics, verified by linkage with the American Medical Association Physician Masterfile, and hospital characteristics, determined with American Hospital Association annual surveys.

Statistical Analysis

Descriptive statistics (means, medians, interquartile ratios, frequencies, and percentages) generated for baseline demographic and clinical characteristics included lipid values, treatments and procedure, and hospital characteristics. Comparisons of characteristics of those who received statin and those who did not receive a statin were made with either a t test for continuous variables or a χ^2 test for categorical data.

First, we assessed the association of statins prescription at time of discharge with 1- and 3-year all-cause mortality. Then, we generated Kaplan-Meier estimates for 1- and 3-year outcome rates. Unadjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for discharge HMG Co-A reductase inhibitor versus no HMG Co-A reductase inhibitor were determined. All calculations were performed with the log-rank test and involved 2-sided probability values with an α value of 0.001.

The following available variables were used to develop the Cox proportional hazards model: demographic, clinical, physician, hospital, and treatment. Demographic and clinical variables entered into the model included age, sex, race, history of myocardial infarction, CABG, PTCA, smoking status, congestive HF, diabetes, hypertension, coronary artery disease (CAD), stroke, chronic obstructive pulmonary diseases, and dementia. Physician specialty (cardiology) and type of hospital (CABG available) were also included in the model. Other in-hospital test/treatment variables included cardiac catheterization, stress test, CABG, and PTCA after admission but before discharge. Finally, medications used on discharge (aspirin, β-blockers, and ACE inhibitors) also were included. In secondary analyses, the results were stratified on the basis of patient age and total cholesterol levels in those patients with available measures.

To account for the natural clustering of patients within hospitals, we used the Huber-White sandwich estimator of variance method to adjust the standard errors of covariates for clustering on hospitals.[9] To assess model performance and to minimize misclassification, we also used the logistic regression modeling approach to calculate receiver-operating characteristics and r^2 to access model discrimination. We calculated the Pearson residual to access lack of fit of residuals and used the Hosmer-Lemeshow goodness-of-fit test method to assess fitness of the models.[10] The SAS system version 6.12 (SAS Institute, Inc) was used for all statistical analyses.

This study was approved by Yale University School of Medicine Institutional Review Board. The institutional review board waived the need for informed consent for these administrative data. The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

Study Population Characteristics

The mean age of the cohort was 79 years, with almost 49% >80 years. Most patients were white (86%), and a large proportion were female (58%). Comorbidities were quite common, as shown in Table 2. A large proportion of patients had a history of diabetes (40%), hypertension (64%), and CAD (58%). On presentation, pulmonary edema was present in ≈75% patients, and ejection fractions were documented in 68% of patients. Of these, 48% had ejection fractions ≤40%, whereas 52% had ejection fractions >40%. In addition, cardiology consultations were obtained for 47% of patients, and 35% of hospitalizations were teaching hospitals.

Patterns of Statin Prescription

In this cohort, 16.7% of HF patients without contraindications for statins received a statin prescription at discharge. Displayed in Table 2 are the baseline characteristics of statin versus no-statin patients. There were significant differences between these groups: The group receiving statins at discharge were younger, were more often male, and had a higher rate of prior myocardial infarction histories, CABG, percutaneous coronary intervention, diabetes, hypertension, and CAD. There were also higher rates of cardiac catheterization and stress testing performed among this group. Similarly, they were more likely to be seen by a cardiologist, admitted to hospitals with a CABG facility, and receive a higher rate of concomitant aspirin, β-blocker, and ACE inhibitor prescriptions on discharge (Table 2).

Mortality at 1 Year

Unadjusted and adjusted HRs are shown in Table 3. In unadjusted analyses, 1-year mortality rates were lower among statin than no-statin patients (HR, 0.62; 95% CI, 0.59 to 0.65). Although after adjustment for potential confounders, including demographic, clinical characteristics, treatment, physician specialty, and hospital characteristics, the observed association between statins and survival attenuated, signifi-

TABLE 2. Patient, Physician, and Hospital Characteristics Stratified by the Prescription of Statins at Discharge

	Total		No Statins at Discharge		Statins at Discharge		
Characteristics	n	%	n	%	n	%	*P*
Cohort	54 960	100	45 797	83.3	9163	16.7	
Age, mean, y	79.4	7.8	80.1	7.8	75.8	6.5	<0.0001
≥80	26 893	48.9	24 276	53.0	2617	28.6	<0.0001
Sex, female	32 091	58.4	27 270	59.5	4821	52.6	<0.0001
Race, white	47 559	86.5	39 478	86.2	8081	88.2	<0.0001
Prior myocardial infarction	16 421	29.9	12 312	26.9	4109	44.8	<0.0001
CABG	12 902	23.5	8906	19.4	3996	43.6	<0.0001
PTCA	5708	10.4	3657	8.0	2051	22.4	<0.0001
Current smoker	4814	8.8	4051	8.8	763	8.3	0.11
CHF	38 212	69.5	31 815	69.5	6397	69.8	0.51
Diabetes	21 881	39.8	17 019	37.2	4862	53.1	<0.0001
Hypertension	35 282	64.2	28 605	62.5	6677	72.9	<0.0001
CAD	31 762	57.8	24 316	53.1	7446	81.3	<0.0001
Stroke	10 275	18.7	8531	18.6	1744	19.0	0.36
Chronic pulmonary disease	17 829	32.4	14 992	32.7	2837	31.0	0.0009
Dementia	5052	9.2	4701	10.3	351	3.8	<0.0001
LBBB	8220	15.0	6728	14.7	1492	16.3	<0.0001
SBP at admission <100 mm Hg	2147	3.9	1814	4.0	333	3.6	0.14
Pulse at admission >100 bpm	14 808	26.9	12 672	27.7	2136	23.3	<0.0001
LVEF, %							<0.0001
<40	17 438	48.0	14 010	47.5	3428	50.3	
≥40	18 882	52.0	15 493	52.5	3389	49.7	
Pulmonary edema	41 444	75.4	34 471	75.3	6973	76.1	0.090
Angina ≥60 min after arrival	10 019	18.2	7509	16.4	2510	27.4	<0.0001
Cardiac arrest	262	0.5	211	0.5	51	0.6	0.22
White blood count >12	8398	15.3	6917	15.1	1481	16.2	0.01
Creatinine >2.5 or BUN >40	10 926	19.9	9039	19.7	1887	20.6	0.06
Glucose >190 mg/dL	11 310	20.6	8891	19.4	2419	26.4	<0.0001
Hematocrit >36	30 877	56.2	25 853	56.5	5024	54.8	0.0043
Total cholesterol, mg/dL*							<0.0001
<200	7769	77.0	5832	77.4	1937	75.6	
200–240	1556	15.4	1175	15.6	381	14.9	
>240	767	7.6	523	6.9	244	9.5	
Cardiac catheterization	2875	5.2	2051	4.5	824	9.0	<0.0001
Stress test	3561	6.5	2604	5.7	957	10.4	<0.0001
Cardiology consultation	25 611	46.6	20 290	44.3	5321	58.1	<0.0001
Cardiac surgery capabilities	19 030	34.6	15 412	33.7	3618	39.5	<0.0001
Teaching hospital	19 368	35.2	15 656	34.2	3712	40.5	<0.0001
Bed size ≥350	13 591	24.7	10 989	24.0	2602	28.4	<0.0001
Aspirin	22 707	41.3	17 543	38.3	5164	56.4	<0.0001
β-Blockers	17 087	31.1	12 712	27.8	4375	47.7	<0.0001
ACEI	30 001	54.6	24 626	53.8	5375	58.7	<0.0001

CHF indicates congestive HF; LBBB, left bundle-branch block; SBP, systolic blood pressure; LVEF, left ventricular ejection fraction; BUN, blood urea nitrogen; and ACEI, ACE inhibitor.

*In those patients who had cholesterol level measured during the index hospitalization.

TABLE 3. Cox Proportional-Hazards Analysis of Statin Treatment Effects on Mortality (1 Year From Discharge)

Model	HR	95% CI	*P*
Unadjusted	0.62	0.59–0.65	<0.001
Adjusted for age, race, and sex	0.71	0.68–0.75	<0.001
Adjusted for age, race, sex, and clinical characteristics	0.78	0.75–0.82	<0.001
Adjusted for age, race, sex, clinical characteristics, and physician specialty	0.78	0.75–0.82	<0.001
Adjusted for age, race, sex, clinical characteristics, physician specialty, and discharge medications	0.80	0.76–0.84	<0.001
Adjusted for age, race, sex, clinical characteristics, physician specialty, discharge medications, and hospital characteristics	0.80	0.76–0.84	<0.001

cant differences for death remained between those patients receiving statins and those who did not (HR, 0.80; 95% CI, 0.76 to 0.84). Table 4 shows covariate-adjusted HRs for 1-year mortality for patients receiving statins compared with those who received no statins as a function of age, total cholesterol, and CAD status.

Mortality at 3 Years

Overall, statin therapy was associated with significant 3-year survival, as shown in the Figure ($P<0.0001$). The 3-year crude mortality was 48.5% in the statin group compared with 62.2% in the no-statin group ($P<0.0001$). After adjustment for potential confounders, including demographic, clinical characteristics, treatments, physician specialty, and hospital characteristics, significant differences for death remained between patients receiving statin and those who did not (HR, 0.82; 95% CI, 0.79 to 0.85), as shown in Table 5. The 3-year adjusted HR is comparable to the 1-year adjusted HR, suggesting persistent benefits of statin therapy over years.

Impact of Cholesterol Level, CAD, and Age on Survival

Statin use was associated with improved survival irrespective of cholesterol level, as shown in Table 4. Paradoxically, patients with the lowest cholesterol had the greatest benefit. Although patients with the highest total cholesterol trended toward lower mortality with statins, this was not statistically significant. Similarly, in an analysis of the impact of CAD on the association between discharge lipid lowering and clinical outcomes, results showed that although patients with CAD were much more likely to be on a statin at discharge, mortality benefits were seen regardless of CAD status.

TABLE 4. HR for 1-Year Mortality by Age, Cholesterol, and CAD Status

Description	HR	95% CI
Age, y		
65–74	0.84	0.77–0.91
75–84	0.80	0.75–0.86
≥85	0.78	0.69–0.87
Total cholesterol, mg/dL		
<200	0.78	0.70–0.88
200–240	0.99	0.73–1.34
>240	0.73	0.48–1.10
History of CAD		
Yes	0.84	0.80–0.87
No	0.88	0.83–0.93

HRs and 95% CIs for death 1 year from discharge in patients prescribed statins vs those not prescribed statins. Adjusted for age, race, sex, clinical, discharge medications, and hospital and physician characteristics.

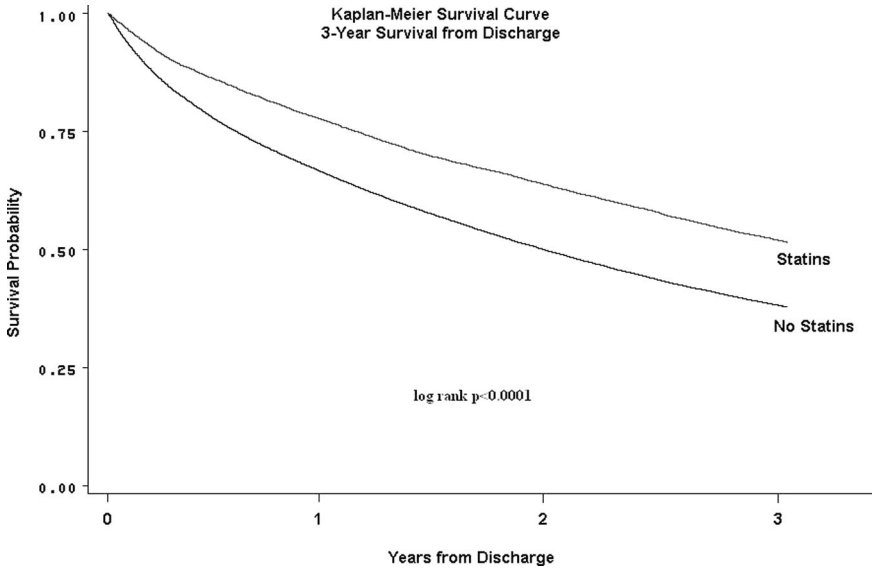
There was no remarkable interaction effect of statin by age on mortality. The risk ratio of the interaction term was 1.00 (95% CI, 0.99 to 1.00) in both the 1- and 3-year models. When age was stratified into 3 groups (65 to 74, 75 to 84, and ≥85 years), the adjusted risk ratios of the 1-year mortality for patients with statin were 0.84 (95% CI, 0.77 to 0.91), 0.80 (95% CI, 0.75 to 0.86), and 0.78 (95% CI, 0.69 to 0.87) for the 3 age groups, respectively. The 3-year mortality survival followed the same pattern, with adjusted risk ratios for stain patients of 0.83 (95% CI, 0.78 to 0.88), 0.82 (95% CI, 0.78 to 0.86), and 0.83 (95% CI, 0.76 to 0.91), respectively.

The 1- and 3-year receiver-operating characteristics were 0.7312 and 0.7443; r^2 was 0.1226 and 0.1392; mean Pearson residuals were 0 (SD, 0.99) and 0 (SD, 1.00); and probability values for goodness of fit were 0.7214 and 0.2724, respectively. These statistics show that the models have been fitted appropriately.

Discussion

In this population-based sample of older Medicare beneficiaries hospitalized with HF, discharge prescription of a statin was associated with substantial short- and long-term mortality reductions. In patients with symptomatic HF of multiple origins, statin prescription at discharge was associated with a 20% reduction in mortality risk at 1 year and an 18% reduction in mortality at 3 years after adjustment for multiple confounders. Improvements in mortality were apparent, regardless of total cholesterol level, CAD status, or patient age. Despite this result and consistent with other findings,[11] few eligible patients with HF are prescribed statins.

An emerging body of evidence suggests the potential value of statins in the management of patients with HF; however, patients with HF are excluded from most statin trials. Patients enrolled in the Cholesterol and Recurrent Events (CARE) trial with asymptomatic left ventricular dysfunction showed similar benefits of statin therapy compared with patients without left ventricular dysfunction.[2] In a post hoc analysis of the Scandinavian Simvastatin Survival Study (4S), there was a significant reduction in the development of subsequent HF



Kaplan-Meier survival curve.

in patients with preserved ventricular function at the time of entry into the study. In this study, the mortality rate in patients developing congestive HF was 25.5% in the simvastatin group compared with 31.9% in the placebo group.[12] Similarly, in the Evaluation of Losartan in the Elderly trial II (ELITE) study, in patients receiving statins at enrollment, mortality was lower (10.6%) compared with those who were not (17.6%).[13] Statin therapy was also associated with a 48% lower risk of death in the subanalysis of the Prospective Randomized Amlodipine Survival Evaluation (PRAISE) trial, which included patients with severe HF of ischemic and nonischemic origins.[14] In another small, single-site study of a cohort of 551 patients with left ventricular systolic dysfunction, statin use was associated with improved 1-year survival and reduced urgent transplantation in both nonischemic and ischemic HF patients (91% versus 72%, $P<0.001$; and 81% versus 63%, $P<0.001$, respectively).[3] After multivariate adjustment, statin therapy remained an independent predictor of improved survival (HR, 0.41; 95% CI, 0.18 to 0.94). However, the small size and single-site nature of this study limited its generalizability. A recent retrospective Canadian study from the province of Ontario also showed beneficial association of statin therapy in HF, but its small size, combined with the data being from a single province again, limits validity.[4] In addition, a single-site study with 137 patients also showed mortality benefit in patients with diastolic HF.[5]

There are several possible mechanisms by which statin therapy may produce a benefit. Statins reduce cardiovascular events in patients with CAD or at high risk for CAD presumably by reducing atherosclerotic progression and plaque rupture. Although the antiatherosclerotic effects of statins are well studied, several smaller studies have demonstrated that statins reduce myocardial necrosis and preserve myocardial viability and ventricular function.[13,15] Most recently, statin use has been shown to be associated with a reduced incidence of atrial fibrillation,[16] a prevalent condition in elderly and an independent risk factor for mortality in patients with HF.[17] Statins have been demonstrated to have important roles in angiogenesis,[18,19] ventricular remodeling,[20–23] angiotensin II signaling, sympathetic nervous system activation,[24–27] oxidative stress,[28] inflammation,[29] thrombofibrinolysis,[30] and endothelial nitric oxide synthesis,[31–33] all of which have important implications in the HF patient.[34] Short-term statin therapy also has been shown to improve endothelial function in chronic HF patients, even after adjustment for cholesterol level.[35,36]

Although this is the largest study to date to assess the impact of statin therapy in a nationally representative cohort of older patients hospitalized with HF, there are outstanding issues to consider. This study was an observational study and does not have the strength of a randomized clinical trial, so its conclusions should be handled with important reservations.

TABLE 5. Cox Proportional-Hazards Analysis of Statin Treatment Effects on Mortality (3 Years From Discharge)

Model	HR	95% CI	*P*
Unadjusted	0.67	0.65–0.69	<0.001
Adjusted for age, race, and sex	0.76	0.74–0.79	<0.001
Adjusted for age, race, sex, and clinical characteristics	0.80	0.75–0.83	<0.001
Adjusted for age, race, sex, clinical characteristics, and physician specialty	0.80	0.75–0.82	<0.001
Adjusted for age, race, sex, clinical characteristics, physician specialty, and discharge medications	0.82	0.79–0.85	<0.001
Adjusted for age, race, sex, clinical characteristics, physician specialty, discharge medications, and hospital characteristics	0.82	0.79–0.85	<0.001

Although we have made robust adjustments for demographic, clinical, physician, and hospital factors, we cannot adjust for all the potential residual confounding factors. We did calculate the Pearson residuals to assess the residuals, which suggest that the models have been fitted appropriately. In addition, younger and perhaps healthier older persons could have been prescribed statins more often, but in our analysis, there were no remarkable effects of statin and age interaction on mortalities. Finally, we were not able to account for medication dose or compliance.

Conclusions

Our data demonstrate that statin therapy is associated with substantially better long-term survival in older patients with HF. These results are consistent with a large body of evidence supporting these agents in patients with HF, regardless of the presence or absence of atherosclerosis or cholesterol levels, and extend these findings to older persons. Given the high mortality rates associated with HF, statin therapy in these patients could have important public health implications. Randomized clinical trials are necessary to address the potential role of these agents in the significant proportion of patients with HF.

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Disclosures

Dr Foody has received honoraria from and served on the speakers' bureaus of Pfizer and Merck. Dr Masoudi has received honoraria from and served on the speakers' bureaus of Pfizer and AstraZeneca. The other authors report no conflicts.

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CLINICAL PERSPECTIVE

Although several small studies have suggested that statins may improve mortality in patients with heart failure (HF), whether these results are generalizable to a nationally representative sample of patients with HF remains unclear. Therefore, we evaluated the association between statin use and survival in 61 939 Medicare beneficiaries hospitalized with a primary discharge diagnosis of HF between April 1998 and June 2001. Of patients eligible for statins, only 16.7% received these medications on discharge. After demographic and clinical characteristics, in-hospital therapy, physician specialty, and hospital characteristics were accounted for, discharge statin therapy was associated with a nearly 20% reduction in 1- and 3-year mortality (HR, 0.80; 95% CI, 0.76 to 0.84; and HR, 0.82; 95% CI, 0.79 to 0.85, respectively). Reductions in mortality were observed regardless of total cholesterol level or coronary artery disease (CAD) status. These observational data suggest that statin therapy may be an important adjunct to more traditional HF therapies, including ACE inhibitors, angiotensin receptor blockers, and β-blockers. However, before the broad application of these findings, randomized clinical trials are required to determine prospectively whether statins will improve outcomes in the diverse group of patients with HF.