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Statin Therapy Is Associated With Improved Survival in Ischemic and Non-Ischemic Heart Failure

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OBJECTIVES This study aimed to investigate the impact of hydroxymethylglutaryl coenzyme A reductase inhibitor (statin) therapy in patients with advanced heart failure (HF).

BACKGROUND Although statins are known to reduce mortality in coronary artery disease (CAD), the impact of statin therapy in patients with HF has not been well studied. Both the potential risks and benefits of statins in HF have been described.

METHODS We studied a cohort of 551 patients with systolic HF (left ventricular ejection fraction [EF] ≤40%) referred to a single university center for clinical management and/or transplant evaluation. Survival without the necessity of urgent heart transplantation was determined.

RESULTS The patients' mean age was 52 ± 13 years; mean EF was 25 ± 7%. Forty-five percent of the cohort had CAD, and 45% were receiving statin therapy, including 73% and 22% of CAD and non-CAD patients with HF, respectively. Patients receiving statins were significantly older and more likely to be male, with higher rates of hypertension, diabetes, and smoking. The EF and cholesterol levels were similar between treated and non-treated patients. Statin use was associated with improved survival without the necessity of urgent transplantation in both non-ischemic and ischemic HF patients (91% vs. 72%, $p < 0.001$ and 81% vs. 63%, $p < 0.001$ at one-year follow-up, respectively). After risk adjustment for age, gender, CAD, cholesterol, diabetes, medications, hemoglobin, creatinine, and New York Heart Association functional class, statin therapy remained an independent predictor of improved survival (hazard ratio 0.41 95% confidence interval 0.18 to 0.94).

CONCLUSIONS Statin therapy is associated with improved survival in patients with ischemic and non-ischemic HF. Randomized trials are needed for confirmation of a therapeutic benefit. (J Am Coll Cardiol 2004;43:642–8) © 2004 by the American College of Cardiology Foundation

Hydroxymethylglutaryl coenzyme A reductase inhibitor (statin) therapy lowers morbidity and mortality in coronary artery disease (CAD) and other atherosclerotic vascular disease, as evidenced by multiple large-scale clinical trials (1–4). Additional analyses of these trials have shown that statin therapy also reduces the risk of developing heart failure (HF) (5,6). A reduction in cardiovascular events with statin therapy has been demonstrated irrespective of baseline low-density lipoprotein (LDL) cholesterol (3). Therefore, it is reasonable to hypothesize that statins would confer a survival benefit in patients with ischemic HF. Yet, the impact of statin therapy on HF progression has not been previously studied. The major clinical trials of statin therapy have generally excluded patients with symptomatic or severe HF (1–4).

Statins have therapeutic properties that are of potential benefit to patients with HF of ischemic and non-ischemic etiologies, irrespective of lipid levels. Statins may improve endothelial function, inhibit inflammatory cytokines, potentiate nitric oxide (NO) synthesis, restore impaired autonomic function, and reverse pathologic myocardial remodeling (7–12). On the other hand, concern has also been raised about the potential adverse effects of statins in HF (13,14). Low cholesterol levels are associated with poor outcomes in advanced HF (15,16), calling into question the safety of lipid-lowering therapy in this population. Furthermore, statins decrease levels of ubiquinone (coenzyme Q10), which may impact ventricular function and exercise tolerance in HF patients (13,14,17).

Statins are included as part of the medical regimen of only a portion of patients with CAD and HF. One-third of ischemic HF patients in one large population cohort (18) and between 11% to 45% of patients in large HF clinical trials were treated with statins (14). Based on autopsy data, up to 33% of the deaths in HF patients are related to acute coronary syndromes (19). If statin therapy is safe and effective in reducing acute coronary events in patients with HF, millions of HF patients who would benefit from such therapy are not currently being treated. Alternatively, if statins have adverse effects in HF, a large number of HF patients are being exposed unnecessarily.

In light of the controversy surrounding statin use in patients with HF, and without the results of ongoing clinical trials (14), we undertook the present study to evaluate the effect of statin therapy in a large, diverse cohort of patients treated for advanced HF of multiple etiologies at a single university center.

METHODS

Patients. The study cohort consisted of 623 consecutive patients referred to a specialized cardiomyopathy center at a university hospital for clinical HF management and/or heart

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Abbreviations and Acronyms

ACE = angiotensin-converting enzyme
CAD = coronary artery disease
CI = confidence interval
EF = ejection fraction
eNOS = endothelial nitric oxide synthase
HF = heart failure
HR = hazard ratio
LDL = low-density lipoprotein
NO = nitric oxide

transplantation evaluation between January 2000 and December 2002. Patients were excluded from analysis if their ejection fraction (EF) was >40% (n = 60) or if baseline data were incomplete (n = 12). The final patient cohort consisted of 551 patients. The Medical Institutional Review Board approved the medical record review.

Data collection. All patients were followed in a comprehensive HF management program, as previously described (20). Detailed information on the patients' medications and doses was recorded at the initial visit and every follow-up visit. Ejection fraction was determined by echocardiography obtained at the time of referral. Medications were determined by the patients' individual HF physician and/or referring physician; medications were not assigned in a randomized manner. Patients were considered to be receiving statin therapy if: 1) therapy was commenced before referral and continued throughout study period; or 2) therapy was started within three months after the referral date and continued throughout the study period.

Laboratory testing, echocardiography, and right heart catheterization occurred within six weeks of the initial referral date. Hemodynamic variables used in analyses were those obtained after optimal medical therapy had been instituted. Previous left heart catheterization reports and angiographic films were reviewed, or, if not done previously, left heart catheterization was performed. Significant CAD was defined as any single stenosis >70% of the cross-section lumen diameter of the involved artery on angiography. Patients were classified as having HF due to non-ischemic cardiomyopathy if they had no history of myocardial infarction and cardiac catheterization was without significant CAD.

End points. All-cause mortality or urgent transplantation (status 1A) was the primary end point of the study. Status 1A transplants were included in the primary end point, because these patients are expected to live less than one week without a transplant and are dependent on intravenous medication, ventricular assist device, or mechanical ventilation, as previously described (21). Non-urgent transplants (status IB and II) were coded as a non-fatal end of follow-up at the time of transplantation. Patients lost to follow-up were censored at the time they were last known to be alive and well.

Statistical analysis. Results are presented as the mean value ± SD for continuous variables and as the percentage of total patients for categorical variables. The independent samples *t* test and chi-square test were used for comparison of continuous and categorical variables, respectively. Survival curves were calculated by the Kaplan-Meier method. Univariate and multivariate Cox regression analyses were employed to calculate the estimated hazard ratio (HR) with 95% confidence interval (CI), where appropriate. The Statistical Package for Social Sciences (SPSS) for Windows, version 11.0 (Chicago, Illinois) was used for all analyses. For survival free from urgent transplantation, the sample size used in our study would allow the detection of a 20% mortality difference, with a power of 0.90 and an alpha level of 0.05.

RESULTS

Baseline characteristics of cohort. The age of the patients ranged from 18 to 84 years. The etiologies of HF included ischemic (45%), idiopathic (25%), valvular, alcoholic, and peripartum. Forty-five percent of the cohort was treated with a statin, including 73% and 22% of ischemic and non-ischemic HF patients, respectively. The characteristics of the cohort are shown in Table 1. The prevalence of individual statin and other lipid-lowering medications is outlined in Table 2.

Patients receiving statin therapy were older and more likely to be male compared with patients not receiving statin therapy. Patients receiving statins had higher rates of CAD, hypertension, diabetes, and smoking. The lipid levels were similar between patients treated and those not treated with statins. The characteristics of the statin and no-statin cohorts are detailed in Table 1.

Relationship between statin therapy and survival. During the follow-up period, there were 73 deaths (32 due to progressive HF, 23 sudden deaths, 2 due to myocardial infarction, and 16 unknown or other causes). There were 101 patients who received heart transplants (60 urgent and 41 non-urgent). Eighty-four patients (15%) were lost to follow-up. Actuarial survival free from urgent transplantation for the entire cohort was 75% at one year and 65% at two years.

Statin therapy was associated with significantly improved survival free from urgent transplantation. Survival without urgent transplantation at one year was 84% in statin-treated and 70% in patients not treated with statins (HR 0.45, 95% CI 0.30 to 0.67). The two-year survival rates were also significantly different; 79% in statin-treated patients and 61% in patients not treated with statins (HR 0.47, 95% CI 0.32 to 0.69). When excluding urgent transplants as an end point, the one-year all-cause mortality rate was 11% in patients receiving statins and 18% in those not receiving statins (HR 0.52, 95% CI 0.30 to 0.90) (Fig. 1). Table 3 outlines differences between survivors free from death or urgent transplantation versus non-survivors at one year, as well as the univariate HR of death or urgent transplantation for each variable. Non-survivors at one year were similar to

Table 1. Characteristics of the Study Cohort: Comparison Between Patients Treated With Statins and Patients Not Treated With Statins

	Total Cohort	Statin Treatment	No Statin Treatment	p Value*
Age (yrs)	52 ± 13	57 ± 11	48 ± 13	0.0001
Male (%)	76%	82%	70%	0.001
BMI (kg/m^2)	27.5 ± 6.2	28.2 ± 6.2	26.9 ± 6.2	0.03
NYHA class III (%)	44%	50%	39%	0.06
NYHA class IV (%)	33%	28%	37%	0.10
Ejection fraction (%)	25 ± 7	25 ± 7	24 ± 8	0.09
Peak $\dot{V}O_2$	13.8 ± 4.9	12.9 ± 3.9	14.8 ± 6.0	0.002
PCWP (mm Hg)	14 ± 5	15 ± 5	14 ± 4	0.12
Baseline history				
Ischemic etiology (%)	45%	73%	22%	0.0001
Smoking† history (%)	73%	80%	66%	0.006
Hypertension (%)	54%	64%	43%	0.0001
Diabetes (%)	24%	33%	16%	0.005
Baseline medications				
Beta-blocker (%)	74%	80%	69%	0.0001
ACEI or ARB (%)	89%	92%	87%	0.08
Spironolactone (%)	43%	39%	46%	0.12
Diuretics (%)	85%	89%	81%	0.006
Laboratory values				
Total cholesterol (mg/dl)	170 ± 57	173 ± 52	168 ± 61	0.34
LDL cholesterol (mg/dl)	100 ± 40	103 ± 42	98 ± 37	0.20
HDL cholesterol (mg/dl)	38 ± 15	38 ± 14	38 ± 16	0.89
Triglycerides (mg/dl)	166 ± 155	170 ± 119	163 ± 198	0.68
Sodium (mmol/l)	136 ± 5	137 ± 4	136 ± 5	0.004
Hemoglobin (g/dl)	13.2 ± 1.9	13.2 ± 1.8	13.2 ± 2.0	0.51
Albumin (g/dl)	3.7 ± 0.7	3.7 ± 0.6	3.6 ± 0.9	0.10
Creatinine (mg/dl)	1.5 ± 1.7	1.5 ± 1.3	1.6 ± 1.9	0.33

*Comparison between statin and no-statin cohorts. †Smoking refers to a previous or current history of smoking. Data are presented as the mean value ± SD or percentage of patients.

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BMI = body mass index; HDL = high density lipoprotein; LDL = low-density lipoprotein; NYHA = New York Heart Association; PCWP = pulmonary capillary wedge pressure; $\dot{V}O_2$ = oxygen consumption.

survivors in terms of age and gender. Non-survivors had significantly higher pulmonary capillary wedge pressures, lower left ventricular EF, lower total cholesterol levels, and lower hemoglobin levels. Non-survivors were significantly less likely to have been treated with beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, and statins. When the cohort was subclassified according to those alive, dead, or undergoing urgent or non-urgent transplantation at one-year follow-up, the rates of statin usage were 47%, 33%, 25%, and 63%, respectively.

Table 2. Prevalence of Lipid-Lowering Medication in the Study Cohort

None	281 (52.6%)
Statins	
Atorvastatin	150 (28.1%)
Simvastatin	56 (10.6%)
Pravastatin	30 (5.6%)
Fluvastatin	7 (1.3%)
Lovastatin	5 (0.6%)
Cerivastatin	1 (0.2%)
Other	
Gemfibrozil	3 (0.6%)
Niacin	2 (0.4%)
Fenofibrate	1 (0.2%)

Improved survival with statin therapy was observed in HF patients with both ischemic and non-ischemic HF etiologies (Fig. 1). Survival free from urgent transplantation in patients with ischemic HF at one year was 80% in statin-treated patients and 57% in patients not treated with statins (HR 0.35, 95% CI 0.19 to 0.62). A significantly higher one-year survival free from urgent transplantation was also demonstrated in patients with non-ischemic heart failure (90% vs. 71%; HR 0.27, 95% CI 0.11 to 0.69). There were

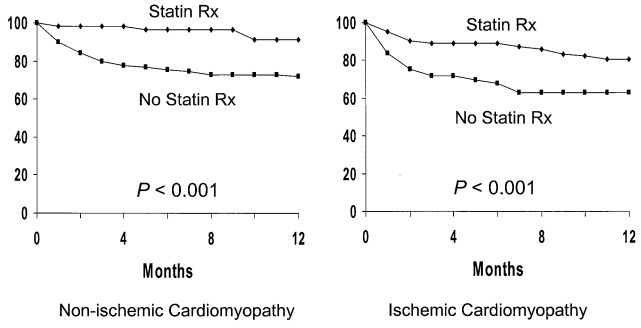

Figure 1. Kaplan-Meier curves demonstrate one-year survival (%) without the need for urgent heart transplantation in cohorts of non-ischemic (n = 298) and ischemic (n = 244) heart failure patients. Rx = therapy.

Table 3. Prediction of One-Year Mortality: Characteristics of Survivors Free From the Necessity of Urgent Transplantation Versus Non-Survivors

	Survivors (n = 437)	Non-Survivors (n = 113)	p Value*	Hazard Ratio (95% CI)†
Statin (%)	49	29	0.0001	0.45 (0.30–0.67)
Age (yrs)	52 ± 13	51 ± 13	NS	—
Male (%)	75	77	NS	—
NYHA class IV (%)	22	76	0.0001	8.46 (4.81–14.88)
Ejection fraction (%)	25 ± 7	23 ± 7	0.03	0.97 (0.95–1.00)
PCWP (mm Hg)	14 ± 4	16 ± 6	0.004	1.09 (1.03–1.16)
ACEI or ARB (%)	95	65	0.0001	0.13 (0.09–1.19)
Beta-blocker (%)	80	47	0.0001	0.25 (0.17–0.37)
Ischemic etiology (%)	49	48	NS	—
Total cholesterol (mg/dl)	178 ± 54	144 ± 58	0.0001	0.99 (0.98–0.99)
Hemoglobin (g/dl)	13.5 ± 1.8	12.5 ± 2.0	0.0001	0.79 (0.71–0.87)
Creatinine (mg/dl)	1.5 ± 1.8	1.6 ± 0.8	NS	—

*By the likelihood ratio test, Cox regression analysis. †Univariate hazard ratio per unit increase for continuous variables and hazard ratio of characteristic for categorical variables.
CI = confidence interval; NS = not significant; other abbreviations as in Table 1.

similar HRs for death from any cause, death from pump failure, and sudden death (Fig. 2).

Statin therapy was associated with a lower age- and gender-adjusted risk of mortality or urgent transplantation (Table 4). After adjustment for demographic and HF prognostic factors, including gender, age, medications, HF etiology, total cholesterol level, New York Heart Association functional class, hemoglobin, creatinine, and pulmonary capillary wedge pressure, the risk of death or urgent transplantation remained significantly lower in the statin cohort than in the no-statin cohort (Table 4). Furthermore, the association between statin therapy and improved survival free from urgent transplantation persisted in clinically significant subgroups of patients, including men and women, those with cholesterol above and below the median value (163 mg/dl), and those who did not receive heart transplants (Fig. 3). Baseline differences in beta-blocker therapy use could not fully explain the lower mortality risk seen with statin therapy, because a similar benefit (HR 0.35, 95% CI 0.17 to 0.72) was seen when the analysis was confined to HF patients treated with optimal HF medical therapy, including both ACE inhibitors and beta-blockers.

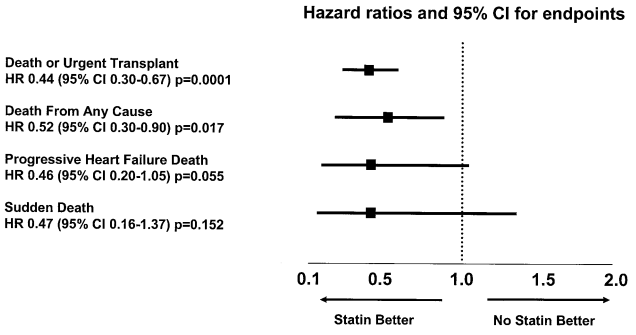

Figure 2. One-year hazard ratios (HRs) and 95% confidence intervals (CIs) for death or urgent transplantation, death from any cause, progressive heart failure death, and sudden death for patients receiving statins compared with those not receiving statins.

DISCUSSION

Although an abundance of clinical evidence supports statin therapy in CAD and other atherosclerotic vascular disease (1–4), the effect of statins on clinical outcomes in patients with HF has not previously been reported. The present study not only demonstrates the safety of statin use in advanced HF, but also shows a strong, independent association between statin therapy and improved survival of patients with both ischemic and non-ischemic HF. Despite the greater abundance of poor prognostic factors in the statin cohort, including CAD, hypertension, smoking, diabetes, and low oxygen consumption on cardiopulmonary exercise testing, statin use was associated with improved outcomes. Furthermore, the improved outcomes were seen regardless of cholesterol level, etiology of HF, or other HF medications. Despite the association between low total cholesterol and impaired HF prognosis seen in this population and reported elsewhere (15,16), patients receiving statins in this cohort had markedly better survival with less need for urgent heart transplantation. There are a variety of potential mechanisms that could account for these observations, including statin effects that may be independent of lipid lowering.

Statins and ischemic heart disease. The anti-atherothrombotic effects of statins clearly have potential for benefit in patients with CAD-associated HF. Based on autopsy data,

Table 4. HR of Death or Urgent Transplant for Statin Treatment Versus No Statin Treatment: Univariate and Multivariate Analyses

	One-Year HR	Two-Year HR
Univariate	0.45 (0.30–0.67)	0.47 (0.32–0.69)
Age- and gender-adjusted	0.44 (0.30–0.67)	0.47 (0.32–0.68)
Multivariate*	0.41 (0.18–0.94)	0.43 (0.20–0.94)

*Multivariate analysis includes gender, age, angiotensin-converting enzyme inhibitor, beta-blocker, heart failure etiology, total cholesterol level, New York Heart Association functional class, hemoglobin, creatinine, and pulmonary capillary wedge pressure after hemodynamically guided therapy.
HR = hazard ratio (95% confidence interval).

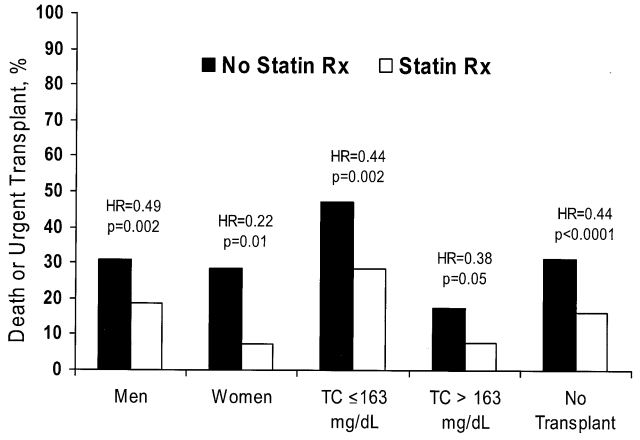

Figure 3. Two-year rates of death or urgent transplantation in statin versus no-statin cohorts. The benefit associated with statin therapy in the total cohort was compared with subgroups of men and women, those with cholesterol above and below the median level (163 mg/dl), and a subgroup excluding patients who underwent elective or urgent transplantation. HR = hazard ratio with statin therapy (Rx); TC = total cholesterol.

40% of the sudden deaths and 26% of the non-sudden cardiovascular deaths in patients with systolic HF were due to acute coronary syndromes, the majority of which were not diagnosed as acute coronary syndrome-related deaths until autopsy (19). Statins promote atherosclerotic plaque stabilization via inhibition of inflammatory macrophages, depletion of the lipid core, and strengthening of the fibrous cap. Statins have clearly been demonstrated to reduce atherothrombotic cardiovascular events in patients with clinically evident atherosclerosis, even in the setting of baseline LDL cholesterol levels of <100 mg/dl (3). Although patients with symptomatic HF have been excluded from these clinical trials, the mechanism for atherosclerotic plaque rupture and the impact of statins on plaque stabilization could reasonably be expected to be similar between patients with and those without HF. Patients with asymptomatic left ventricular dysfunction (EF 25% to 40%) in the Cholesterol And Recurrent Events (CARE) trial derived a similar pravastatin-related risk reduction as those patients without significant left ventricular dysfunction (4).

The anti-ischemic effects of statins may extend beyond plaque stabilization. Experimental studies have consistently demonstrated that statin treatment significantly reduces the extent of myocardial necrosis, preserves myocardial viability, and results in improved ventricular function in models of myocardial ischemia/reperfusion injury. Decreases in ischemic areas, repetitive stunning, and hibernation may lead to improvement of myocardial function (22). Other anti-ischemic characteristics of statins include improvement in coronary endothelial function and possibly neoangiogenesis (23–25).

Statins and myocardial remodeling. Recently, statins have been shown to have a direct impact on pathologic ventricular remodeling and angiotensin II signaling—effects that would have therapeutic potential not only for ischemic HF but also for HF in the absence of CAD. Rodent models of both ischemic and non-ischemic HF have shown statin therapy to be associated with reverse remodeling and prolonged survival (10,11,26,27). In models of HF after myocardial infarction, the pathologic correlates of reverse remodeling included a reduction of matrix metalloproteinase activity in mice treated with fluvastatin and reduced expression of collagen in rats treated with cerivastatin (10,25). In a non-ischemic model of pressure overload in rats with ascending aortic banding, statins prevented left ventricular hypertrophy development via *ras* signaling inhibition (26).

Statins and inflammation. Activation of inflammatory cytokines, such as tumor necrosis factor-alpha and interleukin-6, has been associated with worse symptoms and shortened survival in HF (28,29). Furthermore, cytokines may play a cytotoxic role in the pathophysiology of HF progression (30). Statins are now recognized as anti-inflammatory agents that downregulate inflammatory cytokines and C-reactive protein (7,9,31). Thus, statins may play a therapeutic role in HF via anti-inflammatory actions.

Statins and endothelial function/NO. Endothelial dysfunction of the systemic vasculature characterized by impaired vasodilation and increased vasoconstriction, is seen in HF, whether ischemic or non-ischemic, and may contribute to the exercise intolerance and end-organ dysfunction of chronic HF. Furthermore, endothelial NO synthesis has been shown to be diminished in HF (32). Statins improve endothelial function, an action likely mediated by enhancement of endothelial NO synthase (eNOS) activity (24). Statins have been demonstrated to activate the *Akt* pathway, resulting in a rapid increase in NO bioavailability. The effects of statins on NO and endothelium have therapeutic potential for chronic HF patients. Interestingly, in a recent report of an experimental model of infarct-induced HF, transgenic mice that overexpressed eNOS had better cardiac output, less pulmonary edema, and improved survival compared with non-transgenic mice (33). Statin therapy may have beneficial effects in heart failure through improved endothelial function and enhanced bioavailability of NO.

Statins and neurohormonal systems. Sympathetic nervous system activation, as indexed by plasma norepinephrine levels, is associated with HF severity as well as increased HF mortality (34). Recent animal studies suggest that statins have the ability to normalize sympatho-excitation in HF (12,35), suggesting another therapeutic action for statins in HF. In a recent report of rabbits with pacing-induced HF, administration of simvastatin decreased plasma norepinephrine levels and renal sympathetic nerve activity, as well as normalized baroreceptor responses (12).

Collectively, these studies provide plausible biologic mechanisms by which statins could exert cardiovascular protective effects in patients with advanced HF, thus reducing mortality and the need for urgent heart transplantations. These mechanisms are distinct from that of ACE inhibitors and beta-blockers, and the benefits of statin therapy would be expected to be additive to existing HF therapy, as observed in this study. Although the results of this study should only be regarded as hypothesis-generating, the 14% absolute risk reduction in mortality associated with statin

therapy in advanced HF at one year translates into seven patients as the number needed to treat to save one life or prevent one urgent transplantation. Given the large number of patients with HF and the magnitude of potential benefit with statin therapy, well-designed, prospective, randomized clinical trials are clearly needed. The Gruppo Italiano per lo Studio della Sopravivenza nell' Infarcto miocardico (GISSI) investigators are conducting a clinical trial to assess the impact of statins on mortality in HF, and the RosUvastatiN Impact on VEntricular Remodeling, LipidS, and CytokinEs (UNIVERSE) study is investigating the effects of statins on remodeling (14).

Study limitations. We acknowledge a number of limitations of our study. Our analysis was retrospective in nature, and allocation of statin therapy was not randomized. The duration and dosing of statins were not analyzed. Cholesterol changes due to statin therapy were not recorded. Propensity matching was not performed. Despite adjustment for baseline differences and an abundance of poor prognostic factors in the statin cohort, including older age, CAD, diabetes, and lower peak oxygen consumption, statin treatment could still be a surrogate for other unmeasured variables that reflect a higher quality of care and more aggressive treatment strategies. As such, a causal relationship between the observed associations with statin use and outcomes cannot be concluded. There was too infrequent use of other non-statin lipid-lowering agents to determine the relationship between the use of these agents and clinical outcome.

Conclusions. Our data suggest that statin therapy is safe in HF and furthermore is associated with improved outcomes. Statin therapy may represent a novel treatment for patients with HF, irrespective of HF etiology, LDL cholesterol levels, and the presence or absence of atherosclerosis. This study calls attention to the potential role of statins as HF therapy.

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