

# Statin Use and Survival Outcomes in Elderly Patients With Heart Failure

Joel G. Ray, MD, MSc; Yanyan Gong, MSc; Kathy Sykora, MSc; Jack V. Tu, MD, PhD

**Background:** Coronary artery disease is a leading cause of heart failure. Statins are efficacious drugs for the primary and secondary prevention of coronary heart disease, but their value in persons with heart failure remains unknown.

**Methods:** We performed a population-based retrospective cohort study involving the entire province of Ontario, Canada, restricting participants to those aged 66 to 85 years who were free of cancer and who survived at least 90 days following hospitalization for newly diagnosed heart failure. The primary study outcome was the risk of death from all causes, nonfatal acute myocardial infarction, or nonfatal stroke among persons newly dispensed statins (n=1146) relative to those who were not (n=27 682).

**Results:** The mean age of all participants was 76.5 years, and half were women. During the 7-year study period, death, acute myocardial infarction, or stroke occurred in 217 statin recipients (13.6 per 100 person-years) vs 12 299

nonrecipients (21.8 per 100 person-years; adjusted hazard ratio [HR], 0.72; 95% confidence interval [CI], 0.63-0.83). Most of the benefit from statins was related to a reduction in all-cause mortality (adjusted HR, 0.67; 95% CI, 0.57-0.78). No significant reduction was seen for subsequent myocardial infarction (adjusted HR, 0.81; 95% CI, 0.63-1.03) or stroke (adjusted HR, 0.81; 95% CI, 0.53-1.25).

**Conclusions:** Statin use is associated with a lower risk of death among seniors newly diagnosed as having congestive heart failure. While statin use has been previously shown to be efficacious in patients with coronary heart disease and stroke, we could not control for all prognostic risk factors in the present study, including left ventricular ejection fraction and serum lipid levels. Better evidence can direct clinicians about which patients with heart failure might benefit from these drugs.

*Arch Intern Med.* 2005;165:62-67

**Author Affiliations:** Department of Medicine, St Michael's Hospital, University of Toronto (Dr Ray); Programming and Biostatistics & Canadian Cardiovascular Outcome Research Team, Institute for Clinical Evaluative Sciences (Ms Gong); Canadian Cardiovascular Outcome Research Team, Institute for Clinical Evaluative Sciences (Ms Sykora); and Institute for Clinical Evaluative Science, Department of Medicine, Sunnybrook & Women's College Health Sciences Centre, University of Toronto (Dr Tu), Toronto, Ontario.  
**Financial Disclosure:** None.

**C**ORONARY ARTERY DISEASE is the leading cause of heart failure and left ventricular dysfunction in the Western world.<sup>1</sup> It is estimated that 50% of incident cases of heart failure in persons younger than 75 years are due to coronary artery disease.<sup>2</sup> Myocardial ischemia also plays an important role in cardiac remodeling, thereby worsening the prognosis in affected persons with heart failure.<sup>3</sup>

Statins are safe and efficacious drugs for the primary and secondary prevention of coronary heart disease<sup>4</sup> and stroke.<sup>5</sup> This benefit has been demonstrated in elderly patients,<sup>6</sup> as well as persons with diabetes mellitus<sup>7</sup> and hypertension.<sup>8</sup> In these randomized clinical trials, about a 25% relative risk (RR) reduction in most cardiovascular events was observed after 2 to 5 years of statin use compared with placebo, an effect independent of serum lipid concentration.

Because statins prevent the development of cardiovascular disease and death in high-risk groups,<sup>4-8</sup> some have questioned whether these drugs might benefit persons with heart failure.<sup>9</sup> We examined whether statin use is associated with a lower risk of death and major cardiovascular disease among adults newly diagnosed as having heart failure.

## METHODS

### STUDY POPULATION

We performed a retrospective population-based cohort study of adults aged 66 to 85 years residing in the province of Ontario, Canada. We used linked health care administrative databases covering over 1.4 million senior residents, all of whom were enrolled with the Ontario Health Insurance Plan. This universal insurance plan covers medical care and prescription drug costs for every Ontario senior citizen.

We considered all seniors newly hospitalized with a most responsible diagnosis of heart

failure between April 1, 1995, and December 31, 2001. We included individuals who survived at least 90 days after the index heart failure hospitalization (**Figure 1**). We excluded patients who were hospitalized either for heart failure within 36 months or any form of cancer within 365 days prior to the index heart failure hospitalization discharge date. We also omitted persons dispensed a statin within 365 days before hospital discharge, whose length of stay during the index heart failure admission was more than 60 days and who were directly transferred to a chronic care hospital, as well as those diagnosed as having cancer within 90 days following the index heart failure hospitalization (Figure 1).

## STUDY OUTCOMES AND DATA SOURCES

We evaluated statin use vs nonuse as the exposure of interest. Statin use was defined as the dispensation of at least 1 statin prescription within 90 days following the index heart failure hospitalization discharge date, whereas nonuse was the absence of a statin dispensation. The primary study outcome, defined a priori, was a composite of all-cause mortality, nonfatal acute myocardial infarction, or nonfatal stroke, arising at least 90 days after hospital discharge for heart failure. Individual secondary outcomes included death from all causes, nonfatal acute myocardial infarction, or nonfatal stroke.

The Ontario Drug Benefits Database was used to identify the medications each participant was dispensed before and during the observation period. Hospitalizations were identified using the Canadian Institute for Health Information Discharge Abstract Database to characterize subsequent events and comorbid illnesses, as well as to exclude events before the index heart failure admission. The Discharge Abstract Database contains the unique encrypted health care number, age and sex of the participant, date of admission, and up to 16 diagnoses, as coded by the *International Classification of Diseases, Ninth Revision (ICD-9)*. Participant age, sex, and out-of-hospital mortality were retrieved from the Ontario Registered Persons Database, which contains demographic information and encrypted health care numbers for all individuals eligible for Ontario Health Insurance Plan.

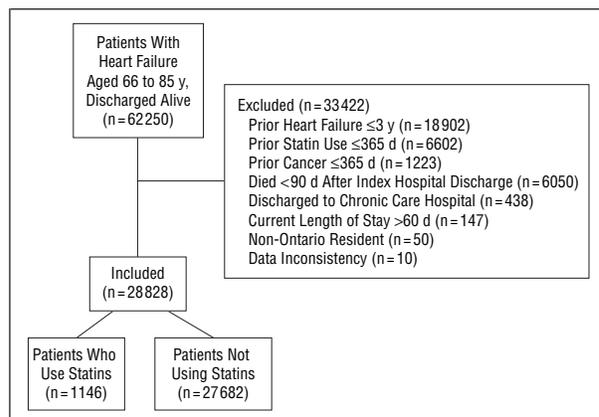
## STATISTICAL ANALYSIS

Characteristics between those with statin use and those without were compared using either a *t* test for continuous variables or the  $\chi^2$  test for categorical data. Time-to-event analyses were conducted using the Cox proportional hazards regression model to derive a hazard ratio (HR) and 95% confidence interval (CI) for all individual and composite outcomes among those with statin use relative to those without.

A participant was censored (ie, determined not to have had a primary or secondary study outcome event) at the point in time in which any of the following occurred:

1. Among those with statin use, more than 180 days elapsed between statin prescriptions, with the censoring date being 180 days after the last documented prescription
2. Among those without statin use, a statin was dispensed any time from 91 days onward after the index heart failure hospitalization discharge date
3. A participant was hospitalized with cancer at any time from 91 days onward after the index heart failure hospitalization discharge date, or
4. A participant reached the end of the period of March 31, 2002, without having experienced a primary or secondary study outcome event.

We censored for newly diagnosed cancer because malignancy accounts for 25% of all deaths in persons 65 years and



**Figure 1.** Flow diagram of eligible and included study participants.

older,<sup>10</sup> which could have influenced the likelihood of being dispensed a statin, as well as the risk of death.

The HR was adjusted for year; sex; age at the time of hospital discharge; the Deyo modified comorbidity index<sup>11</sup> (derived during the index heart failure hospitalization); diagnosed angina, myocardial infarction, stroke, atherosclerosis of the aorta or peripheral arteries, arterial embolism or thrombosis, atrial fibrillation or flutter, cardiomyopathy, hypertension or hypertensive heart disease, diabetes mellitus, dyslipidemia, or mitral or aortic valve disease; and receipt of either coronary angioplasty, coronary stent insertion, coronary artery bypass grafting, carotid endarterectomy, peripheral vascular bypass or peripheral artery endarterectomy, or heart valve surgery. These comorbid conditions and potential confounders were abstracted from the Discharge Abstract Database for all hospitalizations within 36 months before the index heart failure hospitalization, during the index heart failure hospitalization period, as well as within the 90-day period after the index hospitalization discharge date. Adjustment for medications (prescribed oral hypoglycemic agent, insulin, aspirin, clopidogrel, warfarin, angiotensin-converting enzyme inhibitor, angiotensin II receptor antagonist,  $\beta$ -antagonist, furosemide, long-acting nitrate, or spironolactone) was based on a respective Ontario Drug Benefits Database prescription between the index heart failure hospitalization discharge date and the end of the period of observation for each study participant.

Because patients with heart failure are prone to out-of-hospital sudden death,<sup>12-14</sup> we determined the relative proportion of all study deaths that occurred without concomitant admission to the hospital. To explore the relationship between statin use and out-of-hospital death, the same survival analysis was conducted as above, only we additionally censored for any individual who died while hospitalized.

All *P* values were 2-sided, at a significance level of .05. All statistical analyses were performed using SAS for UNIX, Version 8.2 (SAS Institute, Cary, NC). The 3 health care databases were linked anonymously using encrypted individual health card numbers, and the study was approved by the ethics review board of Sunnybrook and Women's College Health Sciences Centre, Toronto, Ontario.

## RESULTS

Of 62 250 seniors assessed for eligibility, 28 828 were included in the final cohort, of which 1146 (3.8%) were statin initiators and 27 682 noninitiators. The reasons for study exclusion are listed in Figure 1. The mean age of all final participants was 76.5 years, and about half were

**Table 1. Characteristics of Study Cohort According to Statin Use\***

Characteristic	Statin Use (n = 1146)	No Statin Use (n = 27 682)	P Value†
Age, y	73.9 ± 5.0	76.6 ± 5.4	<.001
Female sex	534 (46.6)	14 167 (51.2)	.002
Duration of follow-up, mean ± SD, person-months	16.6 ± 15.9	24.4 ± 20.5	<.001
Comorbidity index			
Mean ± SD	1.9 ± 0.9	1.8 ± 1.0	.30
Median (interquartile range)	2 (1-2)	2 (1-2)	NA
Previous angina	571 (49.8)	9587 (34.6)	<.001
Previous acute myocardial infarction	242 (21.1)	3002 (10.8)	<.001
Previous percutaneous coronary intervention or coronary artery bypass surgery	262 (22.9)	1874 (6.8)	<.001
Previous stroke	57 (5.0)	1091 (3.9)	.08
Previous carotid endarterectomy	8 (0.7)	130 (0.5)	.30
Previous valvular heart disease	148 (12.9)	3291 (11.9)	.30
Previous heart valve surgery	34 (3.0)	472 (1.7)	.001
Previous cardiomyopathy	74 (6.5)	1409 (5.1)	.04
Previous hypertension or hypertensive heart disease	527 (46.0)	9854 (35.6)	<.001
Previous aortic or peripheral artery atherosclerosis	32 (2.8)	466 (1.7)	.005
Previous arterial embolism/thrombosis	13 (1.1)	284 (1.0)	.70
Previous atrial fibrillation or atrial flutter	288 (25.1)	9294 (33.6)	<.001
Previous dyslipidemia	216 (18.8)	590 (2.1)	<.001
Previous diabetes mellitus	141 (12.3)	2452 (8.9)	<.001
Subsequent cancer	68 (5.9)	2513 (9.1)	<.001
Subsequently dispensed ACE inhibitors	1024 (89.4)	23 009 (83.1)	<.001
Subsequently dispensed angiotensin II receptor antagonists	203 (17.7)	3042 (11.0)	<.001
Subsequently dispensed spironolactone	296 (25.8)	6034 (21.8)	.001
Subsequently dispensed β-antagonists	763 (66.6)	10 431 (37.7)	<.001
Subsequently dispensed long-acting nitrate	673 (58.7)	13 752 (49.7)	<.001
Subsequently dispensed furosemide	1053 (91.9)	25 803 (93.2)	.08
Subsequently dispensed glucose-lowering drugs	164 (14.3)	3327 (12.0)	.02
Subsequently dispensed aspirin	620 (54.1)	11 538 (41.7)	<.001
Subsequently dispensed clopidogrel	54 (4.7)	414 (1.5)	<.001
Subsequently dispensed warfarin	411 (35.9)	10 483 (37.9)	.20

Abbreviations: ACE, angiotensin-converting enzyme; CI, confidence interval; HR, hazard ratio; NA, not applicable.

\*Data are given as number (percentage) of patients or mean ± SD value unless otherwise specified.

†The *t* test was used for continuous variables and the  $\chi^2$  test for categorical variables.

women. Those with statin use were 2.7 years younger than those without, were more frequently diagnosed as having angina (49.8% vs 34.6%) or acute myocardial infarction (21.1% vs 10.8%), and had undergone more revascularization procedures (22.9% vs 6.8%) within the previous 3 years (**Table 1**). Both groups were comparable in terms of mean comorbidity index (1.9 vs 1.8), but those using statins had higher rates of diagnosed hypertension (46.0 vs 35.6%), dyslipidemia (18.8% vs 2.1%) and diabetes mellitus (12.3% vs 8.9%). Those who began statin use more commonly received certain cardiac medications, including angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, spironolactone, β-antagonists, nitrates, and aspirin (Table 1).

The mean duration of censored follow-up was 16.6 months in the statin group and 24.4 months in the non-statin group. Death from any cause, nonfatal acute myocardial infarction, or nonfatal stroke occurred in 217 statin recipients (13.6 per 100 person-years) vs 12 299 nonrecipients (21.8 per 100 person years), equivalent to a crude HR of 0.60 (95% CI, 0.53-0.69) (**Table 2** and **Figure 2**). After adjusting for multiple potential confounders, the risk for the composite outcome remained significantly lower in association with initiated statins (HR, 0.72; 95% CI, 0.63-0.83), which was mostly related to a reduction

in all-cause mortality (adjusted HR, 0.67; 95% CI, 0.57-0.78) (Table 2). Of the 167 fatalities in the statin group, 67 (40.1%) occurred out of hospital, compared with 4710 of 11 250 deaths (41.9%) among the nonrecipients. The crude and adjusted HR for out-of-hospital death, comparing those using statins and those who did not, were 0.49 (95% CI, 0.39-0.63) and 0.68 (95% CI, 0.53-0.87), respectively.

Nonfatal myocardial infarction occurred in 68 statin recipients (4.1 per 100 person-years) compared with 2091 nonrecipients (3.7 per 100 person-years; crude HR, 1.05; 95% CI, 0.83-1.34). After adjusting for multiple factors, a nonsignificant protective effect was seen in association with dispensed statin use (HR, 0.81; 95% CI, 0.63-1.03) (Table 2). Stroke occurred less frequently but was not significantly reduced with statin use (adjusted HR, 0.81; 95% CI, 0.53-1.25) (Table 2)

## COMMENT

### OVERALL FINDINGS

Among seniors newly hospitalized for heart failure and who survived at least 3 months after discharge, we ob-

**Table 2. All-Cause Mortality, Acute Myocardial Infarction, and Stroke, Comparing New Statin Use With Nonuse Within a Cohort of Seniors With Recent-Onset Congestive Heart Failure**

Event	No. (Rate per 100 Person-years)		Statin Use vs No Statin Use	
	Statin Use (n = 1146)	No Statin Use (n = 27 682)	Crude HR (95% CI)	Adjusted HR* (95% CI)
Primary end point				
All-cause mortality, nonfatal acute myocardial infarction, or nonfatal stroke	217 (13.6)	12 299 (21.8)	0.60 (0.53-0.69)	0.72 (0.63-0.83)
Secondary end points				
All-cause mortality	167 (9.9)	11 250 (19.1)	0.50 (0.43-0.59)	0.67 (0.57-0.78)
Nonfatal acute myocardial infarction	68 (4.1)	2091 (3.7)	1.05 (0.83-1.34)	0.81 (0.63-1.03)
Nonfatal stroke	23 (1.3)	776 (1.3)	0.98 (0.65-1.49)	0.81 (0.53-1.25)

Abbreviations: CI, confidence interval; HR, hazard ratio.

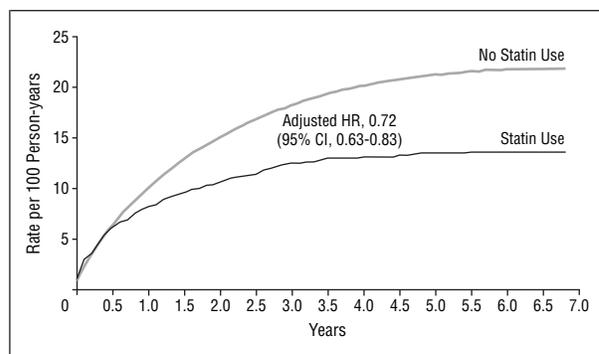
\*Adjusted for year; sex; age; comorbidity index; diagnosed angina, myocardial infarction, stroke, atherosclerosis of the aorta or peripheral arteries, arterial embolism or thrombosis, atrial fibrillation or flutter, cardiomyopathy, hypertension or hypertensive heart disease, diabetes mellitus, dyslipidemia, or mitral or aortic valve disease; receipt of either coronary angioplasty, coronary stent insertion, coronary artery bypass grafting, carotid endarterectomy, peripheral vascular bypass or peripheral artery endarterectomy, or heart valve surgery; or prescribed oral hypoglycemic agent, insulin, aspirin, clopidogrel, warfarin, angiotensin-converting enzyme inhibitor, angiotensin II receptor antagonist,  $\beta$ -antagonist, furosemide, long-acting nitrate, or spironolactone.

served about a 30% RR reduction of death, acute myocardial infarction, or stroke in association with new statin use. This benefit was mainly due to a significant reduction in all-cause mortality.

#### LIMITATIONS AND STRENGTHS

This study was not a randomized clinical trial, and its conclusions should be handled with important reservations. For example, younger, and perhaps healthier, seniors are more likely to be prescribed statins.<sup>15,16</sup> While we adjusted for age, sex, and comorbidity index,<sup>11</sup> data availability did not permit us to control for certain prognosticators, including left ventricular ejection fraction, serum lipid level, heart rate, or blood pressure,<sup>17,18</sup> any of which may have been more favorable among statin recipients. Because some studies have suggested that intrinsically low serum lipid levels may be a negative prognostic factor among patients with heart failure,<sup>19,20</sup> it is possible that those using statin may have been more ill. On the other hand, those new statin users were more commonly diagnosed as having previous myocardial infarction, diabetes mellitus, and hypertension, which are each associated with a higher risk of death among patients with heart failure.<sup>21-23</sup> About half of all potentially eligible patients with heart failure were excluded from our study, primarily because of a history of heart failure or previous statin use (Figure 1). Specifically, 19.8% of persons were excluded owing to the latter. The remainder composed a large group of community-dwelling seniors aged 66 to 85 years, all of whom had survived at least 90 days after hospital discharge, were without overt cancer, and had not received a statin in the 12 months preceding a first heart failure hospitalization. It is within this select group of patients with heart failure that our data might be most applicable.

The reliability of the administrative data set used herein was previously verified through random, blinded chart audit,<sup>24</sup> with 96% and 90% of cases meeting the Framingham<sup>25</sup> and Carlson<sup>26</sup> et al criteria for heart failure, respectively. While our definition of statin use would



**Figure 2.** Cumulative rate per 100 person-years of death or nonfatal acute myocardial infarction or stroke according to prescribed statin use. CI indicates confidence interval; HR, hazard ratio.

have produced less than precise boundaries of drug compliance over time,<sup>27</sup> nondifferential misclassification of drug use should typically underestimate the true relationship between prescribed statins and cardiovascular mortality.<sup>28</sup> Moreover, almost all statin prescriptions were likely accounted for in our study, since these medications are paid for under the universal Ontario Drug Benefits Plan. While we did not assess the propensity for statin use, the factors included in our multivariate analysis closely approximated those used within a propensity score that matched statin initiators to statin noninitiators and showed a protective effect against subsequent acute myocardial infarction.<sup>16</sup>

#### RELATION OF STUDY FINDINGS TO THE PUBLISHED LITERATURE

In several large randomized clinical trials of drug therapies for heart failure, 30% to 50% of all deaths were sudden, presumably due to ventricular arrhythmias.<sup>12-14</sup> In our study, about 40% of all deaths occurred out of hospital, although the actual mechanism of death was not described. More recent evidence suggests that acute coronary artery occlusion likely plays a greater role in arrhythmogenic death among patients with heart failure

than previously recognized. For example, in 1 prospective multicenter study of individuals with heart failure that masked assessment and postmortem examination to determine study outcomes, myocardial infarction explained 42.1% of all sudden deaths.<sup>29</sup> Moreover, 31% of patients originally thought to have a nonischemic cause of heart failure had significant coronary artery disease at autopsy.<sup>29</sup>

We saw a difference in survival between those using statins and those who did not after about 6 months of observation (Figure 2) that was similar to randomized clinical trials of  $\beta$ -blockers<sup>12,13</sup> and spironolactone<sup>14</sup> in patients with heart failure. It is plausible that statins may lower the risk of sudden death in elderly patients with heart failure, in part, by preventing acute coronary artery occlusion. In 1 prospective Swedish cohort study of patients younger than 80 years, and who experienced acute myocardial infarction, the RR for death was 0.75 (95% CI, 0.63-0.89).<sup>30</sup> In a second cohort study of 7220 individuals with 70% or greater coronary artery stenosis, mortality was most significantly reduced among statin recipients older than 80 years (HR, 0.50; 95% CI, 0.26-0.96).<sup>15</sup> While we did not observe a significant reduction in the risk of hospitalization for myocardial infarction or stroke with statin use, we observed a trend in that direction. Compared with nonrecipients, myocardial infarction and stroke were more common among the statin recipients before study entry but were rarer than death thereafter. Two small observational reports that support our findings were published after the present study was completed.<sup>31,32</sup> Both examined persons with chronic heart failure and observed between a 59%<sup>31</sup> and 62%<sup>32</sup> RR reduction of death with statin use.

There are several conceivable biological mechanisms for why statins may specifically protect patients with heart failure from death. Nonhuman animal experiments have found that statins attenuate cardiac remodeling in the presence of induced myocardial infarction<sup>33</sup> and hypertensive heart disease.<sup>34</sup> Statins have also been shown to normalize sympathetic outflow and reflex regulation in exposed rabbits,<sup>35</sup> which might benefit patients with heart failure, in whom excess catecholamine activity increases the risk of death.<sup>12,13</sup> More speculatively, the antithrombotic effects of statins<sup>36</sup> may also be protective against the hypercoagulable state often seen in patients with heart failure.<sup>37</sup>

Epidemiological evidence also supports a specific effect of statins in the prevention and evolution of heart failure. In the Scandinavian Simvastatin Survival Study (4S) trial, 4444 patients with coronary heart disease and no history of heart failure were originally randomized to simvastatin or placebo.<sup>23</sup> In a post hoc analysis by the 4S investigators, the subsequent rates of heart failure were 8.3% and 10.3%, respectively (RR, 0.80; 95% CI, 0.67-0.97). Furthermore, among those who developed heart failure, the respective mortality rates were 25.5% and 31.9% (RR, 0.57; 95% CI 0.38-0.87), 40% of which were sudden deaths.<sup>23</sup> In a recently completed randomized placebo-controlled clinical trial, simvastatin was also associated with significant improvement in New York Heart Association functional class and left ventricular ejection fraction among 63 patients with nonischemic, dilated cardiomyopathy.<sup>38</sup>

It is also noteworthy that statin use was associated with a reduced risk of developing new-onset atrial fibrillation in another study of adults with stable coronary artery disease (adjusted RR, 0.37; 95% CI, 0.18-0.76),<sup>39</sup> given that atrial fibrillation is also an independent risk factor for death in patients with heart failure.<sup>21,22</sup>

## CLINICAL RAMIFICATIONS

Patients with heart failure likely to benefit from statin therapy are those in whom the drug has already been shown to be efficacious, including persons with established coronary artery or cerebrovascular disease, diabetes mellitus, and hypertension.<sup>4-8,23</sup> In elderly persons with heart failure, but who lack these risk factors, the argument for using statins is less convincing. A conservative approach would be to wait for the publication of more compelling evidence. On the other hand, given the extremely high mortality rate in persons with heart failure, some might recommend statin use<sup>23</sup> even with the knowledge that the drugs are expensive and not without adverse effects and that the small potential to do harm remains.

## FUTURE RESEARCH

Observational research should be directed at not only confirming a protective effect of statins in persons with heart failure but also at testing whether these drugs attenuate blood levels of highly sensitive C-reactive protein<sup>40</sup> and brain natriuretic peptide,<sup>41</sup> which are each negative prognostic markers in heart failure. Completed clinical trials might be used to assess whether the triggering of implantable cardioverter defibrillators, or the need for antiarrhythmic agents, is altered by statin use in patients. It remains uncertain if an observational study such as ours, in which administrative data were used, can generate comparable treatment effects with that seen in randomized clinical trials, as some suggest.<sup>42</sup> The Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA) study is expected to assign nearly 5000 patients with chronic symptomatic heart failure to rosuvastatin or matching placebo, but it will not be completed for several years.<sup>43</sup> Until then, the decision to prescribe a statin should remain patient focused, with the relatively low risk of drug-related adverse effects balanced against its expense, as well as the potential impact on quality and extension of life.

**Accepted for Publication:** September 9, 2004.

**Correspondence:** Joel G. Ray, MD, MSc, Department of Medicine, Inner City Health Research Programme, St Michael's Hospital, 30 Bond St, Toronto, Ontario, Canada M5B 1W8 (rayj@smh.toronto.on.ca).

**Acknowledgment:** Ahmed Bayoumi, MD, provided helpful comments on the data analysis.

## REFERENCES

1. Gheorghiadu M, Bonow RO. Chronic heart failure in the United States: a manifestation of coronary artery disease. *Circulation*. 1998;97:282-289.
2. Fox KF, Cowie MR, Wood DA, et al. Coronary artery disease as the cause of incident heart failure in the population. *Eur Heart J*. 2001;22:228-236.

3. Pfeffer MA, Braunwald E. Ventricular remodeling after myocardial infarction: experimental observations and clinical implications. *Circulation*. 1990;81:1161-1172.
4. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet*. 2002;360:7-22.
5. Corvol JC, Bouzamondo A, Sirol M, Hulot JS, Sanchez P, Lechat P. Differential effects of lipid-lowering therapies on stroke prevention: a meta-analysis of randomized trials. *Arch Intern Med*. 2003;163:669-676.
6. Shepherd J, Blauw GJ, Murphy MB; PROSPER study group. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet*. 2002;360:1623-1630.
7. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet*. 2003;361:2005-2016.
8. 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;361:1149-1158.
9. Ashton E, Liew D, Krum H. Should patients with chronic heart failure be treated with "statins"? *Heart Fail Monit*. 2003;3:82-86.
10. Statistics Canada, Population and Public Health Branch. Leading causes of death and hospitalization in Canada. Ottawa, Ontario: Health Canada; 1997.
11. Deyo RA, Cherklin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol*. 1992;45:613-619.
12. Packer M, Bristow MR, Cohn JN, et al; US Carvedilol Heart Failure Study Group. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. *N Engl J Med*. 1996;334:1349-1355.
13. CIBIS-II Investigators and Committees. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet*. 1999;353:9-13.
14. Pitt B, Zannad F, Remme WJ, et al; Randomized Aldactone Evaluation Study Investigators. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med*. 1999;341:709-717.
15. Allen Maycock CA, Muhlestein JB, Horne BD, et al; Intermountain Heart Collaborative Study. Statin therapy is associated with reduced mortality across all age groups of individuals with significant coronary disease, including very elderly patients. *J Am Coll Cardiol*. 2002;40:1777-1785.
16. Seeger JD, Walker AM, Williams PL, Saperia GM, Sacks FM. A propensity score-matched cohort study of the effect of statins, mainly fluvastatin, on the occurrence of acute myocardial infarction. *Am J Cardiol*. 2003;92:1447-1451.
17. Curtis JP, Sokol SI, Wang Y, et al. The association of left ventricular ejection fraction, mortality, and cause of death in stable outpatients with heart failure. *J Am Coll Cardiol*. 2003;42:736-742.
18. 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;290:2581-2587.
19. 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;8:216-224.
20. Rauchhaus M, Clark AL, Doehner W, et al. The relationship between cholesterol and survival in patients with chronic heart failure. *J Am Coll Cardiol*. 2003;42:1933-1940.
21. Mosterd A, Cost B, Hoes AW, et al. The prognosis of heart failure in the general population: The Rotterdam Study. *Eur Heart J*. 2001;22:1318-1327.
22. Blackledge HM, Tomlinson J, Squire IB. Prognosis for patients newly admitted to hospital with heart failure: survival trends in 12 220 index admissions in Leicestershire 1993-2001. *Heart*. 2003;89:615-620.
23. Kjekshus J, Pedersen TR, Olsson AG, Faergeman O, Pyorala K. The effects of simvastatin on the incidence of heart failure in patients with coronary heart disease. *J Card Fail*. 1997;3:249-254.
24. Jong P, Gong Y, Liu PP, Austin PC, Lee DS, Tu JV. Care and outcomes of patients newly hospitalized for heart failure in the community treated by cardiologists compared with other specialists. *Circulation*. 2003;108:184-191.
25. Ho KK, Anderson KM, Kannel WB, et al. Survival after the onset of congestive heart failure in Framingham Heart Study subjects. *Circulation*. 1993;88:107-115.
26. Carlson KJ, Lee DC, Goroll AH, et al. An analysis of physicians' reasons for prescribing long-term digitalis therapy in outpatients. *J Chronic Dis*. 1985;38:733-739.
27. Jackevicius CA, Mamdani M, Tu JV. Adherence with statin therapy in elderly patients with and without acute coronary syndromes. *JAMA*. 2002;288:462-467.
28. Brenner H, Savitz DA, Gefeller O. The effects of joint misclassification of exposure and disease on epidemiologic measures of association. *J Clin Epidemiol*. 1993;46:1195-1202.
29. Uretsky BF, Thygesen K, Armstrong PW, et al. 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;102:611-616.
30. Stenestrand U, Wallentin L; Swedish Register of Cardiac Intensive Care (RIKS-HIA). Early statin treatment following acute myocardial infarction and 1-year survival. *JAMA*. 2001;285:430-436.
31. Horwich TB, MacLellan WR, Fonarow GC. Statin therapy is associated with improved survival in ischemic and non-ischemic heart failure. *J Am Coll Cardiol*. 2004;43:642-648.
32. Mozaffarian D, Nye R, Levy WC. Statin therapy is associated with lower mortality among patients with severe heart failure. *Am J Cardiol*. 2004;93:1124-1129.
33. Hayashidani S, Tsutsui H, Shiomi T, et al. Fluvastatin, a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor, attenuates left ventricular remodeling and failure after experimental myocardial infarction. *Circulation*. 2002;105:868-873.
34. Hasegawa H, Yamamoto R, Takano H, et al. 3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors prevent the development of cardiac hypertrophy and heart failure in rats. *J Mol Cell Cardiol*. 2003;35:953-960.
35. Pliquet RU, Cornish KG, Peuler JD, Zucker IH. Simvastatin normalizes autonomic neural control in experimental heart failure. *Circulation*. 2003;107:2493-2498.
36. Rosenson RS. Non-lipid-lowering effects of statins on atherosclerosis. *Curr Cardiol Rep*. 1999;1:225-232.
37. Lip GY, Gibbs CR. Does heart failure confer a hypercoagulable state? Virchow's triad revisited. *J Am Coll Cardiol*. 1999;33:1424-1426.
38. 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;108:839-843.
39. Young-Xu Y, Jabbour S, Goldberg R, et al. Usefulness of statin drugs in protecting against atrial fibrillation in patients with coronary artery disease. *Am J Cardiol*. 2003;92:1379-1383.
40. Vasan RS, Sullivan LM, Roubenoff R, et al; Framingham Heart Study. Inflammatory markers and risk of heart failure in elderly subjects without prior myocardial infarction: the Framingham Heart Study. *Circulation*. 2003;107:1486-1491.
41. de Lemos JA, McGuire DK, Drazner MH. B-type natriuretic peptide in cardiovascular disease. *Lancet*. 2003;362:316-322.
42. Concato J, Shah N, Horwitz RJ. Randomized, controlled trials, observational studies, and the hierarchy of research designs. *N Engl J Med*. 2000;342:1887-1892.
43. Dunselman P, Hjalmarson A, Kjekshus J, McMurray J, Waagstein F; Executive Committee of the CORONA trial. The statin wars [letter]. *Lancet*. 2003;362:1854.