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ORIGINAL RESEARCH

HEART FAILURE AND CARDIOMYOPATHIES

Impact of Statin Therapy in Heart Failure Patients

Results of a Large Real-World Experience

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ABSTRACT

BACKGROUND The use of statins in patients with heart failure (HF) is controversial. In patients without HF, statins reduce atherosclerotic cardiovascular disease (ASCVD) risk, including HF-related events. However, in some large studies, no benefit was seen in statin-treated HF patients.

OBJECTIVES The purpose of this study was to determine the impact of statin therapy in HF with reduced ejection fraction (HFrEF).

METHODS Intermountain Healthcare medical records identified patients with a HF diagnosis and an ejection fraction of ≤40%. Patients prescribed and not prescribed a statin were compared for major adverse cardiovascular events (MACE) (death, myocardial infarction, stroke) (median of 4.5 years follow-up). Statin use was defined as use at or after a HF diagnosis but at least 60 days before MACE or end of follow-up. Cox proportional hazards regression was used to determine the relationship between statin use and outcomes.

RESULTS A total of 15,010 patients (n = 9,641 [64%] on statins) were studied. Statin use was associated with more frequent ASCVD risk factors yet a lower risk of MACE risk (adjusted HR: 0.53; 95% CI: 0.51-0.56; $P < 0.0001$). Benefit was similar for primary and secondary prevention patients and for prior and new statin prescriptions. Using time-varying hazard ratio analysis, the longer the patient was on a statin, the greater the reduction in risk of MACE ($P < 0.0001$).

CONCLUSIONS These results suggest a potential benefit of selective statin use in the real-world management of HFrEF patients with ASCVD or at high ASCVD risk. (JACC Adv 2023;2:100385) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

The use of statins (HMG-CoA-reductase inhibitors) in patients with heart failure (HF) is controversial.[1-4] In patients without HF, statins reduce the risk of atherosclerotic cardiovascular disease (ASCVD) including HF-related events.[5-10] In contrast, no benefit was observed in statin-treated HF patients in 2 randomized, controlled trials: CORONA (Controlled Rosuvastatin Multinational Study in Heart Failure) and GISSI-HF (Gruppo di Ricerca Heart Failure).[11,12] However, issues with

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ABBREVIATIONS AND ACRONYMS

ASCVD = atherosclerotic cardiovascular disease

CABG = coronary artery bypass graft

CAD = coronary artery disease

HF = heart failure

HFrEF = HF with reduced ejection fraction

HR = hazard ratio

LDL-C = low-density lipoprotein cholesterol

MACE = major adverse cardiovascular events

MACE+ = MACE plus incident HF hospitalization

MI = myocardial infarction

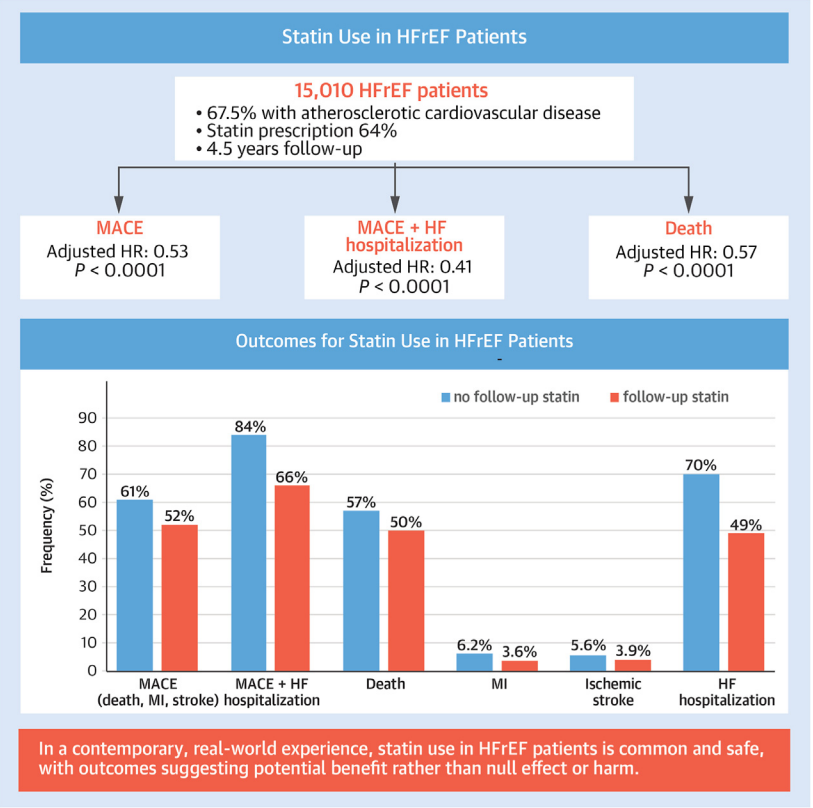
PCI = percutaneous coronary intervention

generalizability of these trials have been raised that may limit their applicability to general clinical practice.[4,13]

Given strong evidence for the broad treatment benefits of statins for ASCVD reduction documented prior to CORONA and GISSI-HF,[5] including from observational studies in HF,[14] a major concern is raised for the possibility of selection bias against enrolling patients at high individual ASCVD risk and with statin-preventable event reduction in these randomized trials, which may have had an important impact on trial outcomes.[12,13,15,16] Characteristics of concern in these trials include advanced age, advanced HF stages, low percentage of ischemic HF patients, low frequency of ischemic events, and high frequency of treatment discontinuations (eg, 31% in GISSI-HF).[12] Furthermore, in clinical practice, treatment with statins continues to be common, that is, reported to be one-half or more of HF patients.[17]

As a result of ongoing controversy and uncertainties about risk/benefit of statins in HF, current international guidelines provide a mixed message. They support selective use in high-risk patients with ASCVD but do not recommend universal application in otherwise statin-qualified patients.[1,7] Therefore, given the uncertainty of benefit and safety of statins in HF patients, we analyzed the impact of statin therapy on outcomes in patients with HF with reduced ejection fraction (HFrEF) in a contemporary, large, single health care system.

CENTRAL ILLUSTRATION Real-World Experience With Statin Use in HFrEF Patients: Comparative MACE, HF Hospitalizations, and Death vs No Statin Use



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Results suggest safety and a potential benefit of selective statin use in the management of HFrEF patients With ASCVD or at high ASCVD Risk.
ASCVD = atherosclerotic cardiovascular disease; HF = heart failure; MACE = major adverse cardiovascular event.

METHODS

STUDY AIMS AND INSTITUTIONAL REVIEW BOARD APPROVAL. The primary study aim was to assess the impact of statin therapy on major adverse cardiovascular events (MACE) in real-world practice in patients with HFrEF within Intermountain Healthcare (**Central Illustration**). Secondary aims included comparisons of HF hospitalization and independent components of the primary endpoint by statin use. Tertiary analyses included outcomes by new vs ongoing statin prescription and by duration of statin therapy. This retrospective database study was approved by the Intermountain Institutional Review Board with a waiver of consent.

INTERMOUNTAIN HEALTHCARE. Intermountain Healthcare is a nonprofit, integrated health care system that included 24 hospitals, 215 clinics, and an affiliated health insurance company in Utah, Idaho, and Nevada at the time of the study. Intermountain Healthcare has an extensive and long-standing (>25 years) centralized electronic medical records system, the enterprise data warehouse. The study used a retrospective observational cohort design. Intermountain Medical Center, the flagship referral hospital of Intermountain Healthcare, has an advanced HF/transplant service, including specialists in the medical, device, and surgical care of HF patients whose management requires advanced care beyond that provided by general cardiologists and internists. However, the study population was not limited to patients cared from by the HF/transplant service.

STUDY POPULATION. To identify the study population, the Intermountain Healthcare enterprise data warehouse was searched between January 1, 2000, and December 31, 2019, for patients with a HF diagnosis and a documented reduced left ventricular ejection fraction of ≤40% on HF presentation. The index date was defined as the date that the patient first had both a clinical diagnosis of HF and a documented left ventricular ejection fraction of ≤40%. Statin use was defined as use at, or any time after a HF diagnosis with an ejection fraction ≤40%, but prior to 60 days before a MACE or end of follow-up. Documentation, timing, and duration of statin prescriptions were determined from the medical records. Patients were stratified by primary and secondary ASCVD risk, that is, whether they had a prior history of myocardial infarction (MI); ischemic stroke; or myocardial, cerebrovascular, or peripheral arterial revascularization.

TABLE 1 Baseline Characteristics Stratified by Statin Use

	No Follow-Up Statin (n = 5,369)	Follow-Up Statin (n = 9,641)	*P* Value
Secondary prevention	53.4% (n = 2,866)	75.4% (n = 7,273)	–
Primary prevention	46.6% (n = 2,503)	24.6% (n = 2,368)	–
Age, y	67.3 ± 17.6	68.1 ± 13.4	0.002
Male	58.6%	70.2%	<0.0001
Race			<0.0001
White	87.9%	90.3%	
Black	1.9%	1.2%	
Hispanic	2.1%	1.8%	
Pacific Islander	2.0%	1.7%	
American Indian	1.0%	0.7%	
Asian	1.2%	1.0%	
Unknown	3.9%	3.3%	
Hypertension	72.9%	83.6%	<0.0001
Hyperlipidemia	42.1%	73.4%	<0.0001
Diabetes	29.2%	45.3%	<0.0001
Depression	21.1%	23.6%	0.001
CAD	51.8%	74.4%	<0.0001
Prior MI	14.4%	25.0%	<0.0001
COPD	19.0%	20.7%	0.01
Asthma	14.8%	15.8%	0.14
PAD	4.2%	6.0%	<0.0001
Prior stroke	4.8%	6.5%	<0.0001
Renal disease	25.0%	28.8%	<0.0001
Dialysis	3.1%	3.0%	0.58
AF	40.9%	39.9%	0.23
Prior ablation for AF	3.7%	3.6%	0.77
Prior cardioversion	6.6%	7.9%	0.004
Pacemaker	4.7%	6.2%	<0.0001
History of cancer	14.2%	14.1%	0.81
Sleep apnea	19.6%	28.1%	<0.0001
Aortic valve disease	6.1%	6.2%	0.78
Mitral valve disease	6.4%	6.4%	0.98
Pulmonary hypertension	25.2%	24.0%	0.10
Liver disease	4.7%	4.6%	0.68
EF (%)	28.3 ± 8.2	28.9 ± 7.9	<0.0001
BNP, n = 11,092	1404.2 ± 1235.1 (median: 1,120)	1263.4 ± 1137.0 (median: 939)	<0.0001
Pre-statin lipids, N = 6,289	n = 280	n = 6,009	
Total cholesterol	158.3 ± 42.9	154.0 ± 45.9	0.12
LDL-C	93.4 ± 33.0	89.3 ± 35.5	0.06
HDL-C	38.5 ± 12.4	38.3 ± 13.0	0.78
Triglycerides	132.4 ± 78.1 (median: 111)	135.0 ± 120.9 (median: 108)	0.62
Median days to starting statin	–	5 (range: −2,604 to 6,648)[a]	–
Median length of follow-up during statin use (d)	–	907 (range: 60-6,250)[a]	–
Prior statin use	23.1%	58.6%	<0.0001

Value are % or mean ± SD unless otherwise indicated. [a]Negative numbers reflect starting statin prior to HF diagnosis.

AF = atrial fibrillation; BNP = B-type natriuretic peptide; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; EF = ejection fraction; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; PAD = peripheral arterial disease.

STUDY ENDPOINTS. The primary endpoint was a composite of MACE, defined as all-cause death, nonfatal MI, or nonfatal ischemic stroke during follow-up. A first secondary MACE endpoint added

TABLE 2 Statin Dosing Details

Statin name prescribed (n = 7,996)	
Atorvastatin	3,185
Cerivastatin	<11[a]
Fluvastatin	29
Lovastatin	195
Pitavastatin	<11[a]
Pravastatin	769
Rosuvastatin	470
Simvastatin	3,339
Statin intensity prescribed (n = 7,960)	
Low	2,181
Moderate	3,478
High	2,301

[a]Frequencies <11 are not reported to be compliant with privacy policy.

the incidence HF hospitalization (MACE+). Other secondary endpoints also included the individual components of the primary endpoint and the endpoints in subgroups defined as at primary or at secondary ASCVD risk, that is, patients without or those with a history of an ASCVD diagnosis or event (eg, MI, stroke, peripheral arterial disease, revascularization), respectively. Prospective tertiary analyses included outcome by new vs ongoing statin prescription and outcome by duration of statin therapy. We compared these MACE outcomes at a median of 4.5 years (range <1-20 years) of follow-up.

STATISTICAL CONSIDERATIONS. The chi-square statistic and Student's *t*-test were used to compare differences in baseline and clinical characteristics among patients taking and not taking a statin. The nonparametric Mann-Whitney test was used to evaluate when parameters were not normally distributed. The chi-square statistic was used to compare differences in outcomes among the statin groups. Cox proportional hazards regression (SPSS, version 24.0) analysis was used to determine hazard ratios (HRs) of follow-up statin use on the outcomes. The covariables used in the model were identified a priori and included baseline characteristics, comorbidities, and medications. See Supplemental Table 1 for the variables that remained in the parsimonious models for each of the outcomes. The primary analysis was whether the patient received a statin prescription at HFrEF diagnosis or at any time afterward but at least 60 days prior to a MACE. Secondary analyses included stratifications by a history of an ASCVD diagnosis (ie, for primary vs secondary prevention), a history of or no history of statin use, and by length of time on statin therapy. The time-varying covariate of time on statin therapy was created by multiplying the days on statin therapy with statin therapy in Cox regression.[18] A *P* value of ≤0.05 was considered significant.

TABLE 3 Frequency of Outcomes and Hazard Ratios for Heart Failure Patients Using vs Not Using Statins During Follow-Up

	Outcome Frequencies		
	No Follow-Up Statin	Follow-Up Statin	*P* Value
MACE (death, MI, stroke)	3,246 (60.5%)	5,024 (52.1%)	<0.0001
MACE + HF hospitalization	7,149 (83.9%)	4,270 (65.8%)	<0.0001
Death	2,793 (56.6%)	5,075 (50.4%)	<0.0001
MI	328 (6.2%)	347 (3.6%)	<0.0001
Ischemic stroke	289 (5.6%)	387 (3.9%)	<0.0001
HF hospitalization	5,937 (69.9%)	3,208 (49.2%)	<0.0001

Statin vs No Statin (Referent)	Univariable	Multivariable
MACE	0.63 (0.60-0.66), $P < 0.0001$	0.53 (0.51-0.56), $P < 0.0001$
MACE + HF hospitalization	0.48 (0.47-0.50), $P < 0.0001$	0.41 (0.39-0.43), $P < 0.0001$
Death	0.57 (0.52-0.62), $P < 0.0001$	0.57 (0.51-0.62), $P < 0.0001$
MI	0.45 (0.39-0.53), $P < 0.0001$	0.41 (0.34-0.48), $P < 0.0001$
Ischemic stroke	0.55 (0.47-0.64), $P < 0.0001$	0.54 (0.46-0.63), $P < 0.0001$
HF hospitalization	0.48 (0.46-0.50), $P < 0.0001$	0.41 (0.39-0.43), $P < 0.0001$

Values are n (%) or HR (95% CI) unless otherwise indicated.

HF = heart failure; MACE = major adverse cardiovascular event (death, MI, or stroke); MI = myocardial infarction.

RESULTS

STUDY DEMOGRAPHICS. A total of 15,010 patients met inclusion criteria and were evaluated in this retrospective observational study. Of study subjects, 9,641 (64%) were treated with a statin at study entry or during follow-up. Baseline demographics are shown in Table 1 by statin use. Age averaged 67.8 years, 66.0% were men, 89.4% were White, 25.6% smoked, and 67.5% had a history of ASCVD. Cardiovascular risk factors (male, hyperlipidemia, hypertension, diabetes, history of ASCVD) were common and were found in a greater proportion of those treated with a statin. However, pre-statin lipid levels were well matched. Average left ventricular ejection fraction was severely reduced and clinically similar in both groups (28.3%, no statin; 28.9%, statin).

Details of statin dosing are shown in Table 2. The most frequently prescribed statins were simvastatin, atorvastatin, pravastatin, and rosuvastatin (Table 2). Statin dose intensity was low in 27%, moderate in 44%, and high in 29% (Table 2).

STUDY OUTCOMES. The frequency of outcomes and HRs for MACE during follow-up by statin use are shown in Table 3 and summarized in the Central Illustration. Despite having a greater burden of

ASCVD risk factors, statin users had a lower risk of MACE during a median follow-up of 4.5 years, even after adjusting for differing baseline characteristics (adjusted HR: 0.53; 95% CI: 0.51-0.56; $P < 0.0001$). Statins also significantly improved MACE+. Assessment of individual MACE and MACE+ endpoints showed that death, nonfatal MI, nonfatal stroke, and HF hospitalization individually were lower in the statin-treated group (Table 3).

SUBGROUP AND SENSITIVITY ANALYSES. The impact of statin use for primary ASCVD prevention is shown in Table 4 and for secondary prevention in Table 5. Statin use was associated with benefit in both prevention groups. Statins were prescribed to 48.6% (n = 2,368) of the 4,871 patients in the primary prevention HF cohort, and this was associated with a multivariable adjusted HR of 0.53 (95% CI: 0.49-0.59). In the secondary prevention HF cohort of 9,139 patients, 79.6% (n = 7,273) were prescribed a statin, and this was associated with a similarly beneficial multivariable HR of 0.53 (95% CI: 0.50-0.57). Rates of each individual MACE endpoint as well and HF hospitalizations were lower in statin-treated patients both in the primary and the secondary prevention cohorts.

In another analysis, follow-up statin use was associated with a lower risk of MACE both in those with and without a history of statin use prior to the diagnosis of HF (Figure 1). By time-varying covariate analysis, the longer a patient was on a statin, the lower the risk of MACE (HR: 0.08, $P < 0.0001$).

DISCUSSION

In this large, single health care system experience, which system offers advanced HF services, statin treatment in patients with HFrEF was common (64% of subjects), and outcomes were favorable. Although statin use was associated with a greater burden of baseline ASCVD risk factors, it also was associated with a lower risk of MACE during follow-up, including after adjustment for the differing baseline characteristics. Risk was lower not only for 2 definitions of MACE but for each of its components (death, nonfatal MI, nonfatal stroke, and HF hospitalization). Benefit was observed both for the primary and for the secondary risk cohort and for prior/ongoing as well as new/post-entry statin prescription. Furthermore, the longer the patient was on a statin, the greater the reduction in risk of a cardiovascular event. These multiple observations are mutually supportive of a beneficial impact of statin therapy in HFrEF patients clinically selected for treatment. Furthermore, no adverse safety signals associated with treatment were reported.

TABLE 4 Baseline Characteristics and Long-Term Outcomes Among a Primary ASCVD Prevention Heart Failure Population Stratified by Statin Use (N = 4,871)

	No Follow-Up Statin (n = 2,503)	Follow-Up Statin (n = 2,368)	*P* Value
Age	61.0 ± 19.0	61.5 ± 14.9	0.31
Male	53.9%	61.6%	<0.0001
Race			0.04
White	84.4%	87.4%	
Black	2.9%	1.8%	
Hispanic	2.2%	2.3%	
Pacific Islander	3.1%	2.3%	
American Indian	1.0%	0.8%	
Asian	1.6%	1.4%	
Unknown	4.8%	4.0%	
Hypertension	61.8%	69.7%	<0.0001
Hyperlipidemia	24.7%	46.6%	<0.0001
Diabetes	19.0%	33.2%	<0.0001
Depression	19.6%	20.7%	0.31
COPD	13.2%	14.1%	0.37
Asthma	15.1%	15.7%	0.61
Renal disease	19.7%	17.9%	0.11
Dialysis	2.1%	1.5%	0.12
AF	31.6%	27.1%	0.001
Prior ablation	2.9%	2.1%	0.07
Prior cardioversion	5.2%	4.5%	0.02
Pacemaker	3.0%	1.9%	0.02
Prior cancer	11.6%	10.9%	0.45
Sleep apnea	16.2%	24.5%	<0.0001
Aortic valve disease	3.6%	3.3%	0.56
Mitral valve disease	5.0%	3.7%	0.02
Pulmonary hypertension	22.9%	19.2%	0.001
Liver disease	4.6%	4.1%	0.39
EF (%)	27.5 ± 8.5	27.5 ± 8.3	0.85
BNP, n = 1,658	1,382.5 ± 1,186.7 (median: 1,094)	1,187.6 ± 1,090.9 (median: 888)	<0.0001
Pre-statin lipids, n = 1,566	n = 96	n = 1,470	
Total cholesterol	160.6 ± 43.0	167.2 ± 49.1	0.20
LDL-C	95.7 ± 32.4	100.2 ± 36.9	0.25
HDL-C	40.2 ± 12.5	38.9 ± 13.5	0.37
Triglycerides	124.2 ± 65.7 (median: 106)	145.0 ± 173.2 (median: 113)	0.72
Median days to starting statin	–	52 (range: −2,604 to 6,401)	–
Median length of follow-up statin use (d)	–	1,028 (range: 60-5,712)	–
Prior statin use	7.2%	26.0%	<0.0001

Continued on the next page

LITERATURE INSIGHTS AND COMPARISONS. Statins (HMG-CoA-reductase inhibitors) received intensive investigative attention during the 1990s and the first decade of the current millennium, and randomized clinical trials firmly established the role of statins in ASCVD prevention. A 2005 meta-analysis of 14 randomized trials in 90,056 patients demonstrated that statin therapy could reduce the 5-year incidence of major coronary events, revascularization, and stroke by about one-fifth per mmol/L reduction in low-density lipoprotein cholesterol (LDL-C), and this

TABLE 4 Continued

	Outcome Frequencies		
	No Follow-Up Statin	Follow-Up Statin	*P* Value
MACE	1,190 (47.5%)	878 (37.1%)	<0.0001
MACE + HF hospitalization	2,617 (75.4%)	755 (53.9%)	<0.0001
Death	1,035 (43.9%)	914 (36.3%)	<0.0001
MI	103 (4.2%)	49 (2.0%)	<0.0001
Stroke	117 (4.8%)	87 (3.6%)	0.03
HF hospitalization	2,234 (64.5%)	632 (45.0%)	<0.0001

Statin vs No Statin (Referent)	Univariable	Multivariable
MACE	0.54 (0.49-0.58), $P < 0.0001$	0.53 (0.49-0.59), $P < 0.0001$
MACE + HF hospitalization	0.45 (0.42-0.49), $P < 0.0001$	0.42 (0.38-0.45), $P < 0.0001$
Death	0.57 (0.52-0.62), $P < 0.0001$	0.57 (0.51-0.62), $P < 0.0001$
MI	0.35 (0.25-0.49), $P < 0.0001$	0.32 (0.23-0.46), $P < 0.0001$
Ischemic stroke	0.52 (0.39-0.70), $P < 0.0001$	0.49 (0.36-0.66), $P < 0.0001$
HF hospitalization	0.47 (0.43-0.51), $P < 0.0001$	0.42 (0.38-0.46), $P < 0.0001$

Values are mean ± SD, %, n (%), or HR (95% CI) unless otherwise indicated. Negative numbers reflect starting statin prior to HF diagnosis.

AF = atrial fibrillation; ASCVD = atherosclerotic cardiovascular disease; BNP = B-type natriuretic peptide; COPD = chronic obstructive pulmonary disease; EF = ejection fraction; HDL-C = high-density lipoprotein cholesterol; HF = heart failure; LDL-C = low-density lipoprotein cholesterol; MACE = major adverse cardiovascular event; MI = myocardial infarction.

benefit was largely independent of the initial lipid profile.[5] A 2010 update, which included 26 trials comprising 170,000 patients, confirmed this benefit and demonstrated that further reductions in LDL-C achieved by more intensive therapy safely produced additional reductions in cardiovascular events.[19] The JUPITER (Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin) (2008) provided a strong impetus for the treatment of high-risk primary prevention subjects (ie, with elevated high-sensitivity C-reactive protein), demonstrating a 44% reduction in the primary ischemic event endpoint with rosuvastatin 20 mg daily.[6]

Although HF patients were poorly represented in early statin trials, these observational studies suggested safety and benefit.[20] However, disappointing results followed in 2 randomized, controlled trials, CORONA and GISSI-HF. Although no adverse safety signals were observed, cardiovascular benefit was not demonstrated. The CORONA trial enrolled 5,011 patients with ischemic systolic HF and age 60 years or more to rosuvastatin 10 mg daily or placebo and followed them for an average of 33 months.[11] Expected reductions in LDL-C were seen, and no adverse safety concerns were observed. However, a significant reduction in the primary endpoint of cardiovascular death, nonfatal MI, or nonfatal stroke was not achieved (HR: 0.92; CI: 0.83-1.02; $P = 0.12$) although a reduction in cardiovascular hospitalizations was noted.[11] The subsequent GISSI-HF trial enrolled 4,574 patients with HF classes 2 to 4 of nonischemic or ischemic etiology and with or without reduced ejection fraction and, similarly, randomized them to rosuvastatin 10 mg daily or placebo.[12] Over a follow-up of 3.9 years, the expected reductions in LDL-C occurred, and no adverse safety concerns were raised, but neither death nor the combination of death and cardiovascular hospitalization was reduced.[12]

To what extent these results are generalizable to general clinical practice has been a source of controversy.[4,13] For example, a 2019 systematic review of 17 studies, including 2 randomized clinical trials and 15 prospective cohort studies comprising 88,100 patients, provided evidence of statin benefit for patients with HF, including 18 to 23% reductions in all-cause and cardiovascular mortality and cardiovascular hospitalization. Our large real-world observational experience supports this proposed benefit of statins in HF.

Lee et al[21] assessed the impact of statin therapy in patients with HF across the spectrum of ejection fractions treated by Kaiser Permanente in California. Statins were beneficial in HFpEF patients, but the trend to reduction in mortality did not reach significance in the HFrEF cohort (HR: 0.86; $P = 0.054$); rate ratio for HF hospitalization was 0.92. Their population differed from ours with a smaller proportion of whites (49% vs 89%) and with a smaller percentage with coronary artery disease (CAD)/ASCVD (30.5% vs 57.4%), followed for a shorter time (2.5 years). These differing characteristics may explain, at least in part, the differing extent of statin impact on outcomes.

Given ongoing controversy and uncertainties about risk/benefit of statins in HF, current international guidelines provide a mixed message.[1,7] The European Society of Cardiology guidelines indicate that the routine use of statins in patients with HF without other indications for their use (eg, CAD) is not recommended. However, they do recommend treatment in patients at high ASCVD risk in order to reduce HF hospitalizations.[1] The American College of Cardiology/American Heart Association cholesterol management guideline gives use of statins its lowest class of recommendation (IIb) for HF with reduced ejection fraction attributable to ischemic heart disease with a reasonable life expectancy.[7]

MECHANISTIC CONSIDERATIONS. Both beneficial effects and harmful potential have been proposed for the therapeutic application of statins in HF. Benefits might originate not only from lipid-lowering and anti-atherosclerotic effects but also from any of a number of pleotropic actions (eg, antioxidant, anti-

inflammatory, antiarrhythmic).[22-25] On the other hand, adverse potential, including reductions in muscular and aerobic performance, reductions in circulating coenzyme Q10, and prosarcopenic effects of statins have been raised, which might be of particular relevance in the HF population.[26-28] Reassuringly, no differential safety signals have been reported in either randomized trials or clinical registry or observational studies, nor did our observational study identify any.

The key controversy of statins in HF thus relates to the question of benefit, both as a drug class and as drug subclasses. Specifically, some have reported that lipophilic statins (eg, atorvastatin) may have a more favorable effect in HF patients than hydrophilic statins (eg, rosuvastatin).[13,29] At the time of this study, only a minority of patients were taking rosuvastatin, so we are unable to further address this proposal.

Clinical trials and observational or registry studies cannot definitively elucidate biological mechanisms of benefit (or harm), which require separate mechanistic trials. However, the possibility that discrepancies between the 2 randomized trials, our trial results, and prior registry and observational studies could be due to study design issues deserves exploration. One concern is for selection biases against enrolling patients at high individual ASCVD risk and/or at risk for statin-preventable events in these trials, which could have had an important impact on trial outcomes.[12,13,15,16] Trial subject characteristics considered to potentially explain the lack of benefit in CORONA and GISSI-HF include advanced age (eg, mean 73 years in CORONA), advanced HF stages (ie, high percentage of classes 2 and 3), a low percentage of ischemic HF patients (ie, in GISSI-HF), populations with a low frequency of ischemic events (reduced power to show benefit), and a high frequency of treatment discontinuations (eg, 31% in GISSI-HF).[11,12]

As age and severity of HF advance, the proportion of deaths due to ASCVD causes diminishes substantially and is overtaken by competing risks.[4,13] These competing mortality risks include end-stage HF, sudden arrhythmic death, renal failure, and cancer, to name a few. As the proportion of statin-responsive events declines, the power to discern a treatment effect in moderate-sized studies such as CORONA and GISSI-HF also declines.

An additional concern is investigator selection bias of the kind we refer to as the "equipoise bias" or "equipoise paradox." If the expectation of benefit is strong in clinicians' minds for certain patients or patient subsets, an important bias exists to not enroll them in a placebo-controlled trial but to treat them outside of the trial. Several examples of "equipoise bias" have been observed in revascularization trials. For example, in the BARI (Bypass Angioplasty Revascularization Investigation) trial, which tested coronary artery bypass graft (CABG) surgery to percutaneous coronary intervention (PCI) revascularization in patients with multivessel CAD, 1,829 of 4,039 qualified patients were randomized, and the other 2,010 patients made up a registry. BARI physicians were able to select PCI rather than CABG for 65% of these registry patients, who underwent PCI

TABLE 5 Results in Secondary ASCVD Prevention Heart Failure Population (N = 10,139)

	No Follow-Up Statin (n = 2,866)	Follow-Up Statin (n = 7,273)	*P* Value
Age	73.0 ± 14.2	70.1 ± 12.1	0.31
Male	62.7%	73.0%	<0.0001
Race			0.27
White	87.9%	90.3%	
Black	1.9%	1.2%	
Hispanic	2.1%	1.8%	
Pacific Islander	2.0%	1.7%	
American Indian	1.0%	0.7%	
Asian	1.2%	1.0%	
Unknown	3.9%	3.3%	
Hypertension	82.7%	88.2%	<0.0001
Hyperlipidemia	57.2%	82.1%	<0.0001
Diabetes	38.1%	49.3%	<0.0001
Depression	22.5%	24.5%	0.03
COPD	24.0%	22.8%	0.20
Asthma	14.7%	15.7%	0.22
CAD	97.1%	98.6%	<0.0001
Prior MI	26.9%	33.2%	<0.0001
PAD	6.7%	7.5%	0.12
Prior stroke	9.0%	8.6%	0.57
Renal disease	29.6%	32.4%	0.007
Dialysis	4.0%	3.5%	0.16
AF	49.0%	44.1%	<0.0001
Prior ablation	4.3%	4.0%	0.52
Prior cardioversion	7.9%	9.1%	0.05
Pacemaker	6.1%	7.6%	0.01
Prior cancer	16.6%	15.2%	0.08
Sleep apnea	22.5%	29.2%	<0.0001
Aortic valve disease	8.3%	7.2%	0.05
Mitral valve disease	7.5%	7.3%	0.63
Pulmonary hypertension	27.2%	25.6%	0.09
Liver disease	4.9%	4.8%	0.79
EF (%)	29.0 ± 7.9	29.4 ± 7.7	0.03
BNP, n = 7,366	1,425.1 ± 1,280.1	1,289.1 ± 1,151.1	<0.0001
Pre-statin lipids, n = 4,723	n = 184	n = 4,539	
Total cholesterol	157.1 ± 42.9	149.7 ± 44.0	0.02
LDL-C	92.2 ± 33.2	85.8 ± 34.2	0.01
HDL-C	37.6 ± 12.3	38.1 ± 12.8	0.64
Triglycerides	136.5 ± 83.5 (median: 116.0)	131.7 ± 97.8 (median: 107.0)	0.18
Median days to starting statin	–	2 (range: −2,422 to 6,648)	–
Median length of follow-up statin use (d)	–	905 (range: 62-6,250)	–
Prior statin use	37.0%	69.1%	<0.0001

Continued on the next page

TABLE 5 Continued

	Outcome Frequencies		
	No Follow-Up Statin	**Follow-Up Statin**	***P* Value**
MACE	2,056 (71.7%)	4,146 (57.0%)	<0.0001
MACE + HF hospitalization	4,532 (89.7%)	3,515 (69.1%)	<0.0001
Death	1,758 (68.1%)	4,161 (55.1%)	<0.0001
MI	225 (8.0%)	298 (4.1%)	<0.0001
Stroke	172 (6.3%)	300 (4.0%)	<0.0001
HF hospitalization	3,703 (73.7%)	2,576 (50.4%)	<0.0001

Statin vs No Statin (Referent)	**Univariable**	**Multivariable**
MACE	0.52 (0.50-0.55), $P < 0.0001$	0.53 (0.50-0.57), $P < 0.0001$
MACE + HF hospitalization	0.42 (0.40-0.44), $P < 0.0001$	0.40 (0.38-0.41), $P < 0.0001$
Death	0.54 (0.51-0.57), $P < 0.0001$	0.59 (0.55-0.62), $P < 0.0001$
MI	0.35 (0.29-0.42), $P < 0.0001$	0.29 (0.24-0.34), $P < 0.0001$
Ischemic stroke	0.49 (0.41-0.60), $P < 0.0001$	0.43 (0.35-0.52), $P < 0.0001$
HF hospitalization	0.44 (0.41-0.46), $P < 0.0001$	0.40 (0.38-0.43), $P < 0.0001$

Values are mean ± SD, %, n (%), or HR (95% CI) unless otherwise indicated. Negative numbers reflect starting statin prior to HF diagnosis

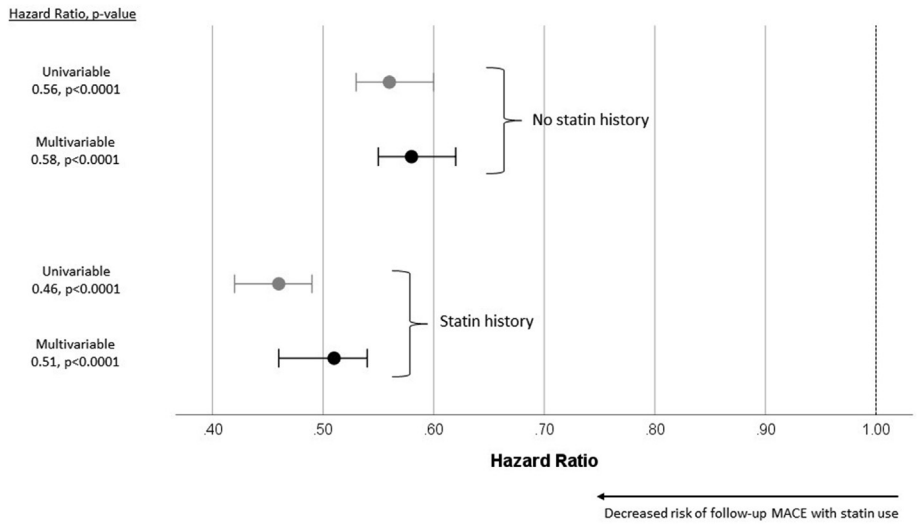
AF = atrial fibrillation; ASCVD = atherosclerotic cardiovascular disease; BNP = B-type natriuretic peptide; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; EF = ejection fraction; HDL-C = high-density lipoprotein cholesterol; HF = heart failure; LDL-C = low-density lipoprotein cholesterol; MACE = major adverse cardiovascular event; MI = myocardial infarction, PAD = peripheral arterial disease.

revascularization without compromising long-term survival, even though the outcomes of PCI were inferior to CABG in randomized patients. The extent to which equipoise bias underlies CORONA and GISSI-HF results deserves further consideration.

CLINICAL IMPLICATIONS. We have confirmed a high percentage of statin prescriptions in HF patients treated within Intermountain Healthcare, similar to other reports.[17] Given this, we are reassured by confirmation of: 1) a lack of a safety signal; and 2) a strong benefit signal in our observational study. Thus, we did not find evidence to recommend changes to the current practice pattern with respect to statin prescription in HF patients.

STRENGTHS AND LIMITATIONS. The study has the strength of its large size and relatively homogeneous approach to therapy within a single health care system. It also benefits from the long-term use of a sophisticated electronic health care record system, which has allowed for clinical evaluation over an extended period of time. In common with all nonrandomized observational studies, our study is subject to potential selection biases and unresolved confounding. We did not have access to cause of death, so that substituting all-cause for cardiovascular mortality likely weakened our MACE and HF outcome comparisons. Also, we did not have access to pharmacy claims data, and, therefore, we do not have consistent information on the adherence to statin use between caregiver visits. Our study population is predominantly of European-American (Caucasian) racial/ethnic heritage, and results may not apply

FIGURE 1 Univariable and Multivariable Hazard Ratios for MACE for Follow-Up Statin Use Stratified by History of Statin Use Prior to HF Diagnosis



HF = heart failure; MACE = major adverse cardiovascular event.

equally to other racial/ethnic groups. Despite having many covariables available for adjustment and efforts made to create parsimonious models (Supplemental Table 1), residual confounding may still exist. Information such as diet, exercise, mental health, and other behaviors may have been helpful in determining whether there were other differences between the groups but were not available.

CONCLUSIONS

The results of this large health care system observational study suggest a potential benefit of selective statin use in the real-world management of HFrEF patients with ASCVD or at high ASCVD risk. These results support ongoing selective use of statins in the HFrEF population and deserve further validation in additional real-world experience and in pragmatic, randomized clinical trials.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Statin treatment in patients with HFrEF is associated with a lower risk of MACE during follow-up. This benefit is observed both in the primary and for the secondary risk cohorts. Furthermore, the longer the patient was on a statin, the greater the reduction in risk of a cardiovascular event.

COMPETENCY IN PATIENT CARE: The use of statins in patients with HF is controversial. Discussions with the patient about the potential benefit of statin therapy should be made.

TRANSLATIONAL OUTLOOK: Although this is an observational study, it provides additional evidence of statin benefit in HF patients and the need for future pragmatic, clinical trials.

REFERENCES

1. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021;42:3599-3726.

2. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report for the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2022;79:e263-e421.

3. Fonarow G. Statins and n-3 fatty acid supplementation in heart failure. *Lancet*. 2008;372:1195-1196.

4. Masoudi FA. Statins for ischemic systolic heart failure. *N Engl J Med*. 2007;357:2301-2304.

5. Baigent C, Keech A, Kearney PM, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet*. 2005;366:1267-1278.

6. Ridker PM, Danielson E, Fonseca FA, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med*. 2008;359:2195-2207.

7. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2019;73(24):e285-e350.

8. Chou R, Dana T, Blazina I, Daeges M, Jeanne TL. Statins for prevention of cardiovascular disease in adults: evidence report and systematic review for the US Preventive Services Task Force. *JAMA*. 2016;316:2008-2024.

9. Afilalo J, Majdan AA, Eisenberg MJ. Intensive statin therapy in acute coronary syndromes and stable coronary heart disease: a comparative meta-analysis of randomised controlled trials. *Heart*. 2007;93:914-921.

10. Preiss D, Campbell RT, Murray HM, et al. The effect of statin therapy on heart failure events: a collaborative meta-analysis of unpublished data from major randomized trials. *Eur Heart J*. 2015;36:1536-1546.

11. Kjekhus J, Apetrei E, Barrios V, et al. Rosuvastatin in older patients with systolic heart failure. *N Engl J Med*. 2007;357:2248-2261.

12. Tavazzi L, Maggioni AP, Marchioli R, et al. Effect of rosuvastatin in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. *Lancet*. 2008;372:1231-1239.

13. Bielecka-Dabrowa A, Bytyçi I, Von Haehling S, et al. Association of statin use and clinical outcomes in heart failure patients: a systematic review and meta-analysis. *Lipids Health Dis*. 2019;18:188.

14. Anker SD, Clark AL, Winkler R, et al. Statin use and survival in patients with chronic heart failure—results from two observational studies with 5200 patients. *Int J Cardiol*. 2006;112:234-242.

15. Feit F, Brooks MM, Sopko G, et al. Long-term clinical outcome in the bypass angioplasty revascularization investigation registry. Comparison with the randomized trial. *Circulation*. 2000;101:2795-2802.

16. Rogers JK, Jhund PS, Perez AC, et al. Effect of rosuvastatin on repeat heart failure hospitalizations: the CORONA trial (controlled rosuvastatin multinational trial in heart failure). *J Am Coll Cardiol HF*. 2014;2:289-297.

17. Kosuma P, Jedsadayanmata A. Prevalence and predictors of statin treatment among patients with chronic heart failure at a tertiary-care center in Thailand. *Clin Med Insights Cardiol*. 2019;13:1179546819855656.

18. Austin PC. Generating survival times to simulate Cox proportional hazards models with time-varying covariates. *Stat Med*. 2012;31:3946-3958.

19. Baigent C, Blackwell L, Emberson J, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet*. 2010;376:1670-1681.

20. Foody JM, Shah R, Galusha D, Masoudi FA, Havranek EP, Krumholz HM. Statins and mortality among elderly patients hospitalized with heart failure. *Circulation*. 2006;113:1086-1092.

21. Lee MS, Duan L, Clare R, Hekimian A, Spencer H, Chen W. Mortality in patients with heart failure and preserved versus reduced left ventricular ejection fraction. *Am J Cardiol*. 2018;122:405-412.

22. Wang CY, Liao JK. Current advances in statin treatment: from molecular mechanisms to clinical practice. *Arch Med Sci*. 2007;3:S91–S96.

23. Albert MA, Danielson E, Rifai N, Ridker PM. Effect of statin therapy on C-reactive protein levels: the pravastatin inflammation/CRP evaluation (PRINCE): a randomized trial and cohort study. *JAMA*. 2001;286:64–70.

24. Ray KK, Cannon CP, Cairns R, et al. Relationship between uncontrolled risk factors and C-reactive protein levels in patients receiving standard or intensive statin therapy for acute coronary syndromes in the PROVE IT-TIMI 22 trial. *J Am Coll Cardiol*. 2005;46:1417–1424.

25. Brown JH, Del Re DP, Sussman MA. The Rac and rho hall of fame: a decade of hypertrophic signaling hits. *Circ Res*. 2006;98:730–742.

26. Ashton E, Windebank E, Skiba M, et al. Why did high-dose rosuvastatin not improve cardiac remodeling in chronic heart failure? Mechanistic insights from the UNIVERSE study. *Int J Cardiol*. 2011;146:404–407.

27. Banach M, Serban C, Ursoniu S, et al. Statin therapy and plasma coenzyme Q10 concentrations–a systematic review and meta-analysis of placebo-controlled trials. *Pharmacol Res*. 2015;99:329–336.

28. Bielecka-Dabrowa A, Fabis J, Mikhailidis DP, et al. Prosarcopenic effects of statins may limit their effectiveness in patients with heart failure. *Trends Pharmacol Sci*. 2018;39:331–353.

29. Lipinski MJ, Cauthen CA, Biondi-Zoccai GG, et al. Meta-analysis of randomized controlled trials of statins versus placebo in patients with heart failure. *Am J Cardiol*. 2009;104:1708–1716.

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APPENDIX For a supplemental table, please see the online version of this paper.