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Statin therapy impact on Long-Term outcomes in acute heart Failure: Retrospective analysis of hospitalized patients

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ABSTRACT

Background: Statin therapy is well-established for treating hyperlipidemia and ischemic heart disease (IHD), but its role in Acute Decompensated Heart Failure (ADHF) remains less clear. Despite varying clinical guidelines, the actual utilization and impact of statin therapy initiation in patients with ADHF with an independent indication for statin therapy have not been thoroughly explored.

Methods: We conducted a retrospective observational study on 5978 patients admitted with ADHF between January 1st, 2007, and December 31st, 2017. Patients were grouped based on their statin therapy status at admission and discharge. We performed multivariable analyses to identify independent predictors of short-term, intermediate-term, and long-term mortality. A sensitivity analysis was also conducted on patients with an independent indication for statin therapy but who were not on statins at admission.

Results: Of the total patient cohort, 73.9% had an indication for statin therapy. However, only 38.2% were treated with statins at admission, and 56.1% were discharged with a statin prescription. Patients discharged with statins were younger, predominantly male, and had a higher prevalence of IHD and other comorbidities. Statin therapy at discharge was an independent negative predictor of 5-year all-cause mortality (hazard ratio 0.80, 95% confidence interval 0.76–0.85). The sensitivity analysis confirmed these findings, demonstrating higher mortality rates in patients not initiated on statins during admission.

Conclusions: The study highlights significant underutilization of statin therapy among patients admitted with ADHF, even when there's an independent indication for such treatment. Importantly, initiation of statin therapy during hospital admission was independently associated with improved long-term survival.

1. Introduction

Benefits of utilizing hospital admissions as an opportunity to identify and initiate evidence-based medical therapies were previously demonstrated across various medical fields,[1–7] among them initiation of heart failure (HF) medications during HF admissions,[2,4,8] and statins initiation after in-hospital diagnosis of coronary disease.[1] .

While HF is not considered an indication for statin therapy, many HF patients have independent indications for statin therapy due to related HF etiologies and comorbidities.[9–11] Despite this, there is limited available data on the proportion of HF patients who have an indication for statin therapy but are not adequately treated, as well as the impact of initiating statin therapy during their HF admission on long-term outcomes. Therefore, it remains uncertain whether the identification of indications and initiation of statin therapy should be pursued as a therapeutic goal during HF admissions.

Abbreviations: ACE-I, Angiotensin converting enzyme inhibitor; ADHF, Acute Decompensated Heart Failure; ARB, Angiotensin receptor blocker; BB, Beta blocker; CABG, Coronary artery bypass grafting; CI, Confidence Interval; COPD, Chronic obstructive pulmonary disease; EF, Ejection fraction; HF, Heart failure; HFrEF, HF with reduced ejection fraction; HR, Hazard ratio; IHD, Ischemic heart disease; MI, Myocardial infarction; MRA, Mineralocorticoid receptor antagonist; PVD, Peripheral vascular disease; SD, Standard deviation; WBC, White blood cells.

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To address this gap in knowledge, we elected to conduct a study to investigate the extents of statin therapy indications, the actual utilization of statin therapy prior to admission and at discharge, and the impact of statin therapy initiation during admission on long-term outcomes, on a contemporary large cohort of patients admitted with acute decompensated HF (ADHF).

2. Methods

This single-center retrospective cohort study utilized data from patients admitted to internal medicine departments at Shamir Medical Center with ADHF, from January 1, 2007, to December 31, 2017. It included all patients aged 18 years and older who had a discharge diagnosis of ADHF (identified by one of the following International Classification of Diseases, Ninth Revision (ICD-9) codes: 428.xx, 429.xx, and 514) as one of their primary admission diagnoses. Patients admitted to the cardiology departments were excluded based on our previous study, which identified significant differences between patients admitted to cardiology departments and internal medicine departments, with the latter group being more representative of the general HF population.[12] As the current study focused on the impact of statin therapy at discharge, patients who died during admission were excluded as well. Demographic and clinical data were extracted from Shamir Medical Center's electronic medical record, while all-cause mortality information was obtained from Israel's Ministry of Internal Affairs database. This study received approval from the local institutional review board at Shamir Medical Center's Helsinki Committee, and patient consent was waived due to the retrospective nature of the study.

A patient was identified as having an indication for statin therapy based on one of two criteria: If the patient had been treated with a statin before admission, it was assumed that this therapy had been initiated due to a recognized indication. Conversely, if the patient had not been treated with a statin before admission, indication was determined based on their comorbidities and low-density lipoprotein cholesterol level at admission, in line with the criteria outlined in the European Society of Cardiology and the European Atherosclerosis Society Guidelines for the Management of Dyslipidemias.[13].

To explore the association between statin therapy and outcomes, patients were grouped based on their statin therapy status at discharge. Categorical variables are presented as counts and percentages, and continuous variables as means and standard deviations or medians and interquartile range, depending on normality of their distribution. The normality of distribution was assessed using the Shapiro-Wilk test. The Chi-square test was used to compare categorical variables, the two-paired student *t*-test was used for normally distributed continuous variables, and the Kruskal-Wallis H test was used for non-normally distributed continuous variables. Kaplan-Meier curves with log-rank tests were employed to compare time-dependent 5-year survival rates.

Cox regression was used to assess the independence of statin therapy at discharge as a predictor of 5-year mortality. As previously described, [14] the variables included in both multivariable analyses were forced into the models based on the focus of our current research (discharge statin therapy), demographic importance (sex), their known association with HF patients outcomes (age,[15] diabetes and ischemic heart disease (IHD),[16] chronic kidney disease,[17] atrial fibrillation,[18] chronic obstructive pulmonary disease,[19] and peripheral vascular disease,[20], or if they demonstrated a numerically strong and statistically highly significant (i.e. a p-value < 0.01) difference in the univariable analysis (discharge beta blocker (BB) and angiotensin converting enzymes inhibitors (ACEI) or angiotensin receptor blockers (ARB) therapy, hemoglobin levels).

To further support our findings and explore the association between the initiation of statin therapy during admission and long-term outcomes, a sensitivity analysis was conducted on a sub-population of patients who had an indication for statin therapy but were not initially treated with a statin upon admission. A repeated survival analysis was performed on this cohort to assess the effect of statin therapy initiation during admission.

Statistical analysis was carried out using R: A Language and Environment for Statistical Computing, R Core Team, R Foundation for Statistical Computing, Vienna, Austria, 2020, https://www.R-project.org.

3. Results

The analysis included 5,978 patients admitted with ADHF between January 1st, 2007, and December 31st, 2017, meeting the inclusion and exclusion criteria and with available information on statin therapy status at discharge. Of those, 4,416 (73.9 %) patients had an indication for statin therapy; however, upon admission, only 2,282 (38.2 %, 51.7 % of patients with an indication) were treated with a statin, and 3,533 (56.1 %, 75.9 % of patients with an indication) were discharged with statin therapy.

Baseline characteristics and clinical indices of the cohort are presented in Table 1.. Compared with patients discharged without statin therapy, patients discharged with statin therapy were younger (median 77, interquartile range (IQR) 69–38 years vs. median 81 IQR 72–87 years, $p < 0.001$), were predominantly male (50.8 % vs. 44.2 %, $p <$

Table 1
Baseline demographic, clinical, pharmacological, and laboratory indices of patients admitted with acute decompensated heart failure.

	Discharge with statin (N = 3,533)	Discharge without statin (N = 2,445)	p value
Female sex – n (%)	1739 (49.2)	1364 (55.8)	< 0.001
Age, years – Median (IQR)	77 (69–83)	81 (72–87)	< 0.001
Medical history – n (%)			
Hypertension	647 (18.3)	463 (18.9)	0.542
Diabetes Mellitus	2,015 (57.0)	1,046 (42.8)	< 0.001
Smoking	605 (17.1)	319 (13.0)	< 0.001
Obesity	876 (24.8)	442 (18.1)	< 0.001
Ischemic heart disease	1695 (48.0)	690 (28.2)	< 0.001
COPD	570 (16.1)	423 (17.3)	0.233
Chronic kidney disease	1260 (35.7)	721 (29.5)	< 0.001
Atrial fibrillation	1113 (31.5)	842 (34.4)	0.017
Peripheral vascular disease	295 (8.3)	118 (4.8)	< 0.001
Medical therapy at admission – n (%)			
Beta-blockers	1412 (40.0)	690 (28.2)	< 0.001
Alpha-blockers	457 (12.9)	196 (8.0)	< 0.001
Calcium Channel blockers	994 (28.1)	530 (21.7)	< 0.001
ACE inhibitor	738 (20.9)	324 (13.3)	< 0.001
ARB	324 (13.3)	177 (7.2)	< 0.001
ACE inhibitor or ARB	1187 (33.6)	497 (20.3)	<0.001
MRA	90 (2.5)	45 (1.8)	0.07
Diuretics	1939 (54.9)	1335 (54.6)	0.83
Digoxin	168 (4.8)	116 (4.7)	0.985
Antiarrhythmics	265 (7.5)	109 (4.5)	<0.0051
Anti-platelets	1713 (48.5)	667 (27.3)	< 0.001
Oral anticoagulants	534 (15.1)	302 (12.4)	0.002
Statins	2163 (61.2)	119 (4.9)	< 0.001
Other lipid-lowering therapy	86 (2.4)	29 (1.2)	< 0.001
Laboratory indices – median [IQR]			
WBC, K/μL	9 [7.1–11.7]	8.9 [7–12.1]	0.842
Hemoglobin, mg/dL	11.8 [10.4–13]	11.5 [10.3–12.9]	0.002
Urea, mg/dL	49.4 [36.4–72.1]	50.6 [36.2–77.5]	0.253
Sodium, mmol/L	138 [135–141]	138 [134–140]	<0.001
Creatinine, mg/dL	1.11 [0.86–1.56]	1.06 [0.82–1.5]	<0.001
Left ventricular EF by echocardiography – n (%)			0.006
Preserved (EF ≥ 50 %)	602 (49.3)	441 (56.8)	
Mildly reduced (EF = 40–49 %)	194 (15.9)	106 (13.6)	
Moderately reduced (EF = 30–39 %)	303 (24.8)	152 (19.6)	
Severely reduced (EF < 30 %)	122 (10.0)	78 (10.0)	
Indication for statin therapy – n (%)	3014.0 (85.3)	1402.0 (57.3)	< 0.001

0.001), had higher rates of IHD (48 % vs. 28.2 %, p < 0.001) and comorbidities including diabetes mellitus, chronic kidney disease, and peripheral vascular disease (PVD), and were more likely to be treated with HF medications including BB (40 % vs. 28.2 %, p < 0.001) and ACEI or ARB (33.6 % vs. 20.3 %, p < 0.001) upon admission. In-hospital procedures and discharge medications are presented in Table 2. Patients discharged with statin therapy were more likely undergo percutaneous coronary angiography and intervention (for intervention: 5.9 % vs. 2.5 %, p < 0.001) during admission, and to be discharged with guideline recommended HF medications including BB (64.4 % vs. 54.7 %, p < 0.001) and ACEI or ARB (49.3 % vs. 35.7 %, p < 0.001).

Short and intermediate outcomes of the study groups are detailed in Table 3. Rates of 30-day mortality and 1-year mortality were significantly higher in patients discharged without statin therapy. Fig. 1 presents the unadjusted 5-year all-cause mortality survival analysis, depicting significantly higher rates of mortality in patients discharged without statin therapy (log-rank p < 0.0001).

Multivariable analyses for independent predictors of outcomes are presented in Table 4. Statin therapy at discharge was persistently found to be an independent negative predictor of 5-year all-cause mortality (Hazard ratio (HR) 0.82, 95 % Confidence Interval (CI) 0.77–0.87, p-value < 0.001). Other identified independent predictors include female sex (HR 0.84, 95 % CI 0.79–0.89, p-value < 0.001), age (HR 1.05 for each additional year, CI 1.04–1.05. p-value < 0.001), Chronic obstructive pulmonary disease (COPD) (HR 1.22, CI 1.13–1.31, p-value < 0.001), low hemoglobin levels at admission (low levels are negative predictors, inversely represented by higher hemoglobin levels positively predicting better 5-year mortality outcomes: HR 0.93 for each increase in 1 mg/dL in hemoglobin levels, CI 0.91–0.94, p-value < 0.001), and chronic kidney disease (CKD) (HR 1.19, CI 1.12–1.27, p-value < 0.001). A combination of ACEI or ARB and BB therapy at discharge was also independently associated with lower 5-year mortality rates (0.86 vs. 0.92, p < 0.001).

The sensitivity analysis subgroup of patients with an indication for statins but not treated with a statin at admission included 2,127 patients, for whom only 851 (40 %) were initiated with statin therapy during admission. A repeated 5-year survival analysis on this cohort demonstrated the same significantly higher rates of mortality in patients for whom statin therapy was not initiated during admission (log-rank p < 0.0001) (Fig. 2).

Table 2
In-hospital procedures and discharge medications of patients admitted with acute decompensated heart failure.

	Discharged with statin (n = 3533)	Discharged without statin (n = 2445)	p value
Procedures performed during hospitalization – n (%)			
Diagnostic coronary angiography	120 (3.4)	27 (1.1)	< 0.001
Percutaneous coronary intervention	207 (5.9)	60 (2.5)	< 0.001
CABG	39 (1.1)	14 (0.6)	0.031
Permanent pacemaker implantation	32 (0.9)	22 (0.9)	0.031
Dialysis	41 (1.2)	32 (1.3)	0.608
Medication at discharge — n (%)			
Beta-blockers	2277 (64.4)	1337 (54.7)	< 0.001
alpha-blockers	640 (18.1)	362 (14.8)	< 0.001
Calcium Channel blockers	1355 (38.4)	819 (33.5)	< 0.001
ACE inhibitor	1100 (31.1)	601 (24.6)	< 0.001
ARB	663 (18.8)	278 (11.4)	< 0.001
ACE inhibitor or ARB	1742 (49.3)	873 (35.7)	<0.001
MRA	106 (3.0)	72 (2.9)	0.901
Diuretics	3010 (85.2)	1949 (79.7)	< 0.001
Antiarrhythmics	376 (10.6)	187 (7.6)	< 0.001
Digoxin	139.0 (3.9)	139.0 (5.7)	0.002
Anti-platelets	2549 (72.1)	2549 (72.1)	< 0.001
Oral anticoagulants	1068 (30.2)	705 (28.8)	0.246
Other lipid-lowering therapy	109 (3.1)	45 (1.8)	0.003

Table 3
Short and intermediate-term clinical outcomes of patients admitted with acute decompensated heart failure.

	Discharged with statin (N = 3533)	Discharged without statin (N = 2445)	p value
Length of stay, days – median [IQR]	5 [3–9]	6 [3–10]	< 0.001
Readmission within 30 days – n (%)	729 (20.6)	535 (21.9)	0.246
Mortality within 30 days – n (%)	108 (3.1)	184 (7.5)	< 0.001
Mortality within 1 year – n (%)	703 (19.9)	798 (32.6)	< 0.001

4. Discussion

In this study, we aimed to investigate the utilization of statin therapy among patients admitted with ADHF between 2007 and 2017 and assess its impact on long-term survival. Our findings indicate substantial underutilization of statin therapy among HF patients with an independent indication for statin treatment. Furthermore, initiation of statin therapy during an ADHF admission was associated with improved long-term survival.

Despite its well-established role in treatment of patients with hyperlipidemia and IHD,[21–23,9,13] it was previously shown that statin therapy is underutilized in selected subgroups of patients, including women and older adults.[24–27] Regarding HF patients, Kosuma, P. and Jedsadayanmata A. reported statin therapy initiation in 55.4 % of patients with newly diagnosed HF, with dyslipidemia, IHD, diabetes and cerebrovascular disease being strong predictors for statin treatment in these patients.[28] We found lower rates of statin therapy among these patients upon admission, and similar rates among patients with an indication for statin therapy. One potential explanation for this discrepancy may be the different settings of HF encounter between these studies: The patients in Kosuma's study were outpatients with newly diagnosed HF, in which statin therapy was initiated during this new HF diagnosis encounter. Our cohort included only inpatients with ADHF, in which many were already previously diagnosed with HF upon admission. It is possible that in some of these patients a previous treatment with statin was discontinued prior to their acute HF admission.

Several observational studies have demonstrated better prognosis with statin therapy in HF patients,[29–32] however two large randomized controlled trials failed to show benefit of statin therapy on cardiovascular mortality or stroke.[10,33] Accordingly, the European society of cardiology guidelines do not recommend routine administration of statins in HF patients.[13] On the other hand, the American College of Cardiology/American Heart Association (ACC/AHA) guidelines suggest statins therapy in patients with HF with reduced ejection fraction (HFrEF) secondary to IHD, based on a pooled analysis of the two aforementioned randomized controlled trials that showed a reduction in HF hospitalizations and slight decrease in MI.[9]]Surprisingly, our study found a significant decrease in long-term all-cause mortality in HF patients treated with statins that was independent of the existence of an independent indication for statin therapy. A reasonable explanation for this finding is that despite the independency of the association of statin therapy with 5-year mortality, there is probably a significant interaction between the independent indication for statin therapy and the actual

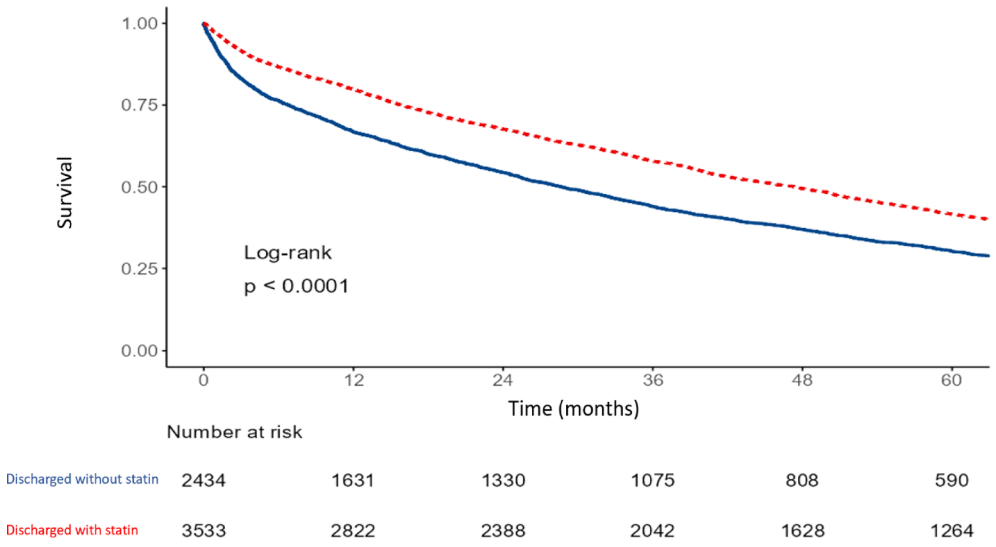

Fig. 1. Kaplan–Meier survival estimates for patients admitted for acute decompensated heart failure stratified by status of statin therapy upon discharge.

Table 4
Multivariable Cox regression analysis for 5-year all-cause mortality.

	5-year mortality HR (95 % CI)	p-value
Discharge with statin therapy	0.82 (0.77–0.87)	<0.001
Female sex	0.84 (0.79–0.89)	<0.001
Age[a]	1.05 (1.04–1.05)	<0.001
Ischemic heart disease	1.04 (0.98–1.11)	0.2
Chronic kidney disease	1.19 (1.12–1.27)	<0.001
Atrial fibrillation	1.00 (0.94–1.07)	0.896
Diabetes mellitus	1.06 (1.00–1.13)	0.068
COPD	1.22 (1.13–1.31)	<0.001
Peripheral vascular disease	1.34 (1.20–1.50)	<0.001
Discharge with ACEI/ARB and BB	0.86 (0.80–0.92)	<0.001
Hemoglobin level at admission[b]	0.93 (0.91–0.94)	<0.001

[a]HR for age represents the change in hazard for each additional year.
[b]HR for hemoglobin represents the change in hazard for each increase of 1 mg/dL. Higher hemoglobin levels act as a positive predictor, reducing risk, while lower levels increase risk. Hence, the HR for an increase in hemoglobin levels is less than 1.0.

treatment with a statin upon discharge, making the generalization of this finding to HF patients without an independent indication for statin therapy questionable.

We observed a notably low prevalence of statin therapy at admission within our cohort – a mere half of the patients with an established indication for statin therapy had been receiving statin treatment prior to admission. Perhaps the high proportion of octogenarians (47 %) within our cohort, coupled with the ongoing debate regarding statin therapy applicability in advanced age,[34] may provide a plausible explanation for these low rates. Also, the high rates of polypharmacy at the older age and the efforts to mitigate it[35], may account for stopping statin therapy in these patients.

Hospital admissions may be viewed as an opportunity to identify and initiate treatment for important health goals beyond the reason for admission. Coexisting chronic conditions are common in admitted patients,[36–38] and addressing them during admissions for other indications was shown to be feasible[39] and associated with reduction in readmissions and healthcare costs.[40] In addition, hospitalization was described as an important opportunity to engage in discussions about goals of care in seriously ill patients.[41] To our knowledge, our study is the first that explored the impact of viewing the ADHF admission as an opportunity to identify an independent indication for statin therapy, not

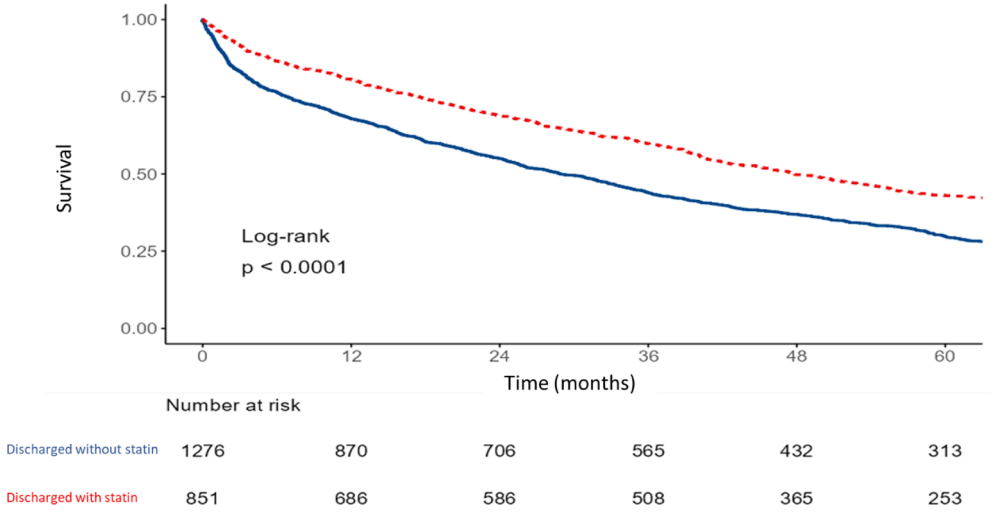

Fig. 2. Kaplan–Meier survival estimates for patients admitted for acute decompensated heart failure with an indication for statin therapy but not initially treated with a statin, stratified by status of statin therapy at discharge.

the HF itself, and initiating statin therapy during this admission. Our sensitivity analysis cohort focused on this scenario, including only patients with an indication for statins but without statin treatment upon admission. In this cohort we found that initiation of statins during the admission was associated with a significant reduction in long-term mortality.

An additional finding in our study was the observation that patients discharged with statin therapy were often better managed in terms of other heart failure medications, evident from their medication profiles at admission and discharge. Notably, these patients were more likely to receive beta-blockers and ACE inhibitors or ARBs. The use of this combination therapy was independently associated with improved outcomes in our Cox regression model. However, it is particularly noteworthy that statin therapy at discharge remained an independent predictor of better outcomes even after adjusting for this factor. This could suggest that while the initiation of statins in these patients might be a marker of more comprehensive and attentive heart failure management, statins themselves might still offer additional, independent benefits. This highlights the need for a holistic approach to heart failure treatment, where the initiation and continuation of statin therapy could be an important component, alongside other key heart failure medications.

Several limitations must be acknowledged regarding the interpretation of our findings. First, as an observational study it cannot infer causality, only association. Second, as this study is based on medical records, it is subject to input errors. Nevertheless, as described elsewhere,[12] the creation of the study cohort included a robust process of data cleaning and internal validation process, significantly minimizing this limitation. Third, we do not have data on post discharge treatment with statins, limiting the strength of our finding of an association between statin therapy and long-term outcomes. Fourth, as previously noted, the study excluded patients admitted to the cardiology department. This exclusion may limit the generalizability of the findings to patients with more severe and complex heart failure, who are typically admitted to cardiology rather than internal medicine departments. Finally, while there was a clinical rationale to adjust for EF groups in our multivariable model, we elected not to include this variable in the model due to its limited availability, with EF measurements being available for only about one-third of the patients in our cohort.

In conclusion, we found substantially lower long-term mortality rates in patients with ADHF who were discharged with statin therapy, especially when they have an independent indication for statin therapy. Further study is warranted to investigate the causal relationship and optimal strategies for improving statin utilization in heart failure patients.

CRediT authorship contribution statement

Antoinette Monayer: Writing – original draft, Visualization, Project administration, Investigation, Conceptualization. **Sa'ar Minha:** Writing – original draft, Visualization, Validation, Supervision, Project administration, Investigation, Data curation, Conceptualization. **Shiri L. Maymon:** Data curation. **David Pereg:** Investigation. **Eran Kalmanovich:** Investigation. **Gil Moravsky:** Validation, Project administration, Formal analysis. **Avishay Grupper:** Visualization, Investigation. **Gil Marcus:** Validation, Project administration, Formal analysis.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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