Association Between Use of Statins and Mortality in Patients With Heart Failure and Ejection Fraction of ≥50%

Urban Alehagen, MD, PhD; Lina Benson, MSc; Magnus Edner, MD, PhD; Ulf Dahlström, MD, PhD; Lars H. Lund, MD, PhD

Background—The pathophysiology of heart failure with preserved ejection fraction is poorly understood, but may involve a systemic proinflammatory state. Therefore, statins might improve outcomes in patients with heart failure with preserved ejection fraction defined as ≥50%.

Methods and Results—Of 46,959 unique patients in the prospective Swedish Heart Failure Registry, 9,140 patients had heart failure and ejection fraction ≥50% (age 77±11 years, 54.0% women), and of these, 3,427 (37.5%) were treated with statins. Propensity scores for statin treatment were derived from 40 baseline variables. The association between statin use and primary (all-cause mortality) and secondary (separately, cardiovascular mortality, and combined all-cause mortality or cardiovascular hospitalization) end points was assessed with Cox regressions in a population matched 1:1 based on age and propensity score. In the matched population, 1-year survival was 85.1% for statin-treated versus 80.9% for untreated patients (hazard ratio, 0.80; 95% confidence interval, 0.72–0.89; P<0.001). Statins were also associated with reduced cardiovascular death (hazard ratio, 0.86; 95% confidence interval, 0.75–0.98; P=0.026) and composite all-cause mortality or cardiovascular hospitalization (hazard ratio, 0.89; 95% confidence interval, 0.82–0.96; P=0.003).

Conclusions—In heart failure with ejection fraction ≥50%, the use of statins was associated with improved outcomes. The mechanisms should be evaluated and the effects tested in a randomized trial. (Circ Heart Fail. 2015;8:862-870. DOI: 10.1161/CIRCHEARTFAILURE.115.002143.)

Key Words: heart failure ■ heart failure with preserved ejection fraction ■ mortality ■ propensity score ■ statin intervention

The positive effect of statin use in patients with ischemic heart disease (IHD) is well documented.2 The major benefits include not only reduced risk of myocardial infarction1 and cardiovascular mortality,5 but also reduced utilization of health resources and positive cost-effectiveness.6 It has been discussed whether statins also have effects on the systemic inflammatory response and whether this could partially explain the beneficial effects.8 This anti-inflammatory effect of statins has also been linked to reduced mortality in other diseases, such as chronic obstructive pulmonary disease10,11 and diabetes mellitus.12

Clinical Perspective on p 870

There are reports indicating that statins are not beneficial in heart failure (HF) with reduced ejection fraction (HFREF), even in the presence of IHD,11,14 but their potential in HF with preserved ejection fraction (HFPEF) remains an open question. HFPEF is common, and diastolic dysfunction is often asymptomatic. The literature indicates that 20%, and in some estimations even >40%, of elderly patients have isolated diastolic dysfunction.15,16 Also, the prevalence of HFPEF might be increasing in the community.17 It is, therefore, surprising that there is not more information regarding the effect of statin therapy in patients with HFPEF. Some small previous reports suggest a potential benefit of statins in HFPEF,18,19 whereas others report contradictory results.19-21

The pathophysiology of HFPEF is poorly understood, but it is believed that comorbidities, such as ageing, hypertension, overweight/obesity, diabetes mellitus, and obstructive pulmonary disease, may induce a systemic proinflammatory state, which may be responsive to statin therapy.22 There are also reports indicating that statins may also improve diastolic function.23 Therefore, the aim was to test the hypothesis that statins are associated with improved outcomes in HFPEF.

Population

The Swedish Heart Failure Registry (RiksSvikt) that was introduced in Sweden in 2000 has been previously described.24 The inclusion
Cut-Off Level of Ejection Fraction
The cut-off in ejection fraction (EF) to define HFPEF is controversial and has been discussed in the literature. We chose EF ≥ 50% for the primary analysis. However, many publications have defined HFPEF as EF ≥ 40%, which among other studies is used in the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM)-Preserved study and in a subgroup analysis of the Gruppo Italiano per lo Studio della Sopravvivenza nell’Insufficienza Cardiaca-Heart Failure (GISSI-HF) trial; therefore, we provided a separate analysis on EF 40% to 49% (Appendix in the Data Supplement).

Use of Statins
The use of statins was defined as prescribed by physician at time of discharge from hospital or outpatient visit.

Outcomes
The Swedish National Board of Health and Welfare (http://www.socialstyrelsen.se) keeps records of cause of death in the Cause of Death Registry and of hospitalizations and their causes in the Patient Registry. These databases were extracted with data until December 31, 2011. For cardiovascular mortality and hospitalization, we included the International Classification of Diseases v. 10 diagnoses I00-I99.

Statistical Analysis
Descriptive data are presented as numbers (n) and percentages or means with standard deviation or median with interquartile range as appropriate. For comparison of continuous variables, we used Student’s t test, whereas the χ² test was used for discrete variables.

Propensity Scores
Propensity scores for treatment with statins were estimated for each patient by use of logistic regression with 40 clinically relevant baseline variables (all numbered variables indicated in Table 1) as independent variables and statin treatment as the dependent variable. All continuous variables were modeled using restricted cubic splines (3 degrees of freedom). The propensity score is the propensity from 0 to 1 to receive treatment given a set of known variables and is used to adjust for potential selection bias, confounding and differences between treatment group in observational studies.

Missing values were handled by estimating one logistic regression model for each pattern of missing values. Each individual then received the propensity score that incorporated all variables with nonmissing values for that individual. An age- and propensity score–matched population was constructed with matching 1:1 without replacement, based on age difference ≤ 5 years and propensity score difference ≤ 0.1. This yielded 2074 patients in each group.

Outcomes
In the overall population, crude survival by statin treatment was assessed with Kaplan–Meier analyses and plotted in the same figure as Kaplan–Meier survival for the matched population (Figure 2). Cox regression models were used to estimate the hazard ratio (HR) and corresponding 95% confidence interval (CI) in the overall population, crude as well as in the matched population. The dependence between matched pairs was modeled within the Cox regression by adding a frailty term assuming a Gaussian distribution.

The proportional hazards assumption was tested by scaled Schoenfeld residuals, and the presence of extreme outliers was assessed by dfitbets. No violations to the proportional hazards assumption or possible influential outliers were found.

In addition to all-cause mortality, we also assessed cardiovascular mortality and a composite end point of time to all-cause mortality or cardiovascular hospitalization. The definition of cardiovascular mortality and cardiovascular hospitalization was based on the ICD codes as presented above. Patients not experiencing an event were censored on December 31, 2011. Additionally, for the end point cardiovascular mortality, censoring also occurred if the patient died from other causes.

For all analyses, a level of significance was set to 5%, and all reported P values are 2-sided. All statistics were performed in R v 3.1.3 (R foundation for Statistical Computing, Vienna, Austria).

Results

Patients
Baseline characteristics of the overall and the matched populations are presented in Table 1. The final population consisted of 9140 patients after exclusion of those with missing information, with

| Information on statin use lacking (N=698) |
| Information on echocardiography lacking or EF<40% (N=46391) |
| Information on follow-up lacking or Inclusion time outside 2001-01-01 to 2011-12-31 (N=1103) |
| Repeated posts on same patient (N=7215) |
| EF 40-49% (N=8847) |

Figure 1. Flow chart over the selection process of the patients from the Swedish Heart Failure Registry. EF indicates ejection fraction.
<table>
<thead>
<tr>
<th>Variables</th>
<th>Missing Information, %</th>
<th>No Statins (n=5713)</th>
<th>Statins (n=3427)</th>
<th>Stand diff, %</th>
<th>P Value</th>
<th>No Statins (n=2074)</th>
<th>Statins (n=2074)</th>
<th>Stand diff, %</th>
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<td>78 (12)</td>
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<td>77 (10)</td>
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<td>IHD, n (%)</td>
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(Continued)
EF <50%, or included in the registry after December 31, 2011, the latter because of lack of cause-specific outcomes (Figure 1). Among 9140 patients with HFPEF, mean age was 77 years (SD, 11), proportion of female patients was 54.0%, and 3427 (37.5%) were treated and 5713 (62.5%) were not treated with statins. In the overall population, differences could be seen in many variables, indicating that the 2 populations could not be directly compared. Patients treated with statins were younger (75 versus 78 years), were more often males (52.1% versus 42.4%), had a higher proportion of diabetes mellitus (35.3% versus 18.6%), and had a higher proportion of IHD (58.7% versus 25.3% not on statins).

However, after matching for propensity score and age, the differences between the groups were considerably reduced or eliminated. The differences in propensity scores between the matched groups were therefore small, and the standard differences were ≤10% for all variables, including important potential confounders, such as age, IHD, hypertension, renal function, level of NT-proBNP, and hemoglobin, which is considered to represent good matching.31 The only variable with a standardized difference >10% was use of nitrates (11%), which was larger in the statin group.

**Mortality Outcomes**

In the overall population, 1-year survival was 87.2% (95% CI, 86.0%–88.4%) in the statin group versus 76.3% (95% CI, 75.1%–77.4%) in the nonstatin group. After 3 years, the
corresponding figures were 69.5% (95% CI, 67.6%–71.3%) versus 54.9% (95% CI, 53.4%–56.4%), and finally after 5 years, survival was 56.8% (95% CI, 54.4%–59.4%) in those on statin treatment versus 38.7% (95% CI, 36.9%–40.6%) in those not on statin treatment (Figure 2).

In the matched population, 1-year survival was 85.1% (95% CI, 83.5%–86.7%) in the statin group versus 80.9% (95% CI, 79.2%–82.7%) in the nonstatin group. The hypothetical number needed to treat for 1 year to prevent one death from any cause was 29. After 3 years, survival was 66.1% (95% CI, 63.8%–68.6%) versus 61.3% (95% CI, 58.9%–63.8%), and number needed to treat was 16; after 5 years, the corresponding figures were 52.9% (95% CI, 49.8%–56.2%) versus 45.0% (95% CI, 41.7%–48.5%), and number needed to treat was 23 (Figure 2).

In Cox regressions, the HRs (95% CI) for the association between statin use and all-cause mortality was 0.59 (95% CI, 0.55–0.63; P<0.001) in crude analysis in the overall population and 0.86 (95% CI, 0.75–0.98; P=0.026) in the matched population (Table 2).

Figure 3 shows a Forest plot illustrating the association between statin use and all-cause mortality in different subgroups for the matched population. There were no statistically significant interactions.

Secondary Outcomes

Regarding the secondary outcomes in the matched population, HRs associated with statin use were as follows: for cardiovascular mortality, HR was 0.86 (95% CI, 0.75–0.98; P=0.026), and for composite all-cause mortality or cardiovascular hospitalization, HR was 0.89 (95% CI, 0.82–0.96; P=0.003).

Analysis of Group With EF 40% to 49%

As there has been controversy in the literature regarding definition of HFPEF and because previous randomized trials included primarily EF <40%, we also performed analyses of the group with HFPEF and EF 40% to 49% (Appendix in the Data Supplement). The results were similar in the EF 40% to 49% groups compared with EF ≥50% groups. There was no statistically significant interaction between statin use and IHD, but the point estimate was toward greater risk reduction in patient with IHD.

Discussion

The potential role of statins in patients with HFPEF is unknown. Therefore, we analyzed one of the largest HF registries in the world, the Swedish Heart Failure Registry (RiksSvikt), and
specifically evaluated the association between statin treatment and outcomes in patients with HFPEF.

Statin use was associated with reduced all-cause mortality in HF with EF ≥50%, with an HR of 0.80. A hypothetical number needed to treat to save one life over one year was 29 in the propensity score–matched analysis. Statin use was also associated with reduced cardiovascular mortality and a reduction in the combined end point of all-cause mortality or cardiovascular hospitalization. Results were similar in HF with EF 40% to 49%.

**Possible Mechanisms of Statin Benefits**

The exact mechanism of the potential statin benefit in HFPEF function is unknown, but there are some interesting data that might support our findings. Paulus and Tschöpe suggest that the mechanisms behind HFPEF may be related to comorbidities (hypertension, obesity, diabetes mellitus, and chronic obstructive pulmonary disease) and the systemic and microvascular inflammation induced by these comorbidities. As a result, cardiomyocytes are exposed to less nitric oxide production, which is associated with reduced cardiovascular mortality and a reduction in the combined end point of all-cause mortality or cardiovascular hospitalization. Results were similar in HF with EF 40% to 49%.

**Table 2. Cox Proportional Hazard Regression Analysis Illustrating the Association Between Statin Use and the Specified Outcome in Patients With Heart Failure and Preserved Ejection Fraction (HFPEF) Defined as ≥50%**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Population/Adjusted for</th>
<th>n Events/n</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>Overall/Crude</td>
<td>3553/9140</td>
<td>0.59</td>
<td>0.55–0.63</td>
<td>&lt;0.001</td>
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<tr>
<td>All-cause mortality</td>
<td>Matched*</td>
<td>1443/4148</td>
<td>0.80</td>
<td>0.72–0.89</td>
<td>&lt;0.001</td>
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<td>CV mortality</td>
<td>Matched*</td>
<td>883/4148</td>
<td>0.86</td>
<td>0.75–0.98</td>
<td>0.026</td>
</tr>
<tr>
<td>All-cause mortality and CV hospitalization</td>
<td>Matched*</td>
<td>2595/4148</td>
<td>0.89</td>
<td>0.82–0.96</td>
<td>0.003</td>
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CI indicates confidence interval; and CV, cardiovascular.

*Matched on propensity score ≤0.1 and age ≤5 y.

In summary, the GISSI-HF study, where only patients with impaired systolic function were included, and thus, not the type of HF discussed here, showed that statins are beneficial in HFREF, even in the presence of IHD and diabetes mellitus. However, in an observational study on HFREF from the Swedish Heart Failure Registry parallel to the present study, we observed a strong interaction.
between statin use and outcomes (HR for mortality, 0.76; 95% CI, 0.70–0.82; \( P < 0.001 \) in the presence of IHD; HR, 0.95; 95% CI, 0.85–1.07; \( P = 0.43 \) in the absence of IHD; \( P \) for interaction, 0.001).\(^{41}\) In this study, we raise the possibility that although statins have no role in HFREF without IHD, the potential benefit in IHD may still not be ruled out. In contrast, in the HFPEF population studied here, no such interaction with IHD was observed, with an associated benefit regardless of IHD (\( P \) for interaction, 0.741; Figure 3). In the EF 40% to 49% group, there was no significant interaction with IHD, but the point estimate was toward greater risk reduction in the presence of IHD, suggesting that the EF 40% to 49% group may represent an interim between HFREF and HF with truly preserved EF. These data are indeed consistent with the hypothesis that HFPEF involves a systematic proinflammatory state with micro- rather than macrovascular dysfunction. However, there are no randomized trials on HFPEF, and as discussed, the pathophysiology of HFPEF may be more amenable to modification by statins. Thus, there is a need for an evaluation of statin treatment in patients with HFPEF. The optimal way would be a large RCT, but as no one yet is performed, the present data are of interest and also hypothesis generating and a strong rationale to perform such a study.

Limitations

Because this is not an RCT, we cannot rule out residual confounding. However, several factors reduce the influence of confounding, like large patient number, long duration of follow-up, extensive covariate availability for generation of and matching, and finally adjustment for propensity scores. Given the complexity of HFPEF and the fact that statins are now generic and inexpensive, a large industry-sponsored trial may be unlikely, but given the high prevalence, poor prognosis, and lack of current therapy, a publicly funded adequately powered RCT of statins in HFPEF would be warranted, perhaps using the novel registry-randomized trial concept.

In the registry, 54.0% were females, representative of most,\(^{42–47}\) but lower than in some, HFPEF populations.

Some clinical variables are missing in the registry, like type of statin used and dose; C-reactive protein and low-density lipoprotein levels; and other potential confounding medications, such as steroids and nonsteroidal anti-inflammatory drugs. However, the extensive number of covariates covers much of the potential factors that may influence statin use and outcomes independent of statin use.

We did not have access to serum lipid levels. Although many treated patients may have had a dyslipidemia indication, this would likely confound toward worse rather than better outcomes in treated patients. We still cannot rule out that the results are in part a reflection of lipid-lowering effects, but the absence of an interaction with IHD and diabetes mellitus supports a potential effect of statins that is independent of vascular disease.

The information on patient adherence to statin therapy during the follow-up time was not possible to obtain from the registry.

Statin use was reported at baseline only, and crossover may have occurred throughout follow-up, but this would only dilute any potentially associated improvement in outcomes.

The results are based on a HF registry from Sweden. It is not certain that the handling of HF patients is the same in different countries, even if the pharmacological treatments are the same. Thus, some of our results might not be directly transferred into other healthcare systems.

As the study is observational, there is always a potential issue regarding bias and confounding. Therefore, we have performed propensity score matching and adjustment for the variables believed to affect bias or confounding. A standardized difference between groups of \( \leq 10\% \) is generally considered inconsequential.\(^{48}\) Of all the variables adjusted for, only one had a standardized difference of \( >10\% \). However, we cannot rule out existence of unknown or unmeasured variables resulting in residual confounding.

The causes of hospitalization have been validated and found to be accurate in Swedish registries,\(^{49}\) but cause of death is based on death certificates and notoriously unreliable,\(^{50}\) and therefore, the outcome cardiovascular mortality should be interpreted with some care. In patients with an indication, nonuse of statins could be because of intolerance or general undertreatment. Use of renin–angiotensin system antagonists and \( \beta \)-blockers was greater in statin-treated patients overall, but after matching, the difference was small. Furthermore, there was no interaction between statin use and diabetes mellitus, coronary disease, or any other subgroup, again suggesting that the favorable association between statins and outcomes in HFPEF was unrelated to these comorbidities.

Conclusions

In patients with HFPEF, the use of statins was associated with reduced all-cause mortality, cardiovascular mortality, and combined all-cause mortality or cardiovascular hospitalization. The mechanisms need to be studied further, and our findings should be tested in an adequately powered RCT.

Sources of Funding

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Disclosures

None.

References


Statin use in patients with ischemic heart disease is recommended in guidelines because it improves outcomes. However, for patients with heart failure with reduced ejection fraction, the use of statins has not been proven beneficial and is presently not recommended, whereas in patients with heart failure and preserved ejection fraction, it is still an open question. We performed a large observational study in the Swedish Heart Failure Registry of 4148 patients with heart failure and preserved ejection fraction defined as EF >50%, with matching of treated and untreated patients by and adjustment for propensity scores for statin use. Statin use in patients with heart failure and preserved ejection fraction was associated with reduced all-cause mortality, cardiovascular mortality, and also a combined end point of all-cause mortality or cardiovascular hospitalization. The results were similar in an additional analysis of patients with HF and an EF of 40% to 49%. No interaction between ischemic heart disease or diabetes mellitus was found. Heart failure and preserved ejection fraction is thought to be associated with comorbidity-driven global inflammation and microvascular dysfunction. Potential benefits of statins in this population may be mediated by the documented anti-inflammatory effects of statins. The present study should be regarded as hypothesis generating and provides a rationale for a randomized trial.
Association Between Use of Statins and Mortality in Patients With Heart Failure and Ejection Fraction of ≥50%

Urban Alehagen, Lina Benson, Magnus Edner, Ulf Dahlström and Lars H. Lund

Circ Heart Fail. 2015;8:862-870; originally published online August 4, 2015;
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Data Supplement (unedited) at:
http://circheartfailure.ahajournals.org/content/suppl/2015/08/04/CIRCHEARTFAILURE.115.002143.DC1
SUPPLEMENTAL MATERIAL

Evaluation of patients with HFPEF with an ejection fraction 40-49%

Supplemental Methods
The Swedish Heart Failure Registry (RiksSvikt) that was used in the manuscript has also been used in the supplemental evaluation. However, in this evaluation patients with HFPEF with an ejection fraction 40-49% have been evaluated.

Supplemental Results
The basal characteristics is presented in Supplemental Table 1.

In the matched population a 1 year survival in the statin group was 85.9% (95%CI 84.3-87.4) vs. 82.4% (95%CI 80.7-84.1) in those without statin therapy. After 3 years the corresponding figures were 69.4% (95%CI 67.1-71.7) vs. 63.0% (95%CI 60.6-65.5), and finally the 5 year figures were 54.9% (95%CI 51.8-58.1) vs. 50.6% (95%CI 47.5-53.8) (Supplemental Figure 1).

In the Cox proportional hazard regressions, the HRs (95% CI) for the association between statin use and all-cause mortality were 0.63 (95%CI 0.58-0.68; p<0.001) in crude analysis in the overall population, and 0.81 (95%CI 0.73-0.90; p<0.001) in the matched population, (Supplemental Table 2).

Regarding the secondary outcomes, in the matched population, HRs associated with statin use: for cardiovascular mortality, HR 0.85 (95% CI 0.74-0.98; p=0.023) and for composite all-cause mortality or cardiovascular hospitalization HR 0.93 (95% CI 0.86-1.01; p=0.076) (Supplemental Table 2).
Interaction analyses have also been performed and a Forest plot do not reveal any significant interaction between statin use and IHD, even though the point estimate could indicate a somewhat greater risk reduction in patients with IHD (Supplemental Figure 2).
### Supplemental Table 1. Baseline characteristics of the un-matched and matched populations of the study population containing participants with heart failure and EF40-49%

<table>
<thead>
<tr>
<th>Variables</th>
<th>No.</th>
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<th>Statins n=4272</th>
<th>Stand diff, %</th>
<th>p-value</th>
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<th>Statins n=2064</th>
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<th>p-value</th>
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</thead>
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<td>786 (3915)</td>
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<td></td>
<td></td>
<td>694 (3745)</td>
<td>787 (3915)</td>
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<td>Married, n (%)</td>
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<td>Single, n (%)</td>
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<td>2982 (97)</td>
<td>20</td>
<td>&lt;0.001</td>
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<td>1455 (96)</td>
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<td>2129 (54)</td>
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<td>2153 (50)</td>
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<td>2982 (97)</td>
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<td>1455 (96)</td>
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<td>728 (38)</td>
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<td>Primary Care, n (%)</td>
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<td>728 (38)</td>
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<td>1108 (58)</td>
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<td>166 (4)</td>
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<td>≥6, n (%)</td>
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<td>&lt;6, n (%)</td>
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<td>Year of registration</td>
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<td>2001-2005, n (%)</td>
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<td>I, n (%)</td>
<td>483 (14)</td>
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<td>II, n (%)</td>
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<td>III, n (%)</td>
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<td>IV, n (%)</td>
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<td>Former, n (%)</td>
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<td>Never, n (%)</td>
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<td>Atrial fibrillation/flutter, n (%)</td>
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<td>Lab exam</td>
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<td>Creatinine clearance, mean mL/min (SD)</td>
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<td>1752 (85)</td>
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<td>β-blocker, n (%)</td>
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<td>543 (26)</td>
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<td>Digoxin, n (%)</td>
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<td>0</td>
<td>345 (17)</td>
<td>362 (18)</td>
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<td>Examination</td>
<td>No. (%)</td>
<td>Nitrates, n (%)</td>
<td>Aspirin, n (%)</td>
<td>Oral anticoagulants, n (%)</td>
<td>Examinations</td>
<td>Mean arterial pressure, mean mmHg (SD)</td>
<td>Pulse pressure, mean mmHg (SD)</td>
<td>Pulse frequency, mean bpm (SD)</td>
<td>BMI, mean (SD)</td>
<td>Chest x-ray, cardiomegaly, n (%)</td>
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<td></td>
<td>31</td>
<td>0</td>
<td>618 (14)</td>
<td>885 (21)</td>
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<td>34 (1)</td>
<td>93 (14)</td>
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<td>1856 (41)</td>
<td>2826 (66)</td>
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<td>35 (1)</td>
<td>56 (18)</td>
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<td>1821 (40)</td>
<td>1469 (35)</td>
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<td>36 (8)</td>
<td>75 (16)</td>
<td>71 (14)</td>
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<td>Stand diff: Standardized Difference, the</td>
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<td>Mean arterial pressure: Derived as systolic</td>
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<td>blood pressure x one-third plus diastolic</td>
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<td>blood pressure x two thirds.</td>
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<td></td>
<td>Note: ACEI: ACE-inhibitors; ARB: Angiotensin II</td>
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<td>receptor blocker; DCM: Dilated cardiomyopathy;</td>
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<td>HCM: Hypertrophic cardiomyopathy; HF: Heart</td>
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<td>failure; IHD: Ischemic heart disease; LVEF:</td>
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<td>Left ventricular ejection fraction; NT-proBNP:</td>
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<td>N-terminal fragment of proBNP; NYHA class: New</td>
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<td>York Heart Association functional class; Stand</td>
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<td>diff: Standardized Difference, the difference</td>
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<td>between the means for the two groups divided by</td>
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<td>the mutual standard deviation.</td>
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<td>Note: p-value: Comparison of the differences</td>
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<td>between the groups using t-test for continuous</td>
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<td>variables and the χ² test for categorical</td>
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<td>Note: Column No. indicates the variables</td>
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<td>included in the derivation of the ps.</td>
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<td>Note: BMI is not included in model for EF40-49%</td>
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<td>due to convergence problems.</td>
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</table>
Supplemental Table 2. Cox proportional hazard regression analysis illustrating the association between statin use and the specified outcome in patients with heart failure and preserved ejection fraction (HFPEF) defined as 40-49%.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Population/adjusted for</th>
<th>n events/ n</th>
<th>Hazard ratio</th>
<th>95%CI</th>
<th>p-value</th>
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<tbody>
<tr>
<td>All-cause mortality</td>
<td>Overall/Crude</td>
<td>2988/8847</td>
<td>0.63</td>
<td>0.58-0.68</td>
<td>&lt;0.001</td>
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<tr>
<td>All-cause mortality</td>
<td>Matched*</td>
<td>1388/4128</td>
<td>0.81</td>
<td>0.73-0.90</td>
<td>&lt;0.001</td>
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<tr>
<td>CV mortality</td>
<td>Matched*</td>
<td>883/4148</td>
<td>0.85</td>
<td>0.74-0.98</td>
<td>0.023</td>
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<tr>
<td>All-cause mortality &amp; CV hospitalization</td>
<td>Matched*</td>
<td>2504/4128</td>
<td>0.93</td>
<td>0.86-1.01</td>
<td>0.076</td>
</tr>
</tbody>
</table>

Note: ps: propensity score
Note: CV: cardiovascular
Note: CI: confidence interval
* Matched on propensity score ≤ 0.1 and age ≤ 5 years.
Supplemental Figure Legends

Supplemental Figure 1. Kaplan-Meier plot illustrating all-cause mortality of those on treatment with statins versus not on statins in the un-matched and matched study populations with heart failure and preserved ejection fraction (HFPEF) and EF 40-49%.

Supplemental Figure 2. Forest plot illustrating hazard ratios for all-cause mortality of those on treatment with statins versus those without statin treatment in the matched population with heart failure and preserved ejection fraction (HFPEF) and EF 40-49%

Note: Squares represent the hazard ratio and the lines represent the 95% confidence interval. Continuous variables were categorized at clinically relevant cutoffs.