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ORIGINAL ARTICLE

Determinants of the survival benefit associated with statins in patients with acute heart failure

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Abstract

Aims The benefit of statins in patients with heart failure (HF) remains controversial and the mechanism of action is largely speculative. We investigated the determinants of the survival benefit associated with statins in HF patients.

Methods and results We enrolled 1680 acute HF patients receiving statins and 2157 patients not receiving statins admitted between 2009 and 2016. The left ventricular (LV) global longitudinal strain (GLS) was assessed as a measure of myocardial contractility. The primary outcome was 5 year all-cause mortality. Statin therapy was independently associated with improved survival in patients with HF with preserved ejection fraction (HFpEF) [adjusted hazard ratio (HR) 0.781, 95% confidence interval (CI) 0.621–0.981, P = 0.034], but not in those with HF with reduced EF (HFrEF) (adjusted HR 0.881, 95% CI 0.712–1.090, P = 0.244). Mortality reduction associated with statin therapy was significant in patients with ischaemic HF (adjusted HR 0.775, 95% CI 0.607–0.989, P = 0.040), but not in those with non-ischaemic HF (adjusted HR 0.895, 95% CI 0.734–1.092, P = 0.275). The relative magnitude of survival benefit with statin therapy increased as LV-EF and LV-GLS increased, with a steeper dose–response relationship in patients with ischaemic HF. In the subgroup of patients with ischaemic HF, survival benefit with statin therapy was confined to those ≤75 years of age.

Conclusions Our study suggests that the survival benefit of statins is confined to patients with HFpEF and those with ischaemic HF. Myocardial contractility may modulate the prognostic effects of statins in HF patients, particularly when the aetiology is ischaemic rather than non-ischaemic.

Keywords Statins; Heart failure; Myocardial function; Mortality

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Introduction

Statin is the current mainstay of treatment for patients with atherosclerotic cardiovascular diseases (CVDs), substantially reducing morbidity and mortality. Considering the well-established effects of statins on the reduction of myocardial infarction,[1] it has been reported that statin therapy can lower the risk of heart failure (HF) due to ischaemic heart disease (IHD), which is the most common cause of HF, by reducing ischaemic myocardial injuries.[2] Recent research also suggests the potential benefits of statins in the setting of non-ischaemic HF. Specifically, a previous study showed that short-term treatment with simvastatin improved symptoms and cardiac function in patient with idiopathic dilated cardiomyopathy.[3] Another study demonstrated that statin therapy was associated with better survival in patients with non-ischaemic HF.[4] It has also been noted that statin therapy reduced the risk for incident HF in patients with breast cancer receiving anthracycline chemotherapy. Beneficial effects of statins in HF patients were subsequently reproduced in a large-scale observational study.[5] Furthermore, there is experimental basis to explain the mechanism underlying the

benefits of statins on morbidity and mortality in HF. Statins have additional beneficial effects, including anti-inflammatory and anti-oxidant properties and favourable effects on endothelial function, angiogenesis, neuro-hormonal activation, and cardiac hypertrophy and left ventricular (LV) remodelling, apart from their lipid-lowering capabilities.[2] These pleiotropic effects of statins could be protective against the pathologic mechanisms leading to development and progression of HF, such as neuro-hormonal imbalance and adverse cardiac remodelling.

In contrast to the expectation, two subsequent randomized controlled trials, namely, The Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA) and *Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico Heart Failure* (GISSI-HF) trials, failed to prove any survival benefits with statin therapy in patients with HF with reduced ejection fraction (HFrEF).[6,7] The current guideline therefore states that the use of statins is of unproven benefit in patients with HFrEF and does not recommend it in this setting.[8] One recent cohort study demonstrated that statin therapy could significantly reduce mortality in patients with HF with preserved EF (HFpEF),[9] although no large randomized controlled study has been yet performed to confirm the beneficial effects of statins in this HFpEF population. These findings suggest that the specific phenotype of HF should be considered when assessing the effects of statins in HF patients, because the response to statin therapy for HF patients may differ depending on their underlying pathophysiologic processes. In HFpEF patients who typically have evidence of a systemic inflammatory state leading to myocardial fibrosis and cardiac filling abnormalities,[10] anti-inflammatory properties of statins could ameliorate these conditions.[11] It has also been suggested that statins may exert protective effects against cardiac fibrosis, through other, less addressed mechanisms, such as inhibition of fibroblast proliferation and suppression of RhoA/Rho-kinase pathway.[12] Intriguingly, it has been suggested that these effects might have little relevance to HFrEF patients, whose dominant pathophysiology is cardiomyocyte loss and stretch.[10,11] Furthermore, the pathophysiologic features, such as the degree of fibrosis, may also be different based on acute vs. chronic HF.[13,14] Indeed, the CORONA and GISSI-HF trials mainly focused on chronic HF, which might be at too advanced a stage of fibrosis to benefit from statin therapy.[14] However, a subgroup analysis of the CORONA trial suggests that statin therapy can be beneficial for a subpopulation of patients with chronic HF with less advanced disease, which may be relatively similar to acute HF, by demonstrating a significant benefit with statin therapy was observed in patients with a low level of galectin-3, a marker of fibrosis.[15]

There are scarce data on the usefulness of clinical and echocardiographic parameters in predicting the effects of statin therapy for acute HF, which provides insight in understanding the potential merits and limitations of statin use in patients with acute HF and an opportunity for tailoring statin therapy based on these parameters. We therefore hypothesized that the survival benefit with statin therapy in patients with acute HF might differ according to their clinical and echocardiographic features, including the cause of HF (ischaemic vs. non-ischaemic) and the type of HF (HFrEF vs. HFpEF).

Methods

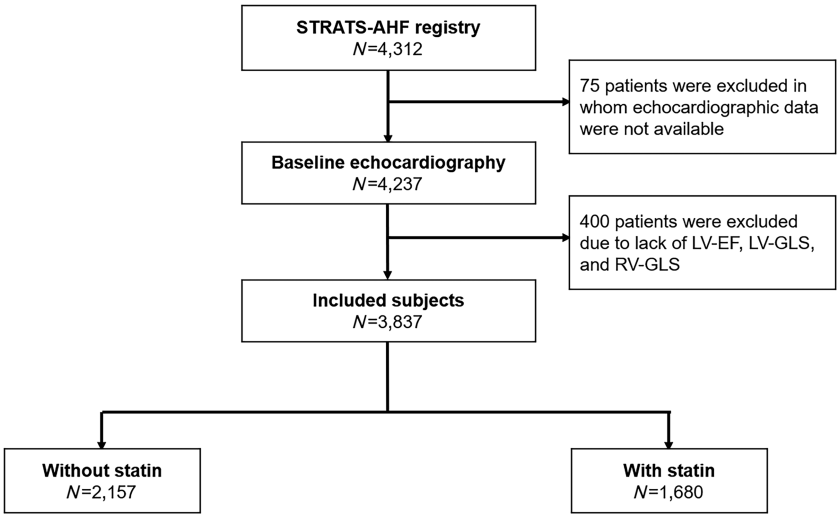
Study design and participants

The STrain for Risk Assessment and Therapeutic Strategies in patients with Acute Heart Failure (STRATS-AHF) registry protocol has been previously described.[16] Briefly, from January 2009 to December 2016, we recruited 4312 consecutive patients hospitalized for acute HF from three tertiary university hospitals. Inclusion criteria were patients who had compatible symptoms and signs of HF and at least one of the following: (i) pulmonary oedema defined as rales on physical examination or congestion on chest radiography or (ii) objective findings of LV systolic dysfunction or relevant structural heart disease (LV hypertrophy and/or left atrial enlargement). Patients with acute coronary syndromes were excluded from the study. The lack of data on LV-global longitudinal strain (GLS) and right ventricular (RV)-GLS was a main exclusion criterion; echocardiography was performed in 4237 (98.3%) patients, and both ventricular GLS was measured in 3837 subjects (90.6%), which was the final sample included in our analysis (*Figure 1*). The study protocol was approved by the ethics committee at each institute and complied with the Declaration of Helsinki. The need for written informed consent was waived.

Variables and definitions

We recorded patients' baseline demographic, anthropometric, clinical, and laboratory data. Patients were diagnosed as having IHD when they satisfied at least one of the following conditions: (i) a presence of significant coronary stenosis (defined as lumen narrowing $>50\%$ in any major epicardial coronary artery) on invasive coronary angiography or coronary computed tomography angiography, (ii) a presence of perfusion decrease on myocardial perfusion imaging or a positive result on other stress-testing modalities, (iii) a previous history of percutaneous coronary intervention or coronary artery bypass graft surgery. The use of medications was determined at discharge for all patients. Echocardiographic examinations were performed according to an established guideline.[17] All images were obtained with commercially available cardiac ultrasound machines with a 2.5 MHz probe. Standard echocardiographic techniques were used for two-

Figure 1 Study population. Flow chart of this study is presented. EF, ejection fraction; GLS, global longitudinal strain; LV, left ventricle; RV, right ventricle; STRATS-AHF, Strain for Risk Assessment and Therapeutic Strategies in Patients with Acute Heart Failure.



dimensional, M-mode, and Doppler measurements. We also measured tissue-Doppler-derived peak-systolic, early, and late-diastolic velocities of the mitral annulus. The biplane Simpson method was used to calculate LV end-systolic and end-diastolic volumes, stroke volume, and LV-EF. HF phenotypes were defined as follows: HF with reduced LV-EF (LV-EF $<$ 40%), and HF with preserved LV-EF (HFpEF) (LV-EF $\geq$ 40%). Echocardiographic images were transferred to the strain core laboratory for strain analysis. Images were uploaded to TomTec Image Arena 4.6 and a module of TomTec (2D Cardiac Performance Analysis) was used to quantify myocardial deformation, as previously described.[16] As GLS is a negative value, the absolute value |x| was used for simpler interpretation. All strain measurements were conducted by independent observers blinded to participants' clinical information and the study design. The value of LV-GLS and RV-GLS were categorized by median values, with 10.1 and 12.9.

The primary outcome was 5 year all-cause mortality and the secondary outcome was hospitalization for heart failure (HHF) during the 5 year. Mortality data were obtained and verified via the centralized database of death records of the Ministry of Public Administration and Security in Republic of Korea.

Statistical analysis

For the comparison between groups, the χ^2 test or Fisher exact test was used for categorical variables as appropriate, and the unpaired Student *t* test was applied for continuous variables. The chronological trend of outcomes was expressed as Kaplan–Meier estimates, and mortality risks between the groups were compared by the log-rank test. Multivariable Cox proportional hazard regression models were used to determine the independent predictors of all-cause mortality. We included variables associated with mortality with a *P* value $<$0.05 in univariate analysis as covariates in multivariate analysis, except the variables showing multicollinearity with others. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated in an unadjusted model and then recalculated after adjusting for age, sex, body mass index, hypertension, diabetes mellitus, IHD, LV-EF, LV-GLS, RV-fractional area change (FAC), RV-GLS, and use of beta-blocker, and renin–angiotensin system inhibitor. The magnitude of mortality reduction with statin therapy according to LV-EF, LV-GLS, RV-FAC, and RV-GLS was estimated using Cox regression analysis. For the primary outcome, subgroup and interaction-term analyses were performed to explore potential effect modifiers. Two-sided *P* values $<$0.05 were considered statistically significant. Statistical tests were performed using SPSS software (version 22, IBM Corp.) and R software (version 3.5.3, R foundation).

Results

Demographic and clinical characteristics

Table 1 summarizes baseline characteristics of study subjects according to type and aetiology of HF. Among the total of 3837 patients, the proportion of patients with ischaemic HFrEF, non-ischaemic HFrEF, ischaemic HFpEF, and non-ischaemic HFpEF was 684 (17.8%), 1300 (33.9%), 570 (14.9%), and 1283 (33.4%), respectively. Briefly, patients with

Table 1 Baseline characteristics according to type and aetiology of HF

	Ischaemic HFrEF (n = 684)	Non-ischaemic HFrEF (n = 1300)	Ischaemic HFpEF (n = 570)	Non-ischaemic HFpEF (n = 1 283)	P value
Demographics					
Age (years)	72.0 ± 10.8	66.4 ± 15.1	74.6 ± 10.3	72.4 ± 14.1	<0.001
Men	465 (68.0)	773 (59.5)	279 (48.9)	521 (40.6)	<0.001
BMI (kg/m^2)	22.9 ± 3.6	23.1 ± 4.1	24.0 ± 4.0	23.3 ± 3.9	<0.001
Medical history					
Hypertension	441 (64.5)	643 (49.5)	433 (76.0)	710 (55.3)	<0.001
Diabetes mellitus	339 (49.6)	387 (29.8)	270 (47.4)	325 (25.3)	<0.001
Chronic heart failure	258 (37.7)	473 (37.2)	192 (33.7)	466 (36.9)	0.444
Atrial fibrillation	117 (17.4)	378 (29.7)	119 (21.1)	774 (60.7)	<0.001
Hyperlipidaemia	412 (60.2)	823 (63.3)	344 (60.4)	833 (64.9)	0.111
Physical examination					
SBP (mmHg)	126.7 ± 25.2	125.9 ± 26.1	134.9 ± 30.2	130.4 ± 27.1	<0.001
DBP (mmHg)	73.9 ± 15.3	75.8 ± 17.5	73.3 ± 17.3	73.7 ± 16.4	0.002
NYHA class					0.251
I/II	32 (6.3)	73 (7.6)	37 (9.4)	71 (8.9)	
III	280 (55.1)	513 (53.5)	225 (57.1)	445 (55.9)	
IV	196 (38.6)	372 (38.8)	132 (33.5)	280 (35.2)	
Laboratory findings					
Haemoglobin (mg/dL)	12.1 ± 2.2	12.7 ± 2.3	11.5 ± 2.3	12.0 ± 2.3	<0.001
Creatinine (mg/dL)	1.9 ± 2.1	1.5 ± 1.8	1.7 ± 1.7	1.4 ± 1.8	<0.001
BNP (pg/mL)	1305.0 (680.0–2643.0)	1355.5 (574.8–2672.5)	695.5 (312.0–1553.8)	732.0 (348.8–1454.0)	<0.001
NT-proBNP (pg/mL)	6668.5 (2431.8–16573.3)	5670.0 (2509.5–12986.2)	3432.5 (1100.0–8787.8)	3257.7 (1193.8–7610.6)	<0.001
CRP (mg/dL)	1.7 (0.4–6.5)	0.9 (0.2–4.4)	1.1 (0.1–5.2)	1.1 (0.2–4.3)	0.001
Echocardiographic data					
LA diameter	44.3 ± 8.2	45.6 ± 9.1	43.5 ± 9.2	45.6 ± 10.8	<0.001
E/e′	21.9 ± 12.4	20.1 ± 11.6	17.0 ± 8.9	17.4 ± 10.6	<0.001
LV-EF (%)	28.0 ± 6.8	26.8 ± 7.1	52.8 ± 8.5	54.4 ± 8.7	<0.001
LV-GLS (%)	8.1 ± 3.3	8.0 ± 3.3	13.4 ± 4.5	10.8 ± 5.0	<0.001
RV-GLS (%)	12.0 ± 5.6	11.1 ± 5.9	15.5 ± 6.3	13.0 ± 6.4	<0.001
RV-FAC (%)	37.5 ± 14.6	33.7 ± 15.2	41.6 ± 15.0	38.3 ± 14.8	<0.001
Medication at discharge					
Beta-blocker	462 (67.5)	833 (65.4)	396 (69.5)	688 (54.5)	<0.001
RAS inhibitor	538 (78.7)	973 (76.4)	412 (72.3)	733 (58.1)	<0.001
MRA	352 (51.5)	657 (51.6)	206 (#6.1)	516 (40.9)	<0.001
Statin	446 (65.2)	452 (34.8)	395 (69.3)	387 (30.2)	<0.001

BMI, body mass index; BNP, B-type natriuretic peptide; CRP, C-reactive protein; DBP, diastolic blood pressure; EF, ejection fraction; FAC, fractional area change; GLS, global longitudinal strain; HF, heart failure; LA, left atrial; LV, left ventricular; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association; RAS, renin–angiotensin system; SBP, systolic blood pressure.
Values given as number (percentage), mean ± standard deviation, or median (interquartile range) unless otherwise indicated.

ischaemic HFrEF and ischaemic HFpEF were older; had a higher prevalence of diabetes mellitus; and were more frequently prescribed with statins at discharge, than their counterparts. On the other hand, patients with ischaemic HFpEF and non-ischaemic HFpEF were more frequently women; had a greater BMI; had a higher prevalence of hypertension and atrial fibrillation; and had lower levels of B-type natriuretic peptide and N-terminal pro B-type natriuretic peptide, than their counterparts. The proportion of new onset HF and the distribution of New York Heart Association Functional class were not significantly different across the groups. Baseline characteristics according to statin use were presented in Supporting information, *Table S1*. We found that 32.5% of patients with non-ischaemic HF (839 of 2583) were prescribed with statins according to current guideline recommendations.

Association between statin therapy and survival

During the 5 year follow-up, 1528 (39.8%) patients died, and they had more unfavourable baseline characteristics (*Table S1*). Patients who died had significantly lower LV-GLS, RV-GLS, and RV-FAC than survivors, while differences in LV-EF were not significant.

Table 2 presents the results of Cox regression analyses of the association between clinical and echocardiographic characteristics and mortality. Statin treatment was significantly associated with reduced mortality (unadjusted HR 0.761; 95% CI 0.687–0.843; $P < 0.001$) and remained significant in multivariate analysis (adjusted HR 0.839; 95% CI 0.718–0.980; $P = 0.027$). Patients with reduced LV-GLS had higher morality, but LV-EF was not associated with mortality (HR 1.003, 95% CI 0.996–1.009, $P = 0.461$).

When patients were stratified into 4 groups according to type and aetiology of HF, patients with non-ischaemic HFrEF had the highest mortality, followed by those with ischaemic HFrEF and those with non-ischaemic HFpEF, while patients with ischaemic HFrEF had the lowest mortality, without reaching statistical significance (*Figure S1*). Notably, survival benefits of statin use were significantly different according to type and aetiology of HF. Among the HF subtypes of HFrEF and HFpEF, statin treatment was independently associated with a significant mortality reduction in HFpEF group (adjusted HR 0.781, 95% CI 0.621–0.981, $P = 0.034$); however, in HFrEF group, the reduction in mortality was smaller and was not significant (adjusted HR 0.881, 95% CI 0.712–1.090, $P = 0.244$) (*Figure 2A,B*). When patients were stratified into two groups according to ischaemic vs. non-ischaemic aetiology of HF, statin treatment was significantly and independently associated with a mortality reduction in ischaemic HF group (HR 0.775; 95% CI 0.607–0.989; $P = 0.040$), but not in non-ischaemic HF group (HR 0.895; 95% CI 0.734–1.092; $P = 0.275$) (*Figure 2C,D*). Similar trends were observed in the Kaplan–Meier survival curves, demonstrating a more pronounced reduction in mortality among patients with HFpEF and those with ischaemic HF than their counterparts (*Figure S2*). Regarding HHF, HFpEF group and non-ischaemic HF group were seemed to receive clinical benefits from statin use, while statistical significance was attenuated (*Figure S3*). Mortality risk reduction of statin therapy by three LV-EF strata according to current guidelines (LV-EF $<40\%$, LV-EF 40–49%, and LV-EF $\geq 50\%$) were presented as *Figure S4*.[8]

Effect of myocardial contractility and ischaemic aetiology on association between statin therapy and survival

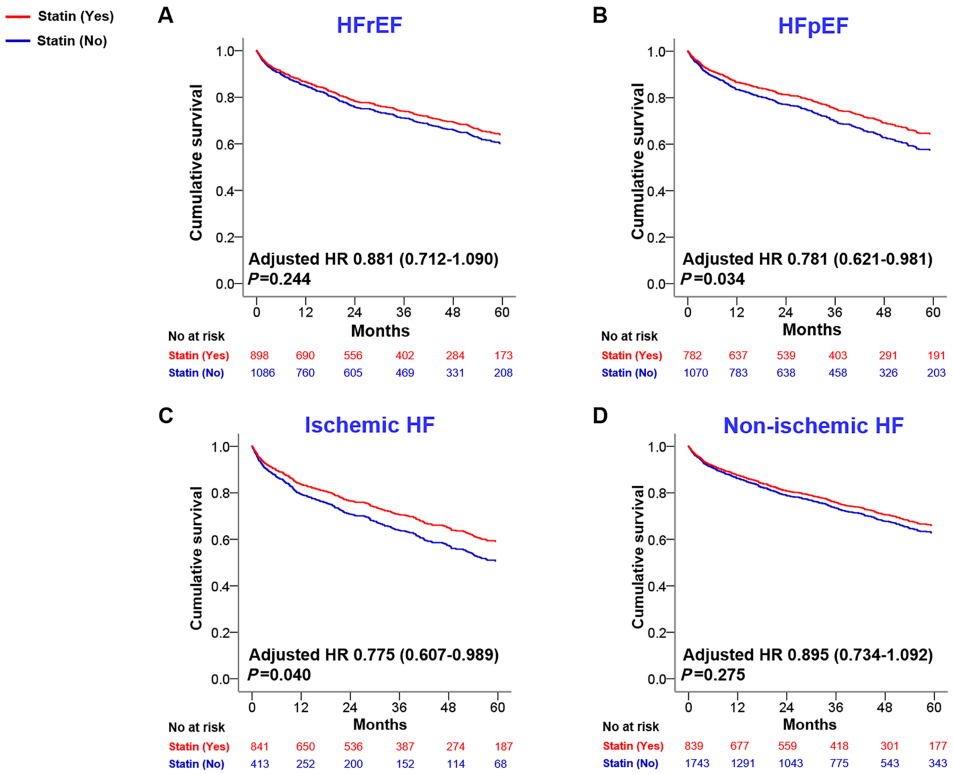
In Cox regression analysis, the relative magnitude of survival benefit with statin therapy (i.e., the relative HR for statin users in comparison with non-users) increased as the value of LV-EF increased in the overall patients (*Figure 3A*). The magnitude of this association between increasing LV-EF and a greater mortality reduction with statin therapy was more pronounced ischaemic HF group (*Figure 3B*) than non-ischaemic HF group (*Figure 3C*). Similar associations were observed for LV-GLS; the relative magnitude of survival

Table 2 Cox-proportional hazard regression analysis for mortality

	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Age	1.047	1.042–1.052	<0.001	1.048	1.041–1.056	<0.001
Men	0.997	0.901–1.102	0.950	1.221	1.056–1.412	0.007
Body mass index	0.921	0.908–0.934	<0.001	0.933	0.914–0.952	<0.001
Diabetes mellitus	1.322	1.193–1.465	<0.001	1.628	1.401–1.891	<0.001
LV-GLS	0.952	0.942–0.963	<0.001	0.955	0.935–0.976	<0.001
Beta-blocker use	0.627	0.567–0.694	<0.001	0.816	0.697–0.955	0.011
RAS inhibitor use	0.644	0.579–0.715	<0.001	0.754	0.639–0.889	0.001
Statin use	0.761	0.687–0.843	<0.001	0.839	0.718–0.980	0.027

CI, confidence interval; GLS, global longitudinal strain; HR, hazard ratio; RAS, renin–angiotensin system.
Included variables are age, sex, body mass index, hypertension, diabetes mellitus, ischaemic heart disease, hyperlipidaemia, beta-blocker, renin–angiotensin system inhibitor, mineralocorticoid receptor antagonist, statin, diuretics, left ventricular GLS, left ventricular ejection fraction, right ventricular fractional area change, and right ventricular GLS.

Figure 2 Hazard ratios for mortality in statin users vs. non-users according to type and aetiology of heart failure. Multivariable-adjusted survival curves demonstrating the difference in all-cause mortality between statin users and non-users at 5 year follow-up. Note a smaller mortality reduction with statin therapy in the HFrEF group (A) compared with that in the HFpEF group (B). Mortality reduction with statin therapy was also smaller in non-ischaemic HF group (D) than ischaemic HF group (C). Adjusted comparisons were based on multivariate Cox regression models. HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.



benefit with statin therapy increased as LV-GLS increased in the overall patients (*Figure 3D*), with a steeper dose–response relationship in ischaemic HF group (*Figure 3E*) than non-ischaemic HF group (*Figure 3F*). Conversely, the relative magnitude of survival benefit with statin therapy decreased as the value of RV-FAC and RV-GLS increased in the overall patients (*Figure 4A,D*). The magnitude of association between RV-FAC and survival benefit was similar in both ischaemic and non-ischaemic HF groups (*Figure 4B,C*). For RV-GLS, the magnitude of this association was more evident in ischaemic HF group than non-ischaemic HF group (*Figure 4E* vs. *4E*).

Subgroup analyses

There was a significant interaction between statin use and the aetiology of HF (i.e., ischaemic vs. non-ischaemic HF) for all-cause mortality (*P* for interaction = 0.003). When patients were stratified into ischaemic vs. non-ischaemic HF groups, statin therapy was significantly associated with lower mortality risk across most pre-specified subgroups in ischaemic HF group, but not in non-ischaemic HF group (*Figure 5A, B*). In ischaemic HF group, a significant interaction was present between statin use and age for mortality (*P* for interaction = 0.025), with a greater mortality reduction with statin therapy in younger patients (≤75 years) than in older patients (>75 years). There were no significant interactions between statin use and all other variables used to define subgroups. In non-ischaemic HF group, there were no significant interactions between statin use and subgroups.

Discussion

The main findings of our study are as follows: (i) statin therapy was significantly associated with improved adjusted survival among patients with HFpEF and those with ischaemic HF, but not among patients with HFrEF and those with non-ischaemic HF; (ii) the relative magnitude of survival benefit with statin therapy increased as LV-EF and LV-GLS increased, with a more pronounced association in patients with ischaemic HF than those with non-ischaemic HF; (iii) the survival benefit with statin therapy decreased as RV-FAC and

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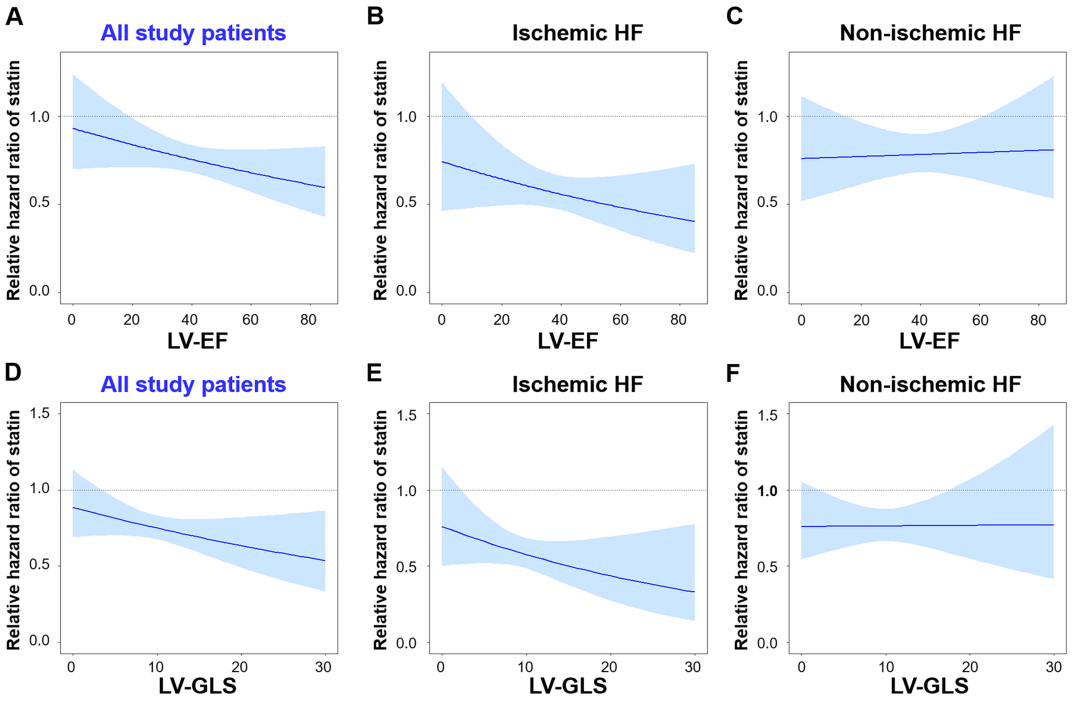
Figure 3 Relative magnitude of survival benefit with statin therapy by left ventricular systolic function. Cox regression analysis showing the multivariable-adjusted relative hazard ratios (solid line) and 95% confidence intervals (shaded area). Note that the magnitude of mortality reduction with statin therapy substantially increased as LV-EF increased in the overall study patients (A). This association was more pronounced in patients with ischaemic HF (B) than those with non-ischaemic HF (C). Similar associations were found for LV-GLS (D–F). HF, heart failure; LV-EF, left ventricular-ejection fraction; LV-GLS, left ventricular-global longitudinal strain.



RV-GLS increased, with less difference in the magnitude of associations according to the presence or absence of ischaemic aetiology; and (iv) in ischaemic HF patients, survival benefit with statin therapy was confined to younger patients (≤75 years) (Take home figure).

Our study demonstrated that 1 year and 5 year all-cause mortality was 21.4% and 39.8%, respectively, which is a high number but in line with previous studies.[18,19] Therefore, the need for developing or identifying novel therapeutic agents and strategies is imperative to improve the prognosis of HF patients, and the efforts to uncover new treatment targets for HF based on its pathophysiology are ongoing. Among several pathophysiological mechanisms of HF, inflammation and endothelial dysfunction have recently gained increasing attention as potential therapeutic targets for HF, particularly HFpEF.[20,21] Several lines of evidence suggest that statins can reduce inflammation, by showing the reduction of CRP and other inflammatory markers with statin therapy.[3,22] It has also been reported that statin therapy can improve nitric oxide bioavailability and mobilize circulating endothelial progenitor cells, all supporting the protective effects of statins on endothelial function.[23,24] Given that inflammatory process and endothelial dysfunction are important pathophysiological factors of HFpEF, the magnitude of clinical benefit with statin therapy may be greater in patients with HFpEF than those with HFrEF. This can explain the negative results from the large-scale randomized trials assessing the effect of statin therapy on mortality in the HF population, which included only a very small proportion (10%) of patients with HFpEF (the GISSI-HF trial) or even excluded them from participation (the CORONA trial).[6,7] In our study, in which approximately half of the study population was HFpEF, the survival benefit with statin therapy was greater in patients with HFpEF than those with HFrEF, although the interaction was not significant. This finding supports the emerging hypothesis that statins may be selectively effective for the treatment of patients with HFpEF, while simultaneously, being ineffective in HFrEF.[11]

In the present study, statin therapy was significantly associated with lower mortality rates in patients with ischaemic HF, but not in those with non-ischaemic HF. This is in line with a prior study demonstrating a trend towards a more profound survival benefit with statins in HF patients with ischaemic aetiology.[25] Considering that acute coronary syndromes constituted approximately 40% of the causes of sudden cardiovascular deaths and 26% of non-sudden deaths in HF patients,[26] anti-atherothrombotic effects of statins may confer a greater survival benefit in patients with ischaemic

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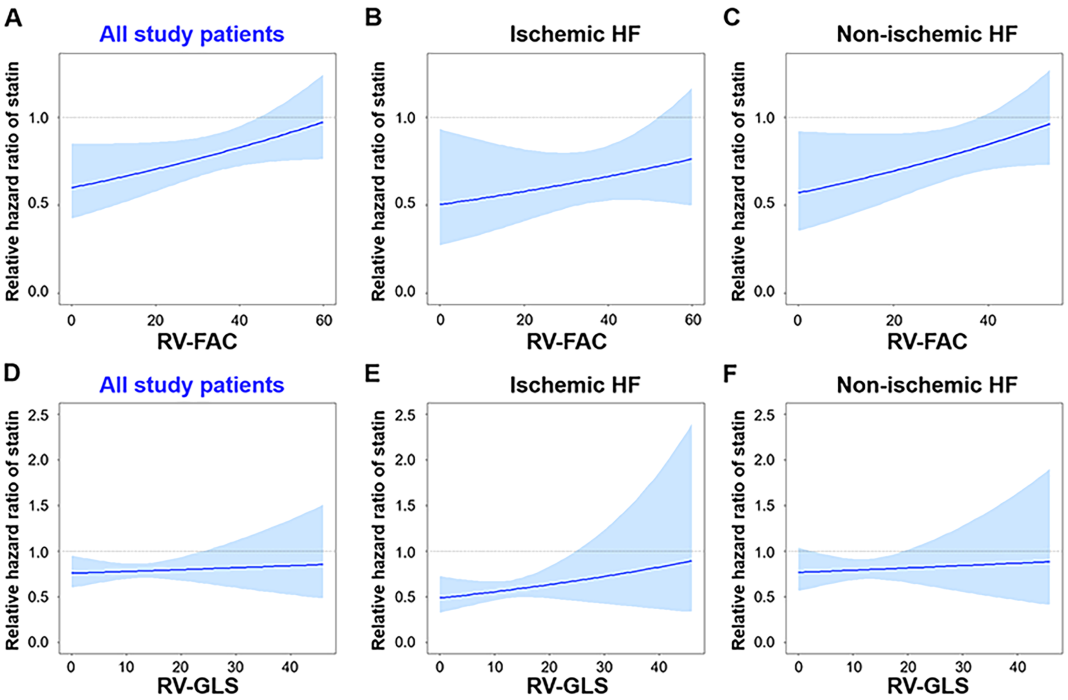
Figure 4 Relative magnitude of survival benefit with statin therapy by right ventricular systolic function. Cox regression analysis showing the multivariable-adjusted relative hazard ratios (solid line) and 95% confidence intervals (shaded area). Note that the magnitude of mortality reduction with statin therapy substantially decreased as RV-FAC increased in the overall study patients (A). The magnitude of association between RV-FAC and survival benefit was similar in both ischaemic (B) and non-ischaemic HF groups (C). The magnitude of mortality reduction with statin therapy decreased as RV-GLS increased in the overall study patients, with a less steep slope (D) than in the case of RV-FAC. The magnitude of this association was more evident in ischaemic HF group (E) than non-ischaemic HF group (F). HF, heart failure; RV-FAC, right ventricular-fractional area change; RV-GLS, right ventricular-global longitudinal strain.



HF than those with non-ischaemic HF.[4] Our study also showed that, in patients with ischaemic HF, the survival benefit with statin therapy increased as LV-EF and LV-GLS increased, but this association was attenuated in those with non-ischaemic HF. This finding suggests that beneficial effects of statin therapy can be maximized in patients with the combination of HFpEF and ischaemic HF. It seems plausible that statin therapy may be more effective in this population than others, collectively considering its anti-inflammatory or anti-fibrotic effects on myocardium and anti-atherosclerotic effects on vasculature.[27,28] In this regard, developing or discovering novel biomarkers reflecting pro-inflammatory and pro-fibrotic processes in HF will be of paramount importance to identify which HF patients most benefit from statin therapy.

Our subgroup analysis demonstrated that, in patients with ischaemic HF, the survival benefit with statin therapy was confined to the subgroup of those 75 years of age and younger. This finding is not surprising considering that previous studies have raised concerns regarding the risk of statin therapy in older adults. Specifically, a previous randomized controlled trial showed that there was a direction towards increased all-cause mortality with statin therapy compared with usual care among individuals 75 years and older.[29] Statin-associated musculoskeletal adverse events, including myalgia, myositis, myopathy, tendinopathy, tendon disorder, and arthralgia, has been recognized as a possible mechanism, because these conditions could contribute to physical deconditioning and frailty and might be particularly problematic in elderly.[30] There also remains a risk of statin-induced cognitive impairment, which could again contribute to poor functional status, an elevated fall risk, and disability, although a recent study reported that statin use was not associated with decline in memory or cognition in community-dwelling elderly aged 70 to 90 years over 6 years.[31] These unintended adverse effects related to statin therapy might entail more serious consequences in elderly with HF than those without, since HF per se is an important risk factor for frailty and cognitive impairment.[32,33] Moreover, prior studies suggest that, among patients suffering from HF, those with ischaemic aetiology may have higher risks for cognitive impairment and detrimental brain structural changes than their counterparts.[34,35] Taken together, even though several evidence support the net benefit of statin therapy for primary

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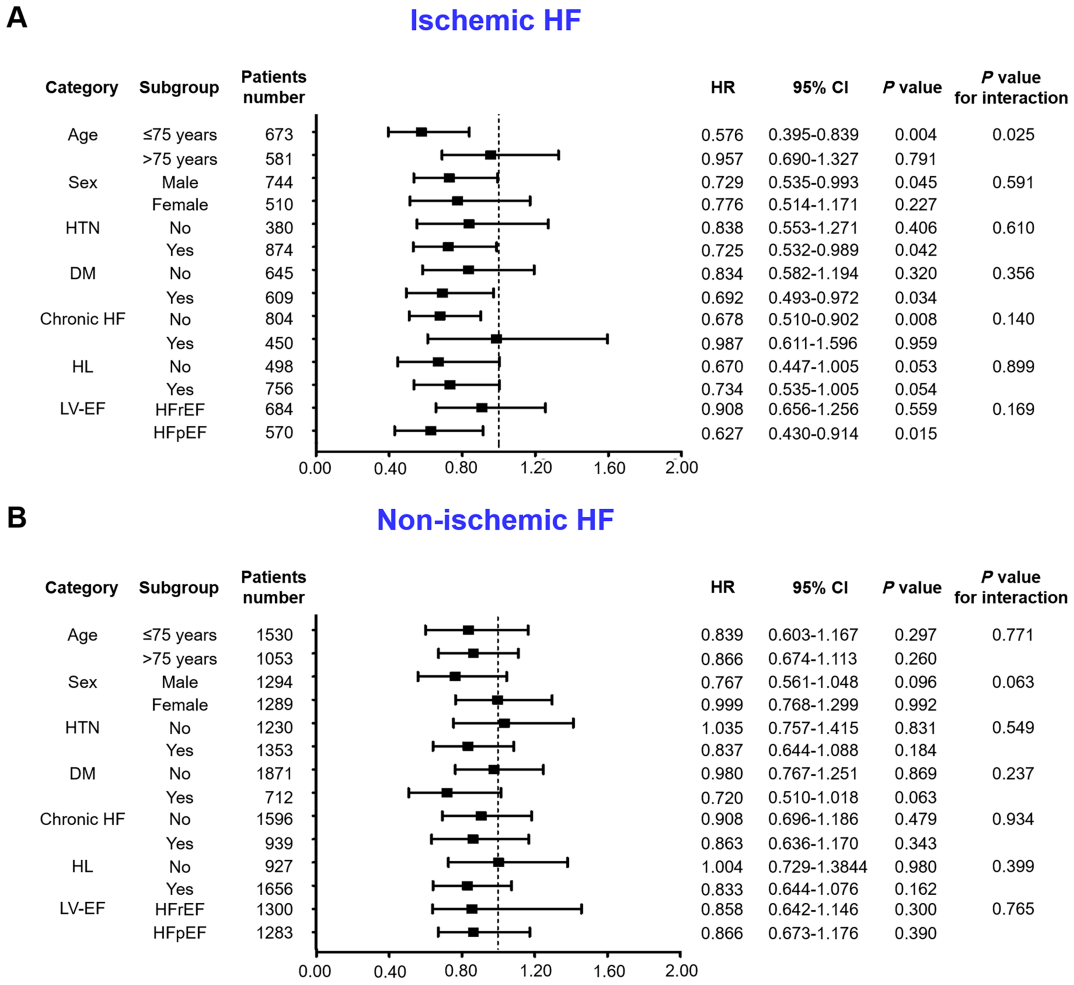
Figure 5 Forest plot depicting multivariable-adjusted subgroup analyses. Forest plots of adjusted hazard ratios for the relationship between relevant subgroups and all-cause mortality according to statin therapy in patients with ischaemic HF (A) and those with non-ischaemic HF (B). Interaction *P* values are shown. The hazard ratio within each stratum was adjusted for the independent variables shown in *Table 2*. CI, confidence interval; DM, diabetes mellitus, HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HL, hyperlipidaemia; HR, hazard ratio; HTN, hypertension; LV-EF, left ventricular-ejection fraction; LV-GLS, left ventricular-global longitudinal strain. Take home figure: Postulated associations between aetiology of heart failure, myocardial contractility, and effect of statin therapy. Ischaemic aetiology for HF and LV and RV myocardial contractility may be associated with the magnitude of survival benefits with statin therapy in patients with acute HF. HF, heart failure; LV, left ventricular; RV, right ventricular.



prevention in the general population of the elderly aged 75 years and over,[36] whether this is true in the elderly with HF is unknown. Further studies are needed to determine whether prescribing or continuing statins for the elderly with HF, particularly those with ischaemic HF, is beneficial or harmful.

Study limitations

First, because of the lack of data on types and doses of statins, we could not examine the dose–response relationship between statin use and mortality in patients with HF, which may strengthen the causality power of this cohort study. On the other hand, considering that lipoprotein has the property to bind to lipopolysaccharide and to reduce its endotoxin activity, concern has been raised that there is an optimal lipoprotein concentration below which lipid-lowering might be deleterious because of inadequate lipopolysaccharide binding.[37] Given the higher endotoxin levels, measured by the ratio of lipopolysaccharide to lipopolysaccharide-binding protein, in patients with HF,[38] and potential detrimental effects of aggressive lipid-lowering with statins in these patients, even the direction of the effects of statins may differ in those treated with high- vs. low-dose statin therapy. Further studies are therefore needed to fully address this issue.

Second, our study has limitations that are inherent to all cohort studies, including selection bias and unmeasured confounders. In addition, since the STRATS-AHF registry was designed to evaluate all-cause mortality as a primary endpoint, we could not analyse the effects of statins on the subsequent use of invasive procedures, such as cardiac catheterization and device implantation, and adverse clinical outcomes, such as myocardial infarction and stroke, which might strengthen the relevance of our findings. Future randomized trials are certainly needed to confirm our findings. It is hoped that our study will contribute to the selection of the optimal study population for new trials investigating the survival benefit with statins for HF. Third, because statin use was only determined at discharge, we did not account for patients whose statin use was planned to begin after discharge. Fourth, 32.9% of patients with ischaemic HF were not prescribed with statins at discharge in our study. Considering that statin intolerance is reported to occur in 20% to 30% of patients in previous studies,[27,39,40] statin intolerance may partly explain our findings of non-use of statins in ischaemic HF group. However, the specific causes of non-use of statins in ischaemic HF group were not identified in this study. Finally, as we exclusively enrolled and analysed Korean patients, it is uncertain whether our findings could be generalized to other ethnicities.

Conclusions

The survival benefit with statin therapy was limited to patients with HFpEF and patients having ischaemic aetiology. Among patients with ischaemic HF, this benefit was confined to patients aged 75 years or less. Echocardiographic assessment could further identify subgroups of HF patients with different response to statin treatment, such as the relatively reduced benefit of statins in ischaemic HF patients with impaired LV systolic function as compared with their counterparts. These findings suggest that the variation in beneficial effects of statins on HF may be partly attributed to age, ischaemic aetiology, and varying degrees of myocardial dysfunction, and thus, a careful assessment of clinical and echocardiographic features can potentially guide statin therapy in patients with HF and predict their response.

Conflict of interest

None.

Funding

None.

Clinical Trial Registration

Registry: ClinicalTrials.gov Number: NCT03513653 (https://clinicaltrials.gov/ct2/show/NCT03513653).

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Morality by type and aetiology of HF.
Multivariable-adjusted survival curves demonstrating the difference in all-cause mortality among 4 groups according to type and aetiology of HF: ischaemic HFrEF, non-ischaemic HFrEF, ischaemic HFpEF, and non-ischaemic HFpEF.
HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio.
Figure S2. Clinical outcomes according to statin therapy stratified by heart failure type and aetiology.
Unadjusted Kaplan–Meier survival curves demonstrate the difference in all-cause mortality between statin users and non-users at 5-year follow-up in patients with HFrEF (A) and those with HFpEF. Comparisons were performed with the log-rank test.
HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.
Figure S3. Risks of HHF in statin users and non-users according to HF type and aetiology.
Multivariable-adjusted survival curves demonstrating the difference in survival free from HHF between statin users and non-users at 5-year follow-up. Note a relatively smaller reduction in HHF with statin therapy in the HFrEF group (A) compared with that in the HFpEF group (B). The reduction in HHF with statin therapy was also smaller in non-ischaemic HF group (D) than ischaemic HF group (C).
HF, heart failure; HHF, hospitalization for heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio.
Figure S4. Hazard ratios for mortality in statin users versus non-users based on three LVEF strata according to the ESC guideline.
Multivariable-adjusted survival curves demonstrating the difference in all-cause mortality between statin users and non-users at 5-year follow-up. Note a relatively smaller mortality reduction with statin therapy in patients with LVEF $<$40% (A) and in patients with LVEF 40–49% (B) compared with that in patients with LVEF $\geq$50% (C). HF, heart failure; HR, hazard ratio; LVEF, left ventricular ejection fraction.
Table S1. Baseline characteristics of study population.
Table S2. Baseline characteristics according to 5-year mortality.

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