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ORIGINAL RESEARCH

Characteristics, Predictors, and Clinical Outcomes in Heart Failure With Reduced Ejection Fraction According to a 1-Year Left Ventricular Ejection Fraction Following Sacubitril/Valsartan Treatment

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BACKGROUND: Optimal medical treatment can lead to improvement in left ventricular ejection fraction (LVEF) in patients with heart failure with reduced EF (HFrEF). We investigated the characteristics, predictors, and outcomes of HFrEF according to the 1-year LVEF following angiotensin receptor–neprilysin inhibitors therapy (ARNI).

METHODS AND RESULTS: Using the STRATS-HF-ARNI (Strain for Risk Assessment and Therapeutic Strategies in Patients With Heart Failure Treated With Angiotensin Receptor-Neprilysin Inhibitor) registry, we identified 1074 patients with HFrEF who took ARNI and underwent baseline and 1-year echocardiography. Patients were classified as HF with improved ejection fraction (HFimpEF) and persistent HFrEF (perHFrEF) (1-year LVEF >40% and ≤40%). The primary and secondary outcomes were all-cause and cardiac mortality from the 1-year follow-up. Among 1074 included patients, 498 (46.4%) had HFimpEF, and 576 (53.6%) had perHFrEF. Older age, male sex, and large LV end-diastolic volumes were positive predictors of perHFrEF, whereas atrial fibrillation and high systolic blood pressure were identified as inverse predictors. Patients with HFimpEF showed lower all-cause and cardiac mortality rates (both log-rank $P<0.001$). In the multivariable analysis, perHFrEF (hazard ratio, 2.402 [95% CI, 1.251–4.610]; $P=0.008$) was an independent predictor of poor outcomes. The risk of all-cause mortality decreased as the 1-year LVEF increased up to 40%; however, no additional risk reduction was observed beyond 40%. Compared with patients taking renin-angiotensin-aldosterone system inhibitors in the STRATS-AHF (Strain for Risk Assessment and Therapeutic Strategies in Patients With Acute Heart Failure) registry, those in the STRATS-HF-ARNI registry demonstrated better outcomes in both HFimpEF and perHFrEF.

CONCLUSIONS: Patients with HFimpEF had better prognosis than those with perHFrEF, and ARNI treatment in HFrEF could be more beneficial than renin-angiotensin-aldosterone system inhibitors for both HFimpEF and perHFrEF.

REGISTRATION: URL: https://www.who.int/clinical-trials-registry-platform; Unique identifier: KCT0008098.

Key Words: ARNI ■ ejection fraction ■ heart failure ■ mortality

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CLINICAL PERSPECTIVE

What Is New?

- Among patients with heart failure with reduced ejection fraction (HFrEF) treated with angiotensin receptor–neprilysin inhibitors, 45.6% were diagnosed with HF with improved EF (HFimpEF) at 1-year follow-up; older age, male sex, and a large left ventricular end-diastolic volume were identified as positive predictors for persistent HFrEF, whereas atrial fibrillation and systolic blood pressure were identified as inverse predictors.
- Patients with HFimpEF exhibited lower all-cause and cardiac mortality rates compared with those with persistent HFrEF; the risks of all-cause mortality decreased as the 1-year left ventricular EF approached 40%; no additional improvement was observed beyond this threshold.
- Compared with patients taking renin-angiotensin-aldosterone system inhibitors in the STRATS-AHF (Strain for Risk Assessment and Therapeutic Strategies in Patients With Acute Heart Failure) registry, those in the STRATS-HF-ARNI (Strain for Risk Assessment and Therapeutic Strategies in Patients With Heart Failure Treated With Angiotensin Receptor-Neprilysin Inhibitor) registry demonstrated better outcomes in both HFimpEF and persistent HFrEF groups.

What Are the Clinical Implications?

- Considering the observed prognostic differences, defining HFimpEF with a follow-up left ventricular EF of 40% would be appropriate, although further studies are required to validate our results.
- Because adherence to guideline-directed medical therapy is beneficial not only for patients with persistent HFrEF but also for those with HFimpEF, patients should adhere to guideline-directed medical therapy incorporating angiotensin receptor–neprilysin inhibitors regardless of the 1-year left ventricular EF (≤40% or >40%).

Nonstandard Abbreviations and Acronyms

ARNI	angiotensin receptor–neprilysin inhibitor
GDMT	guideline-directed medical therapy
HFimpEF	heart failure with improved ejection fraction
HFrEF	heart failure with reduced ejection fraction
RASi	renin-angiotensin-aldosterone system inhibitor

Heart failure (HF) is recognized as a global epidemic and poses a significant clinical and social burden.[1,2] Previous studies have attempted to identify the prognostic factors and elucidate therapeutic approaches, with clinical guidelines playing a pivotal role in providing comprehensive strategies to improve clinical outcomes.[3–5] Current guidelines categorize patients with HF based on their left ventricular ejection fraction (LVEF): LVEF ≤40% (HF with reduced EF [HFrEF]), LVEF 41% to 49% (HF with midrange EF), and LVEF ≥50% (HF with preserved EF).[3–5]

Sacubitril/valsartan, an angiotensin receptor–neprilysin inhibitor (ARNI), was developed to counteract neurohumoral overactivation, leading to volume overload and pathologic remodeling in patients with HF, while minimizing the risks of severe angioedema.[6,7] Demonstrating superior outcomes in reducing all-cause mortality, cardiovascular mortality, and hospitalization due to worsening HF compared with enalapril,[8] ARNI has become a cornerstone in guideline-directed medical therapy (GDMT) for HFrEF.[3–5]

Recent studies have explored patients with HF with a history of an LVEF of ≤40% who later present with a higher LVEF. These patients are now identified as having HF with improved ejection fraction (HFimpEF), distinguishing them from those with HF with midrange EF or HF with preserved EF owing to their distinct prognoses.[9,10] However, limited data are available on the characteristics, predictors, and clinical outcomes of HFimpEF, especially among those treated with ARNI.[9,11]

Using data from the multicenter registry, we identified patients with HFrEF taking ARNI and classified them as either the group with HFimpEF or the group with persistent HFrEF based on the 1-year echocardiography findings. Subsequently, we investigated the clinical characteristics, predictors, and outcomes of these patients.

METHODS

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Ethical Statement and Data Availability

This study was conducted according to the principles of the Declaration of Helsinki. This study was approved by the Institutional Review Board of Seoul National University Hospital (IRB no. J-2212-034-1383) and Seoul National University Bundang Hospital (IRB no. B-2005-615-108). The requirement for informed consent was waived because anonymized data were analyzed.

Study Design

The STRATS-HF-ARNI (Strain for Risk Assessment and Therapeutic Strategies in Patients With Heart Failure treated With Angiotensin Receptor-Neprilysin Inhibitor) study was registered with the Clinical Research Information Service of the Ministry of Health and Welfare of the Republic of Korea (registration number: KCT0008098). Briefly, we consecutively included 2757 patients who were diagnosed with HFrEF and treated with ARNI at 2 tertiary medical institutes in South Korea (Seoul National University Hospital, Seoul, and Seoul National University Bundang Hospital, Seongnam-si, Gyeonggi-do) between 2017 and 2022. Among them, patients without baseline echocardiography at the participating institutes or those who initiated ARNI treatment before their visit to the participating institutes (n=1383) were excluded. Subsequently, patients who either died or discontinued ARNI treatment before the 1-year follow-up (n=110), as well as those who were lost to follow-up before 1 year or did not undergo echocardiography at 1-year follow-up (n=190) were excluded (Figure 1A). Baseline characteristics of those who did not undergo a 1-year follow-up are presented in Table S1.

As the STRATS-HF-ARNI registry comprised patients with HF treated with ARNI, we additionally conducted an analysis using data from the STRATS-AHF (Strain for Risk Assessment and Therapeutic Strategies in Patients With Acute Heart Failure) registry. After identifying patients taking renin-angiotensin-aldosterone system inhibitors (RASis) in the STRATS-AHF registry, the clinical outcomes of HFimpEF and persistent HFrEF reported in the 2 registries were compared according to the medication used. Detailed information about the STRATS-AHF registry has been published elsewhere.[12–14]

Study Variables and Definitions

All echocardiographic examinations were conducted by cardiologists certified by the Korean Society of Echocardiography. Echocardiographic images were acquired using standard ultrasound devices purchased from GE, Philips, and Siemens, following the American Society of Echocardiography guidelines.[15] The LVEF values at baseline and the 1-year follow-up were calculated using the biplane Simpson method. Patients with HFrEF (LVEF ≤40%) at baseline were stratified into those with a 1-year LVEF of >40% (HFimpEF) and those with a 1-year LVEF of ≤40% (persistent HFrEF), based on the echocardiographic findings at the 1-year follow-up. The group with HFimpEF was divided into the following subgroups: patients with HF with a 1-year LVEF

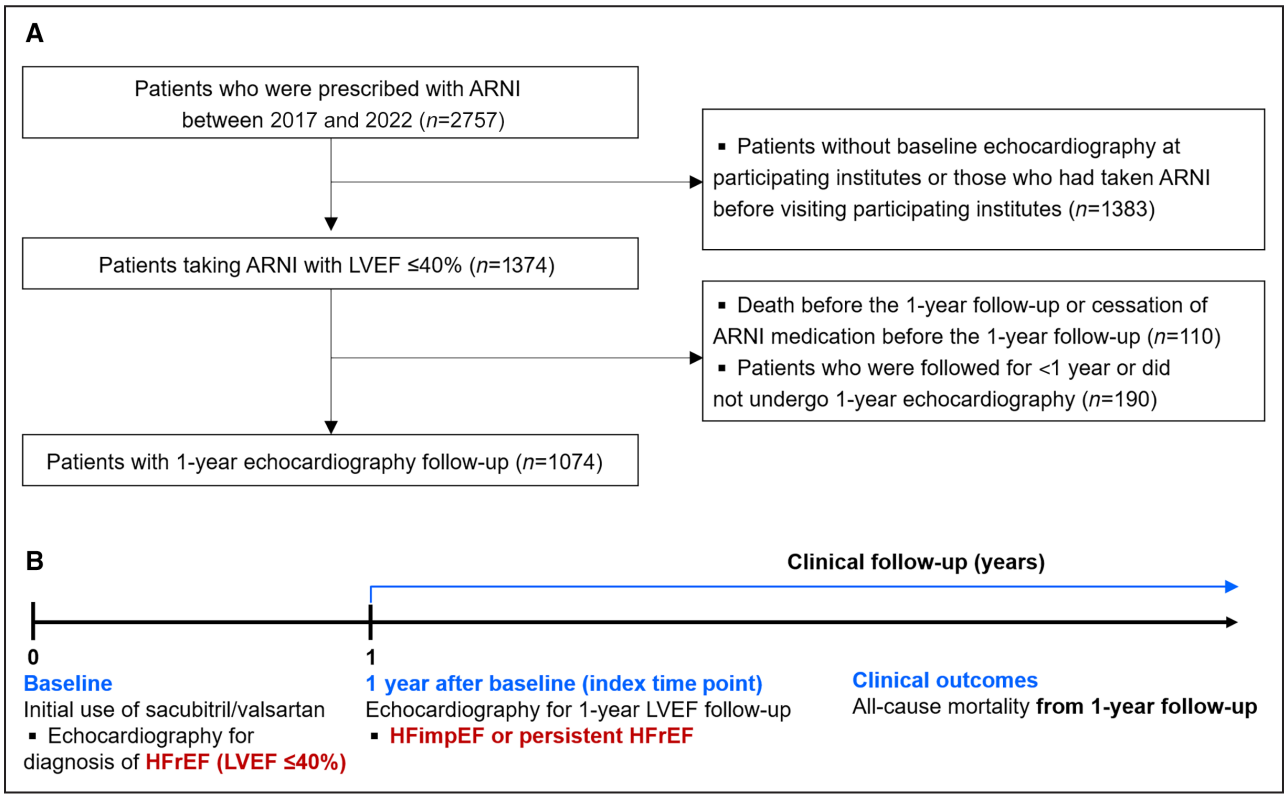

Figure 1. Schematic diagram of the study process.
Illustrations of the study population (**A**) and study flow chart (**B**) are presented. ARNI indicates angiotensin receptor–neprilysin inhibitor; HFimpEF, heart failure with improved ejection fraction; HFrEF, heart failure with reduced ejection fraction; and LVEF, left ventricular ejection fraction.

of 41% to 49% and patients with HF with a 1-year LVEF of ≥50%. Moreover, the group with persistent HFrEF was divided into the following subgroups: patients with HF with a 1-year LVEF of 31% to 40% and patients with HF with a 1-year LVEF of ≤30%.[16]

The index time point was defined as the 1-year follow-up from baseline enrollment in the STRATS-HF-ARNI registry. The primary and secondary outcomes were all-cause and cardiac mortality from the 1-year follow-up echocardiography (Figure 1B). The mortality data were obtained and verified using a centralized database of death records managed by the Korean Government's Ministry of Public Administration and Security. The medication data included the use of beta-blockers, mineralocorticoid receptor antagonists, and sodium-glucose cotransporter 2 inhibitors. RASi use was defined as the administration of either an angiotensin-converting enzyme inhibitor or an angiotensin II receptor blocker as recorded in the STRATS-AHF registry.

Statistical Analysis

Data were presented as the means±SD or medians with interquartile ranges for continuous variables and as numbers and frequencies for categorical variables. For group comparisons, the chi-square test (or Fisher's exact test for small expected cell counts) was used for categorical variables and the unpaired Student's *t* test for continuous variables. A multivariable logistic regression model was employed to investigate the predictors of HFimpEF and persistent HF with preserved EF. Variables with a *P* value of <0.1 in the univariable logistic regression analysis were included in the multivariable model, adjusted for age, sex, hypertension, atrial fibrillation, systolic blood pressure (SBP), left ventricular end-diastolic volume (LVEDV), and pulmonary artery systolic pressure. Considering the possibility of a survival bias, we additionally performed a logistic regression analysis including patients who either died or discontinued ARNI treatment before the 1-year follow-up, as well as those who were lost to follow-up before 1 year or did not undergo echocardiography at 1-year follow-up as a sensitivity analysis. A sensitivity analysis for cardiac mortality was also performed to consider the competing risk of death from noncardiac causes. The chronological trend of clinical outcomes after the 1-year follow-up was depicted using Kaplan–Meier estimates, and the log-rank test was used to compare the differences in clinical outcomes according to the 1-year LVEF. A multivariable Cox proportional hazards regression model was used to identify the independent prognostic factors. Variables with a *P* value of <0.1 in the univariable Cox regression analysis were included in the multivariable model, adjusting for covariates including age, end-stage renal disease, stroke, SBP at 1 year, LVEF at 1 year, LVEDV at 1 year, and pulmonary artery systolic pressure at 1 year. The odds ratios (ORs) from logistic regression and hazard ratios (HRs) from the Cox model were presented along with the corresponding 95% CIs and *P* values. The nonlinearities in the associations between 1-year LVEF and the risk of all-cause mortality from the 1-year follow-up were assessed using restricted cubic splines after adjusting for covariates. For sensitivity analysis, propensity score matching (PSM) was employed to match variables including age, sex, ischemic cardiomyopathy, hypertension, diabetes, end-stage renal disease, SBP, diastolic blood pressure, LVEF, LVEDV, use of beta-blockers, and mineralocorticoid receptor antagonists between the STRATS-HF-ARNI registry (patients with HFrEF treated with ARNIs) and the STRATS-AHF registry (patients with HFrEF treated with RASis). Statistical significance was set at a *P* value of <0.05. Statistical analyses were conducted using the IBM SPSS version 23 (SPSS Inc., Chicago, IL) and R programming version 4.3.0 (The R Foundation for Statistical Computing, Vienna, Austria, http://www.R-project.org).

RESULTS

Clinical Characteristics and Predictors of LVEF Improvement

Among patients enrolled in the STRATS-HF-ARNI registry, 1074 patients who underwent baseline and the 1-year follow-up echocardiography (mean age, 64.5±13.4 years; men, 741 [69.0%]) were analyzed in this study (Figure 1). Of them, 369 (34.4%) had hypertension, 286 (26.6%) had diabetes, 52 (4.8%) had end-stage renal disease, 91 (8.5%) had a history of stroke, and 361 (24.3%) had atrial fibrillation. The ΔLVEF between baseline and the 1-year echocardiography was 11.3±12.6% (median, 8.4%; interquartile range, 1.1%–20.1%).

The clinical characteristics according to the 1-year LVEF are presented in Table 1. Briefly, 498 patients (46.4%) were diagnosed with HFimpEF based on the echocardiographic findings at 1-year follow-up, and 576 patients (53.6%) were diagnosed with persistent HFrEF. In terms of baseline characteristics, patients with persistent HFrEF were 2 years older, predominantly men, showed less history of atrial fibrillation, and had a lower blood pressure, a larger LVEDV, and a higher pulmonary artery systolic pressure than those with HFimpEF. No differences were observed in the history of beta-blockers, mineralocorticoid receptor antagonists, and sodium-glucose cotransporter 2 inhibitor treatment as well as in NT-proBNP (N-terminal pro-B-type natriuretic peptide) levels and LVEF at baseline between the 2 groups. Clinical characteristics

Table 1. Clinical Characteristics According to the 1-Year Follow-Up HF Phenotypes

	HFimpEF (n=498)	Persistent HFrEF (n=576)	*P* value
At baseline			
Demographic data			
Age, y	63.4±14.0	65.5±12.7	0.010
Male sex, %	311 (62.4)	430 (74.7)	<0.001
Body mass index, kg/m^2	24.5±4.4	24.9±3.9	0.166
Cause of HFrEF			0.688
Ischemic cardiomyopathy	138 (27.7)	166 (28.8)	
Nonischemic cardiomyopathy	360 (72.3)	410 (71.2)	
Past medical history, %			
Hypertension	153 (30.7)	216 (37.5)	0.020
Diabetes	122 (24.5)	164 (28.5)	0.142
End-stage renal disease	25 (5.0)	27 (4.7)	0.800
Stroke	35 (7.0)	56 (9.7)	0.114
Atrial fibrillation	136 (27.3)	125 (21.7)	0.033
Physical examination			
SBP, mm Hg	121.6±20.5	118.4±18.6	0.009
DBP, mm Hg	72.0±15.2	70.1±13.6	0.035
Laboratory examination			
Hemoglobin, g/dL	13.3±2.2	13.5±2.0	0.347
N-terminal pro-B-type natriuretic peptide, pg/mL	1490.0 (543.1–4000.0)	1470.0 (607.1–3845.4)	0.474
Echocardiographic parameters			
LVEF, %	29.4±6.8	28.9±6.3	0.246
LVEDV, mL	159.9±56.4	182.5±63.6	<0.001
LVESV, mL	114.2±46.5	131.5±52.9	<0.001
E/*e*′	18.2±11.7	19.6±12.1	0.063
LAVI, mL/m^2	60.5±25.9	64.9±37.2	0.054
PASP, mm Hg	36.1±12.6	38.5±15.2	0.010
Medication, %			
Beta-blocker	457 (91.8)	512 (89.0)	0.133
Mineralocorticoid receptor antagonist	259 (52.1)	282 (49.0)	0.316
Sodium-glucose cotransporter 2 inhibitors	89 (17.9)	91 (15.8)	0.363
Initial sacubitril/valsartan daily dose more than 100 mg	125 (25.1)	130 (22.6)	0.331
At index timepoint (1-year follow-up)			
Physical examination			
SBP, mm Hg	118.9±19.1	116.0±17.8	0.010
DBP, mm Hg	68.9±11.4	68.2±11.9	0.368
Echocardiographic parameters			
LVEF, %	50.7±7.0	31.6±5.9	<0.001
ΔLVEF from baseline, %	21.3±10.3	2.7±6.4	<0.001
LVEDV, mL	108.6±34.7	166.0±61.1	<0.001
LVESV, mL	54.9±21.2	115.1±48.5	<0.001
E/*e*′	12.0±6.4	15.7±9.1	<0.001
LAVI, mL/m^2	46.1±24.7	57.2±36.7	<0.001
PASP, mm Hg	29.4±7.6	33.1±13.2	<0.001

DBP indicates diastolic blood pressure; HF, heart failure; HFimpEF, heart failure with improved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LAVI, left atrial volume index; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; PASP, pulmonary artery systolic pressure; and SBP, systolic blood pressure.

according to further stratification within each group with HFimpEF and persistent HFrEF are presented in Tables S2 and S3, respectively.

We explored the predictors of persistent HFrEF after 1 year of ARNI treatment (Table 2). After adjusting for baseline covariates, older age (OR, 1.024 [95% CI, 1.013–1.036]; *P*<0.001), male sex (OR, 1.443 [95% CI, 1.052–1.979]; *P*=0.023), and a larger LVEDV at baseline (OR, 1.006 [95% CI, 1.004–1.009]; *P*<0.001) were positive predictors of persistent HFrEF. By contrast, atrial fibrillation (OR, 0.710 [95% CI, 0.514–0.981]; *P*=0.038) and a higher SBP (OR, 0.988 [95% CI, 0.981–0.995]; *P*=0.002) were inversely associated with persistent HFrEF. The results of the sensitivity analysis, which were performed in the cohort that did not exclude patients who did not undergo 1-year follow-up echocardiography, are presented as Tables S4 and S5.

Outcomes of HFimpEF and Persistent HFrEF Based on the 1-Year LVEF

During the follow-up period (median, 2.3 years; interquartile range, 1.4–3.5 years), 78 patients (7.3%) died after the index time point. No prognostic difference was found between the 2 participating medical institutions (Figure S1).

As shown in the Kaplan–Meier curves, patients with HFimpEF exhibited lower all-cause (Figure 2A) and cardiac mortality rates (Figure 2B) than those with persistent HFrEF (both log-rank *P*<0.001). In the multivariable Cox regression analysis, persistent HFrEF was significantly associated with an increased risk of all-cause mortality (HR, 2.402 [95% CI, 1.251–4.610]; *P*=0.008). Other independent predictors were age (HR, 1.054 [95% CI, 1.027–1.081]; *P*<0.001), end-stage renal disease (HR, 3.883 [95% CI, 1.473–10.235]; *P*=0.006), SBP at 1 year (HR, 0.971 [95% CI, 0.956–0.986]; *P*<0.001), and pulmonary artery systolic pressure at 1 year (HR, 1.035 [95% CI, 1.018–1.052]; *P*<0.001) (Table 3). The results for cardiac mortality were presented in Tables S6 and S7.

Table 2. Baseline Predictors for Persistent HFrEF at 1-Year Follow-Up Echocardiography

	Odds ratio	95% CI	*P* value
Per 1 year increase in age	1.024	1.013–1.036	<0.001
Male sex	1.443	1.052–1.979	0.023
Hypertension	1.322	0.970–1.801	0.078
Atrial fibrillation	0.710	0.514–0.981	0.038
Per 1 mm Hg increase in systolic blood pressure, mm Hg	0.988	0.981–0.995	0.002
Per 1 mL increase in left ventricular end-diastolic volume, mL	1.006	1.004–1.009	<0.001
Per 1 mm Hg increase in pulmonary artery systolic pressure, mm Hg	1.007	0.996–1.017	0.208

HFrEF indicates heart failure with reduced ejection fraction.

To explore the prognostic association between the 1-year LVEF and clinical outcomes, we further classified patients with HFimpEF using a 1-year LVEF cutoff value of 50% and those with persistent HFrEF using a 1-year LVEF cutoff value of 30%. When further stratifying the group with HFimpEF according to the 1-year LVEF, those with a 1-year LVEF of ≥50% showed a similar prognosis compared with those with a 1-year LVEF of 40% to 49% (log-rank *P*=0.478) (Figure 3A). On the contrary, when stratifying the group with persistent HFrEF according to the 1-year LVEF, patients with a 1-year LVEF of ≤30% presented worse clinical outcomes than those with an LVEF of 31% to 40% (log-rank *P*=0.002) (Figure 3B). The analyses for cardiac mortality were presented in Figure S2 with similar results. In line with these findings, restricted cubic spline curves revealed a decline in the risk of all-cause mortality until the LVEF at 1 year reached 40%; however, an additional risk reduction was not observed beyond a 1-year LVEF of 40% (Figure 3C).

Prognostic Difference Between Patients Taking ARNI and Those Taking RASi in the Groups With HFimpEF and Persistent HFrEF

To compare the prognosis between patients taking ARNIs and those taking RASis in each HF phenotype of HFimpEF and persistent HFrEF, we identified patients from the STRATS-AHF registry who received RASis and underwent baseline and the 1-year echocardiography. The baseline characteristics of patients from the STRATS-AHF and STRATS-HF-ARNI registries are presented in Table S8. The proportions of patients with HFimpEF (45.6% versus 46.4%, *P*=0.764) and ΔLVEF (12.6±13.9 versus 11.3±12.5, *P*=0.064) were similar between the STRATS-AHF registry and STRATS-ARNI registry (Figure 4A). When the clinical outcomes of the subgroups with HFimpEF (Figure 4B) and persistent HFrEF were analyzed (Figure 4C), patients in the STRATS-HF-ARNI consistently showed a lower all-cause mortality than those in the STRATS-AHF registry, regardless of their 1-year LVEF (both log-rank *P*<0.001).

Recognizing the differences in the baseline characteristics between patients in the STRATS-AHF and STRATS-HF-ARNI registries, the clinical outcomes were further compared using a PSM cohort. The clinical characteristics of the PSM cohorts of the groups with HFimpEF and persistent HFrEF are shown in Table S9. In the PSM cohort, patients in the STRATS-HF-ARNI

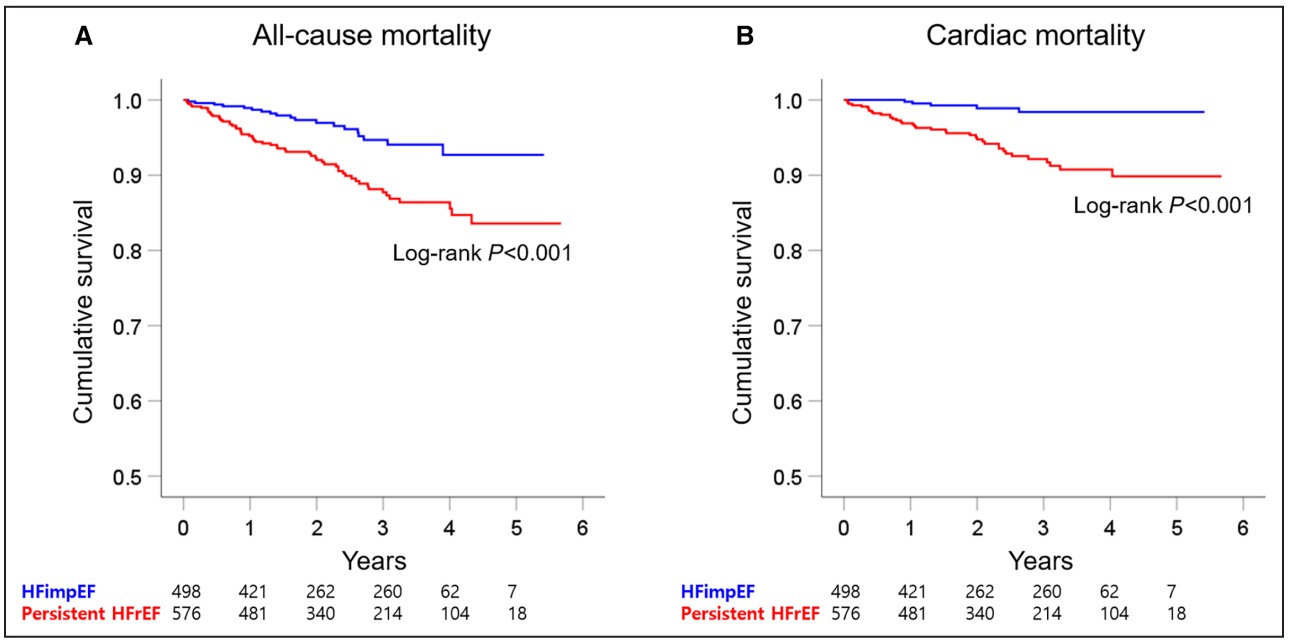

Figure 2. Comparison of clinical outcomes between the groups with HFimpEF and persistent HFrEF.
Kaplan–Meier survival curves of all-cause mortality (**A**) and cardiac mortality (**B**) according to the heart failure phenotype are presented. HFimpEF indicates heart failure with improved ejection fraction; and HFrEF, heart failure with reduced ejection fraction.

registry demonstrated superior clinical outcomes than those in the STRATS-AHF registry regardless of the HF phenotype on the 1-year echocardiography (Figure S3).

DISCUSSION

Using the STRATS-HF-ARNI registry, we analyzed the clinical characteristics, predictors, and outcomes of patients with HFimpEF and those with persistent HFrEF based on the echocardiographic findings at 1-year follow-up. The major findings of our study were as follows: (1) among patients with HFrEF treated with ARNIs who underwent echocardiography at 1-year follow-up, 45.6% were diagnosed with HFimpEF; (2) older age, male sex, and a larger LVEDV were identified as positive predictors for persistent HFrEF, whereas atrial fibrillation and a higher SBP were identified as inverse predictors for persistent HFrEF; (3) the group with HFimpEF exhibited lower all-cause and cardiac mortality rates compared with the group with persistent HFrEF, and the risks of all-cause mortality decreased as the 1-year LVEF approached 40% although no additional improvement was observed in the all-cause mortality rate beyond this threshold; and (4) compared with patients taking RASis in the STRATS-AHF registry, those in the STRATS-HF-ARNI registry demonstrated better outcomes in both the groups with HFimpEF and persistent HFrEF.

Table 3. Independent Predictors for All-Cause Mortality From 1-Year Follow-Up

	Hazard ratio	95% CI	*P* value
Per 1 y increase in age	1.054	1.027–1.081	<0.001
End-stage renal disease	3.883	1.473–10.235	0.006
Stroke	1.768	0.922–3.390	0.086
Persistent heart failure with reduced ejection fraction	2.402	1.251–4.610	0.008
Per 1 mm Hg increase in systolic blood pressure at 1-y	0.971	0.956–0.986	<0.001
Per 1 mL increase in, left ventricular end-diastolic volume at 1-y	0.995	0.995–1.005	0.895
Per 1 mm Hg increase in pulmonary artery systolic pressure at 1-y	1.035	1.018–1.052	<0.001

Based on studies that have elucidated effective medical treatments for HFrEF,[17–21] GDMT using beta-blockers, mineralocorticoid receptor antagonists, sodium-glucose cotransporter 2 inhibitors, and RASis/ARNIs is now widely acknowledged as a gold standard in managing HFrEF.[3,4] GDMT has not only demonstrated its benefits in reducing all-cause mortality and hospitalization for worsening HF but has also been associated with LVEF improvement and LV reverse remodeling in some patients with HFrEF.[10,22–24] Thus, patients who were initially classified as having HFrEF, but later experienced LVEF recovery with GDMT, were now identified as having HFimpEF, given their more favorable prognostic outcomes compared with patients with HF with preserved EF and those with persistent

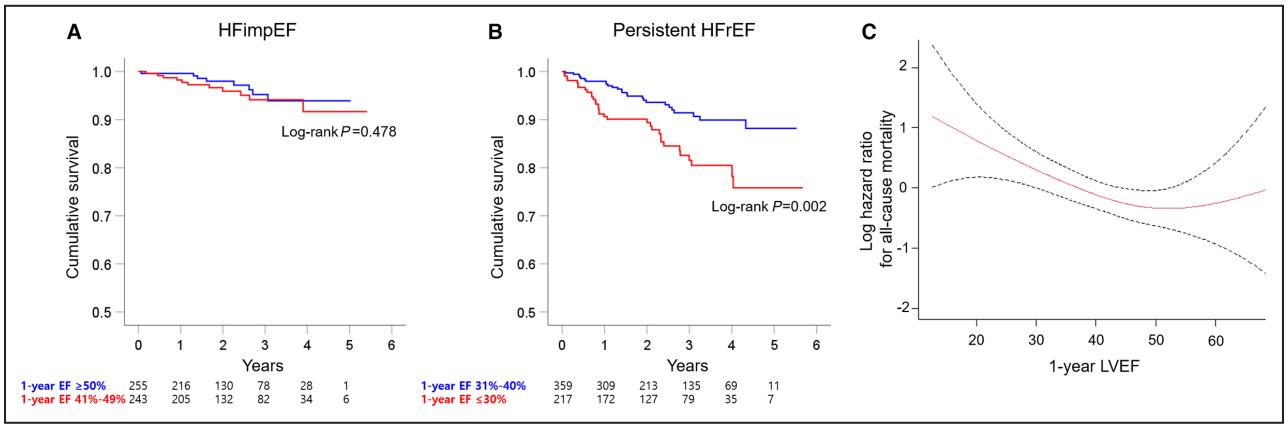

Figure 3. All-cause mortality in association with the subclassification of a 1-year LVEF.
In the groups with HFimpEF (**A**) and persistent HFrEF (**B**), the patients were subcategorized into 2 groups based on their 1-year LVEF: HFimpEF into HFpEF at 1 year (LVEF ≥50%) and HFmrEF at 1 year (LVEF 40%–49%), and persistent HFrEF into HF with severely reduced EF (LVEF ≤30%) and HF with moderately reduced EF (LVEF 31%–40%). The restricted cubic spline curves illustrate the association between the 1-year LVEF and outcomes (**C**). HFimpEF indicates heart failure with improved ejection fraction; HFmrEF, heart failure with midrange ejection fraction; HFpEF, heart failure with preserved ejection fraction; and LVEF, left ventricular ejection fraction.

HFrEF.[10,25] Despite LVEF improvement, however, the majority of patients with HFimpEF still showed impaired global longitudinal strain,[26] sparking interests in both predicting LVEF improvement and effectively managing patients with HFimpEF.

In the examination of predictors for LVEF improvement during follow-up, our findings align with those of previous studies, identifying young age, female sex, and atrial fibrillation as independent predictors for HFimpEF (Table 2).[9,11] This suggests that patients with atrial fibrillation-mediated cardiomyopathy, a well-known reversible cause of HF not only induced by tachycardia but also by heart rate irregularity even under properly controlled heart rate, are more likely to benefit from GDMT and experience LVEF improvement during the follow-up.[27,28] Although a previous history of hypertension was initially identified as a risk factor for persistent HFrEF in the univariable analysis, its significance diminished in the multivariable analysis. Conversely, SBP emerged as an inversely associated

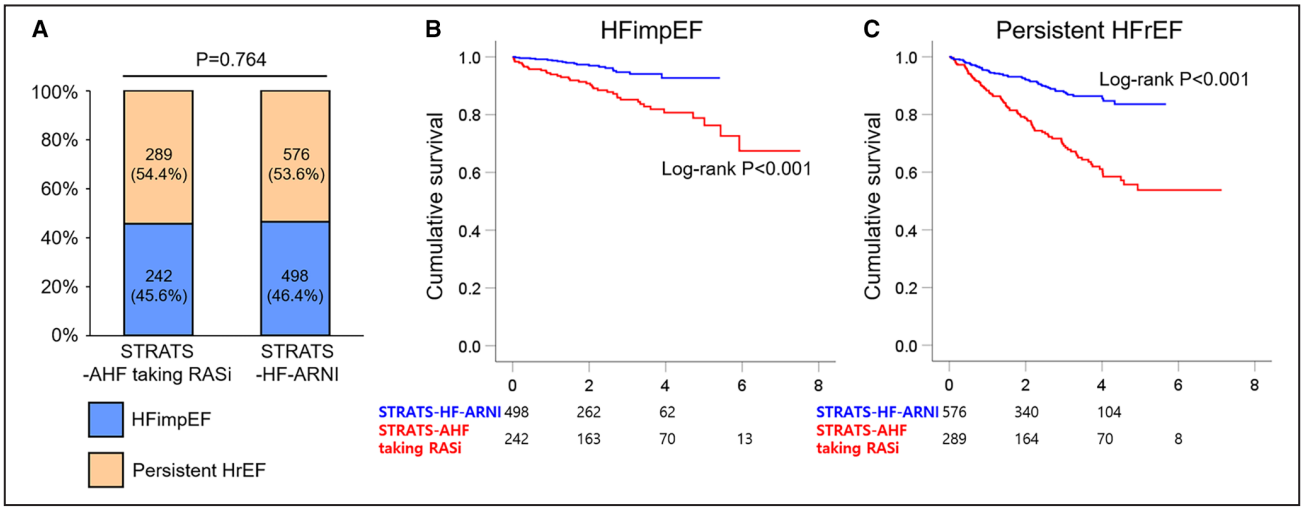

Figure 4. Comparison of clinical outcomes between patients taking RASis from the STRATS-AHF registry and those from the STRATS-HF-ARNI registry.
A, The proportions of patients with HFimpEF and persistent HFrEF from each registry. Kaplan–Meier curves represent the clinical outcomes of patients in the STRATS-HF-ARNI registry and those in the STRATS-AHF registry who had HFimpEF (**B**) and persistent HFrEF (**C**) treated with RASis. HFimpEF indicates heart failure with improved ejection fraction; HFrEF, heart failure with reduced ejection fraction; RASi, renin-angiotensin-aldosterone system inhibitor; STRATS-AHF, Strain for Risk Assessment and Therapeutic Strategies in Patients With Acute Heart Failure; and STRATS-HF-ARNI, Strain for Risk Assessment and Therapeutic Strategies in Patients With Heart Failure Treated With Angiotensin Receptor-Neprilysin Inhibitors.

factor for persistent HFrEF as well as an independent risk factor for poor clinical outcomes. This complex observation may stem from the nonlinear association between blood pressure and outcomes; some studies have reported an association between low blood pressure and increased risks of all-cause mortality, as well as an association between hypertension and poor clinical outcomes in patients with HFrEF.[11,29,30] To interpret this nonlinear association, previous studies have suggested that low SBP could prevent clinicians from applying GDMT, which might further reduce SBP, whereas high SBP is a significant risk factor among patients with HFrEF.[29,31,32] Further studies are demanded to provide explanations for the relationship between baseline blood pressure, on-treatment blood pressure after taking ARNIs, and clinical outcomes.

Despite the increasing interest in HFimpEF, the cutoff value of follow-up LVEF for defining HFimpEF remains controversial. Several studies have adopted a follow-up LVEF of >40% as a criterion for diagnosing HFimpEF.[9,10,29] However, others have adopted a follow-up LVEF of ≥50% as a valid criterion.[33] Upon further stratification of persistent HFrEF and HFimpEF with LVEF values of 30% and 50%, respectively, a prognostic difference was observed between patients with a 1-year LVEF of ≤30% and those with a 1-year LVEF of 31% to 40%. However, no prognostic difference was found between patients with a 1-year LVEF of 41% to 49% and those with a 1-year LVEF of ≥50%. The restricted cubic spline curve supported this observation by demonstrating that the risk of mortality decreased as the 1-year LVEF increased up to 40%; however, no further risk reduction was observed beyond a 1-year LVEF of 40%. Taken together, defining HFimpEF with a follow-up LVEF of 40% might not be counterintuitive considering the observed prognostic differences, although further studies are required to validate our results.

By comparing the clinical outcomes of patients with HFimpEF and those with persistent HF from the STRATS-AHF and STRATS-HF-ARNI registries, we could provide valuable suggestions for managing these patients. Currently, limited information is available on how to manage patients with HFimpEF, except for the TRED-HF (Therapy Withdrawal in Recovered Dilated Cardiomyopathy–Heart Failure) trial suggesting that discontinuing or reducing pharmacological treatment could lead to HFrEF relapse following treatment withdrawal.[34] In the original population and the PSM cohort, patients from the STRATS-HF-ARNI registry had lower blood pressure but a higher prevalence of taking beta-blockers compared with those from the STRATS-AHF registry, for both the groups with HFimpEF and persistent HFrEF (Tables S8 and S9). As previously mentioned, low blood pressure is an independent risk factor for poor clinical outcomes. Nevertheless, patients from the STRATS-HF-ARNI registry, who were treated with ARNIs and more frequently prescribed with beta-blockers, were associated with superior outcomes compared with those from the STRATS-AHF registry, regardless of the HF phenotype. Taking these considerations into account, adherence to GDMT could be beneficial not only for patients with persistent HFrEF but also for those with HFimpEF; regardless of the 1-year LVEF (≤40% or >40%), patients should adhere to GDMT incorporating ARNIs. Furthermore, our findings align with the current guidelines, suggesting that ARNIs may be preferred over RASis in patients with HFrEF owing to their superior benefits observed.[3,4]

Study Limitations

This study has several limitations. First, this is a retrospective cohort study from a multicenter registry rather than a randomized trial. Therefore, although a multivariable analysis and the PSM were performed to reduce the risks of biases, some confounding factors might not be considered. Second, we analyzed only East Asian patients who visited 2 large tertiary medical institutes. Thus, further investigation is needed to assess the generalizability of the study findings to other races or ethnicities. Additionally, we designed this study to analyze patients who underwent 1-year echocardiography to define HFimpEF and persistent HFrEF; accordingly, we enrolled only patients who underwent 1-year follow-up echocardiography. Although we provided a sensitivity analysis that included those who died before the 1-year follow-up or did not undergo 1-year echocardiography in predicting HFimpEF and persistent HFrEF, this approach may have led to selection and lead-time biases and careful consideration for the possibility of biases is demanded.

CONCLUSIONS

We conducted a comprehensive analysis of the characteristics, predictors, and outcomes of patients with HFimpEF and persistent HFrEF receiving ARNIs. As the 1-year LVEF increased up to 40%, the risk of all-cause mortality progressively decreased. Meanwhile, no additional risk reduction was observed beyond a 1-year LVEF of 40%. Compared with patients taking RASi in the STRATS-AHF registry, both the groups with HFimpEF and persistent HFrEF were associated in the STRATS-HF-ARNI registry with better clinical outcomes, indicating a preference for ARNIs over RASis.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S9
Figures S1–S3

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