



ORIGINAL RESEARCH

Phenotyping Heart Failure According to the Longitudinal Ejection Fraction Change: Myocardial Strain, Predictors, and Outcomes

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BACKGROUND: Many patients with heart failure (HF) experience changes in left ventricular ejection fraction (LVEF) during follow-up. We sought to evaluate the predictors and outcomes of different HF phenotypes according to longitudinal changes in EF.

METHODS AND RESULTS: A total of 2104 patients with acute HF underwent echocardiography at baseline and follow-up. Global longitudinal strain was measured at index admission. HF phenotypes were defined as persistent HF with reduced EF (persistent HFrEF, LVEF \leq 40% at baseline and follow-up), heart failure with improved ejection fraction (LVEF \leq 40% at baseline and improved to $>$ 40% at follow-up), heart failure with declined ejection fraction (LVEF $>$ 40% at baseline and declined to \leq 40% at follow up), and persistent HF with preserved EF (persistent HFpEF, LVEF $>$ 40% at baseline and follow-up). Overall, 1130 patients had HFrEF at baseline; during follow-up, 54.2% and 46.8% had persistent HFrEF and heart failure with improved ejection fraction, respectively. Among 975 patients with HFpEF at baseline, 89.5% and 10.5% had persistent HFpEF and heart failure with declined ejection fraction at follow-up, respectively. The 5-year all-cause mortality rates were 43.1%, 33.1%, 24%, and 17% for heart failure with declined ejection fraction, persistent HFrEF, persistent HFpEF, and heart failure with improved ejection fraction, respectively (global log-rank $P < 0.001$). In multivariable analyses, each 1% increase in global longitudinal strain (greater contractility) was associated with 10% increased odds for heart failure with improved ejection fraction among patients with HFrEF at baseline and 7% reduced odds for heart failure with declined ejection fraction among patients with HFpEF at baseline.

CONCLUSIONS: LVEF changed during follow-up. Each HF phenotype according to longitudinal LVEF changes has a distinct prognosis. Global longitudinal strain can be used to predict the HF phenotype.

REGISTRATION: URL: <https://www.clinicaltrials.gov>; Unique identifier: NCT03513653.

Key Words: ejection fraction change ■ heart failure ■ HFdEF ■ HFief ■ myocardial strain

Currently, heart failure (HF) is categorized based on left ventricular ejection fraction (LVEF). Patients with EF $<$ 40 and \geq 40% are defined as HF with reduced EF (HFrEF) and preserved EF (HFpEF), respectively.¹ LVEF is not static, but changes over time. For example, many patients with HFrEF benefit from pharmacological and/or nonpharmacological therapies, and

their LVEF improves during follow-up.^{2,3} Similarly, some patients with HFpEF experience a decline in LVEF.⁴

A few studies, including ours,^{3,5,6} showed that patients with improved EF (HFief) had better prognosis than those with persistent HFrEF and that those with declined EF (HFdEF) had worse outcomes than those with persistent HFpEF; patients with HFief as well as

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CLINICAL PERSPECTIVE

What Is New?

- We reclassified 2105 patients with heart failure according to the longitudinal changes in left ventricular ejection fraction during follow-up.
- Nearly half of patients with heart failure with reduced ejection fraction at the index admission developed heart failure with improved ejection fraction, and these patients had the best prognosis; whereas 11% of patients with heart failure with preserved ejection fraction at the index admission developed heart failure with declined ejection fraction, and these patients had the worst prognosis.
- Global longitudinal strain was a significant predictor of both heart failure with improved ejection fraction and heart failure with declined ejection fraction, independent of left ventricular ejection fraction, and each heart failure phenotype according to longitudinal left ventricular ejection fraction changes has a distinct prognosis, and global longitudinal strain can be used to predict the HF phenotype.

What Are The Clinical Implications?

- Because heart failure phenotypes according to the longitudinal left ventricular ejection fraction change have a distinct prognosis, repeated echocardiographic evaluations and re-phenotyping should be considered in all patients with heart failure.

Nonstandard Abbreviations and Acronyms

AHF	acute heart failure
GLS	global longitudinal strain
HFdEF	heart failure with declined ejection fraction
HFIEF	heart failure with improved ejection fraction
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
LVEF	left ventricular ejection fraction

those with HFdEF have distinct prognosis and differential responses to medical therapy. Therefore, it is of clinical interest to identify predictors of longitudinal changes in LVEF in patients with HF.

Myocardial strain is based on the speckle-tracking method and measures the contractility of the myocardium directly. It assesses reliably the systolic function,⁷

and predicts the outcomes of HF independently of LVEF.^{8,9} Because the change in LVEF during follow-up may be determined by the contractility of the myocardium, myocardial strain may have a fundamental value to predict the LVEF change.

We hypothesized that myocardial strain may predict the changes in LVEF in HF. The aims of this study were as follows: first, we evaluated the longitudinal changes in LVEF; secondly, we identified predictors of LVEF change, including the role of myocardial strain; and thirdly, we compared the outcomes of the HF phenotypes according to their LVEF change in a large cohort of patients with acute HF.

METHODS

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

Patients

The STRATS-AHF (Strain for Risk Assessment and Therapeutic Strategies in patients with Acute Heart Failure) registry (ClinicalTrials.gov/, NCT: 03513653) included 4312 patients who were hospitalized for acute HF in 3 tertiary university hospitals between January 2009 and December 2016. Detailed information and primary outcomes have been reported elsewhere.⁸ In line with the aim of the study, we included only patients who underwent echocardiographic examination at the index admission and at least 1 additional time during follow-up. The vital statuses of all patients were collected from the National Death Records.

The study protocol was approved by the ethics committee at each hospital. Written informed consent was waived by the institutional review board. The study complied with the Declaration of Helsinki.

Echocardiography and Strain Analysis

Patients underwent echocardiography during the index admission (median time interval between admission and echocardiography: 1 day; interquartile range [IQR]: 0–2 days) and at least 1 additional time during follow-up. In cases with multiple echocardiographic examinations, we took the last examination (median time interval between admission and follow-up echocardiography: 406 days; IQR: 270–676 days). Standard techniques were used in accordance with the American Society of Echocardiography guidelines.¹⁰ LVEF was calculated by Simpson's biplane method. Detailed measurements of global longitudinal strain (GLS) have been provided elsewhere.⁸ In brief, echocardiographic images were obtained and analyzed using Image-Arena (Tomtec Imaging System, Munich, Germany), a vendor-independent

program, at the strain core laboratory.¹¹ Peak GLS was computed automatically. All strain measurements were performed by strain specialists blinded to other patient data.

Study Variables and Definitions

Based on echocardiographic findings at the index admission for acute HF, patients were categorized as having either HFrEF (LVEF \leq 40%), or HFpEF (LVEF $>$ 40%).¹² Among patients with HFrEF at the index admission, those whose LVEF improved to $>$ 40% or remained \leq 40% were defined as having HFIEF or persistent HFrEF, respectively. Similarly, among patients with HFpEF at the index admission, HFdEF and persistent HFpEF were defined as those who had \leq 40% and LVEF $>$ 40% at follow-up, respectively.

Because GLS is a negative value, we used the absolute value $|x|$ for a simpler interpretation. Therefore, in this study a higher positive value for absolute GLS is regarded as more myocardial contractility. Because different centers measured the levels of different types of natriuretic peptides (ie, B-type natriuretic peptide versus N-terminal-pro B-type natriuretic peptide), we transformed the natriuretic peptide level into natriuretic peptide percentiles to compare the natriuretic peptide levels throughout the centers.

The primary outcome was the changes in HF phenotypes during follow-up. The secondary outcome included the 5-year all-cause mortality and hospitalization for HF according to the HF phenotypes.

Statistical Analysis

Data were presented as numbers and frequencies for categorical variables and as means \pm SD or medians with IQRs for continuous variables. For comparisons among groups, the χ^2 test (or Fisher exact test when any expected count was $<$ 5 for a 2 \times 2 table) was used for categorical variables, and the unpaired Student *t* test, 1-way ANOVA, Mann Whitney *U* test, or Kruskal-Wallis test was used for continuous variables.

Pearson's correlation was used to calculate the association between LVEF and GLS. The chronological trend of the outcomes was expressed as Kaplan-Meier estimates and compared according to the HF phenotypes. A multivariable binary logistic regression was used to determine the independent predictors of HFIEF and HFdEF. We included all variables found to be statistically significant ($P<$ 0.05) in the univariate analysis as covariates in the multivariable analysis, excluding those with $>$ 10% of data that were missing or those having multicollinearity with other variables.

A 2-sided $P<$ 0.05 was considered to indicate a statistically significant difference. Statistical tests were performed using SPSS, V.23 (IBM, Armonk, NY) and R programming version 3.3.0 (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline Characteristics of the Study Population

Of 4312 patients who were included in the STRATS-AHF Registry, 2104 patients had at least 2 echocardiography examinations. Overall, 1130 patients had HFrEF at the index admission; among these, 613 (54.2%) had persistent HFrEF and 517 (45.8%) had HFIEF. Likewise, of 974 patients with HFpEF at the index admission, 872 (89.5%) and 102 (10.5%) developed persistent HFpEF and HFdEF, respectively (Figure 1).

The baseline characteristics differed significantly between the groups. Among patients with HFrEF, patients with HFIEF were younger (67.0 \pm 13.7 years versus 63.3 \pm 14.2 years, $P<$ 0.001), less likely to be male (68.5% versus 58.6%, $P=$ 0.001), and less likely to have ischemic heart disease (34.6% versus 28.0%, $P=$ 0.019) than those with HFIEF. Natriuretic peptide levels did not differ between the groups. Regarding the echocardiographic parameters, patients with HFIEF had higher LVEF (26.7 \pm 7.0% versus 28.8 \pm 7.0%, $P<$ 0.001) and higher GLS (7.9 \pm 3.2% versus 8.7 \pm 3.4%, $P<$ 0.001) than those with persistent HFrEF. In addition, they received more β -blockers at discharge from the index admission (68.4% versus 75.7%, $P=$ 0.006).

Regarding patients with HFpEF at the index admission, HFdEF had a higher natriuretic peptide level (40.3 \pm 26.9 percentiles versus 59.8 \pm 26.7 percentiles, $P<$ 0.001), lower LVEF (54.8 \pm 8.6% versus 49.0 \pm 6.8%, $P<$ 0.001), and lower GLS (14.1 \pm 4.6% versus 11.8 \pm 4.5%, $P<$ 0.001) than persistent HFpEF (Table 1).

Changes in LVEF During Follow-Up

In all patients with HFrEF at the index admission, LVEF increased from 27.7 \pm 7.1% at the index admission to 39.9 \pm 14.0% at the follow-up echocardiography (paired *t* test, $P<$ 0.001). In HFIEF, the LVEF improved from 28.8 \pm 7.0% to 52.8 \pm 7.8%. In 60.5% of the patients, LVEF improved to $>$ 50% regardless of the severity of baseline LVEF impairment (in patients with LVEF \leq 20% at baseline, LVEF improved from 17.1 \pm 2.5% to 54.0 \pm 7.3% at follow-up; 20% $<$ LVEF \leq 30%, 25.8 \pm 6.3% to 52.8 \pm 7.6%; 30% $<$ LVEF \leq 40%, 35.3 \pm 2.8% to 52.4 \pm 8.2%). By contrast, in persistent HFrEF, the LVEF changed only marginally from 26.7 \pm 7.0% to 29.0 \pm 7.2%. The change in LVEF according to baseline LVEF impairment was marginal as well (in patients with LVEF \leq 20% at baseline: LVEF improved from 17.1 \pm 2.8% to 24.7 \pm 7.7% at follow-up; 20% $<$ LVEF \leq 30%, 25.6 \pm 2.9% to 28.6 \pm 6.3%; 30% $<$ LVEF \leq 40%, 34.6 \pm 2.8% to 32.4 \pm 6.2%) (Figure 2A). The change in LVEF was similar in patients with and without ischemic heart disease, and in those with sinus rhythm and atrial fibrillation.

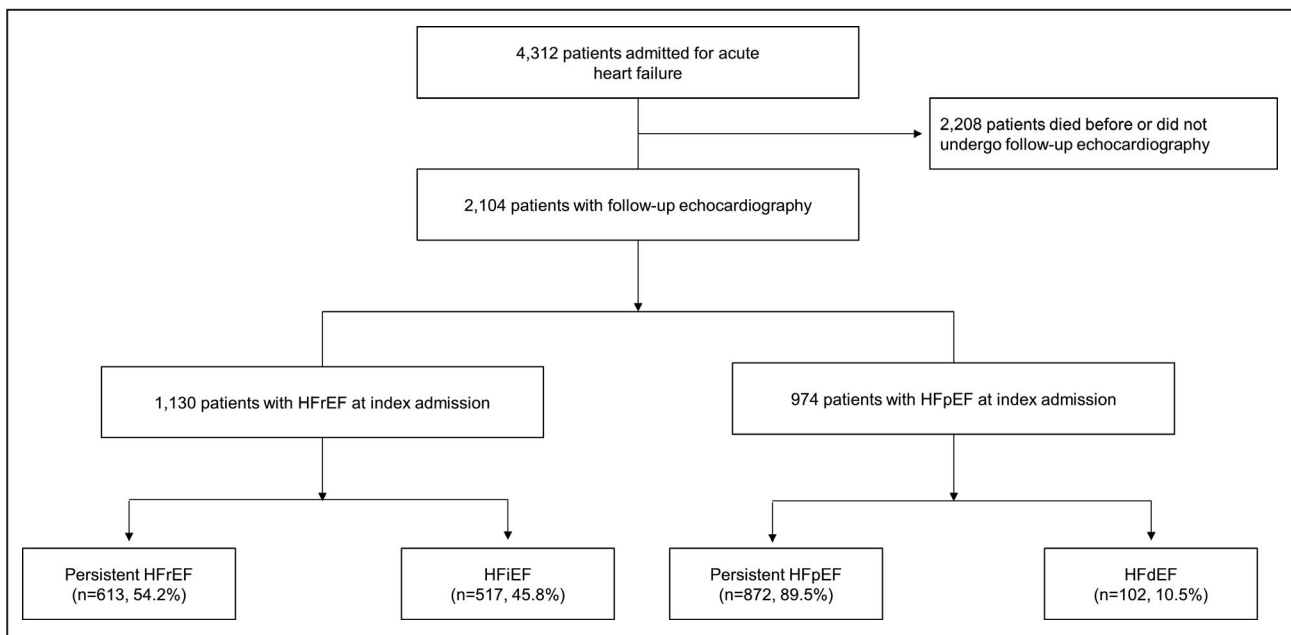


Figure 1. Study population

HFrEF, heart failure with reduced ejection fraction; HFief, heart failure with improved ejection fraction; HFpEF, heart failure with preserved ejection fraction; and HFdEF, heart failure with declined ejection fraction.

Among patients with HFpEF, the LVEF changed minimally from $54.2 \pm 8.6\%$ at the index admission to $54.6 \pm 11.0\%$ at the follow-up (paired *t* test $P < 0.001$). In HFdEF, LVEF declined from $49.0 \pm 6.8\%$ to $31.5 \pm 6.6\%$, and 64.7% of the patients had a decline to $< 35\%$ regardless of baseline LVEF (in patients with $40\% < \text{LVEF} \leq 50\%$ at baseline, LVEF declined from $44.9 \pm 2.9\%$ to $31.3 \pm 7.3\%$ at follow-up; $50\% < \text{LVEF} \leq 60\%$, $54.8 \pm 2.9\%$ to $32.3 \pm 5.6\%$; $\text{LVEF} > 60\%$, $62.9 \pm 1.5\%$ to $30.6 \pm 4.0\%$), whereas in patients with persistent HFpEF, the LVEF change was marginal (in patients with $40\% < \text{LVEF} \leq 50\%$ at baseline, LVEF changed from $45.3 \pm 2.9\%$ to $52.7 \pm 7.3\%$ at follow-up; $50\% < \text{LVEF} \leq 60\%$, $55.6 \pm 2.8\%$ to $57.9 \pm 6.7\%$; $\text{LVEF} > 60\%$, $66.0 \pm 4.0\%$ to $62.2 \pm 6.5\%$) (Figure 2B).

Predictors of LVEF Change

The mean GLS and LVEF were $10.8 \pm 4.8\%$ and $39.8 \pm 15.3\%$, respectively. There was a significant correlation between GLS and LVEF ($r = 0.67$, $P < 0.001$). When stratifying the patients according to GLS tertiles, the proportion of persistent HFrEF and that of HFdEF were highest in the lowest GLS tertile (Figure 3A).

In a multivariate analysis, each 1% increase in GLS was associated with 10% increased odds for HFief (odds ratio [OR], 1.10; 95% CI, 1.05–1.14; $P < 0.001$) along with age, male sex, body mass index, heart rate, serum sodium level, and LV end-diastolic diameter (Table 2). For easier interpretation, we categorized GLS using the median value. GLS above the median was

associated with 49% increased odds for HFief (OR, 1.49; 95% CI, 1.10–2.01; $P < 0.001$).

Regarding HFdEF, high natriuretic peptide levels and left ventricular end-diastolic dimension as well as low left atrium diameter, LVEF, and GLS were independent predictors of HFdEF. In multivariable analysis, GLS less than the median was associated with 2.12-fold increased odds for HFief (OR, 2.12; 95% CI, 1.21–3.70, $P = 0.008$).

GLS had an incremental value for predicting both HFief and HFdEF in addition to other predictors (Figure 3B).

Outcomes

The median follow-up duration was 1304 days (IQR, 784–1835 days). At 5 years, 533 (25.3%) patients died. In the Kaplan-Meier survival analysis, there was no difference in mortality between HFrEF and HFpEF (Figure 4A). However, under stratification by HF phenotypes, patients with HFief had the lowest, and those with HFdEF had the highest mortality. The 5-year all-cause mortality rates were 43.1, 33.1, 24, and 17% for HFdEF, persistent HFrEF, persistent HFpEF, and HFief, respectively (global log-rank $P < 0.001$, pairwise P value between all groups < 0.05 , except between persistent HFrEF and HFdEF with $P = 0.055$) (Figure 4B). Similar findings were observed for the composite of all-cause mortality and hospitalization for HF (Figure 4C). Regarding the timing of echocardiography follow-up, 913 (43.4%) patients had follow-up echocardiography ≤ 1 year

Table 1. Baseline Characteristics of the Patients at the Index Admission

	Persistent HF _r EF (n=613)	HF _i EF (n=517)	P Value	Persistent HF _p EF (n=872)	HF _d EF (n=102)	P Value
Age, y	67.0±13.7	63.3±14.2	<0.001	71.1±12.6	73.2±12.6	0.110
Men, %	68.5%	58.6%	0.001	42.5%	50.0%	0.170
Body mass index, kg/m	23.4±4.1	24.0±4.9	0.033	24.2±4.1	22.9±3.3	0.001
Past medical history						
Hypertension	52.2%	51.6%	0.852	60.4%	65.7%	0.297
Diabetes mellitus	36.7%	32.5%	0.139	32.5%	34.3%	0.717
Ischemic heart disease	34.6%	28.0%	0.019	30.5%	37.3%	0.162
Atrial fibrillation	23.5%	26.9%	0.192	35.5%	34.3%	0.819
NYHA functional class			0.638			0.701
I/II	8.8%	8.7%		6.8%	5.4%	
III	47.3%	50.2%		48.4%	52.7%	
IV	43.9%	41.1%		44.8%	41.9%	
Physical examination						
Systolic BP, mm Hg	124.2±23.4	130.1±25.3	<0.001	131.3±27.3	126.5±32.1	0.101
Diastolic BP, mm Hg	73.6±14.8	78.2±17.8	<0.001	73.9±16.5	73.0±18.0	0.616
Heart rate, beats/min	89.3±23.3	96.6±24.9	<0.001	83.7±24.6	83.8±25.3	0.987
Laboratory findings						
Hemoglobin, mg/dL	12.7±2.1	12.8±2.5	0.856	12.0±2.3	11.6±2.3	0.109
Sodium, mmol/L	136.6±5.2	137.5±4.5	0.002	136.8±5.0	136.8±5.5	0.982
Potassium, mmol/L	4.2±0.7	4.2±0.6	0.762	4.2±0.7	4.1±0.8	0.339
BUN, mg/dL	25.5±16.3	24.7±16.3	0.406	24.5±15.3	27.1±15.0	0.107
Creatinine, mg/dL	1.5±1.9	1.6±1.9	0.521	1.5±1.7	1.8±2.0	0.093
CKD, %	43.3%	37.3%	0.052	44.0%	57.7%	0.011
BNP, pg/mL	1579±1296	1730±1976	0.496	976±1218	2450±3015	0.062
NT-proBNP, pg/mL	9259±12819	8543±12328	0.452	6113±8356	11524±11207	<0.001
NP 100 percentiles	53.0±26.4	50.8±26.8	0.202	40.3±26.9	59.8±26.7	<0.001
Echocardiographic parameters						
LVEDD, mm	60.7±9.1	57.0±8.1	<0.001	49.2±7.2	51.7±7.6	0.001
LA diameter, mm	45.8±8.9	45.5±8.7	0.632	46.1±10.0	42.9±10.7	0.003
LA volume index, mL/m ²	61.9±38.9	55.1±24.0	0.001	64.4±48.4	46.1±10.0	0.043
E-wave, m/s	0.9±0.5	0.9±0.3	0.154	0.9±0.4	0.8±0.4	0.095
A-wave, m/s	1.0±4.6	1.7±12.6	0.348	0.8±0.3	0.8±0.3	0.367
DT, ms	158.8±61.8	159.3±66.4	0.906	206.6±102.4	202.7±91.9	0.740
E/e'	21.0±13.5	19.8±9.4	0.116	17.0±9.8	16.1±8.1	0.419
LVEF, %	26.7±7.0	28.8±7.0	<0.001	54.8±8.6	49.0±6.8	<0.001
GLS (%)	7.9±3.2	8.7±3.4	<0.001	14.1±4.6	11.8±4.5	<0.001
Medication at discharge						
ACE inhibitor or ARB	84.3%	82.7%	0.464	66.9%	78.0%	0.024
β-blocker	68.4%	75.7%	0.006	63.3%	63.0%	0.954
MRA	58.6%	54.4%	0.157	42.8%	40.0%	0.591

ACE indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor-blocker; BP, blood pressure; BUN, blood urea nitrogen; BNP, B-type natriuretic peptide; CKD, chronic kidney disease; DT, deceleration time; E/e', mitral E wave to mitral tissue Doppler e' wave; GLS, global longitudinal strain; HF, heart failure; HF_dEF, heart failure with declined ejection fraction; HF_iEF, heart failure with improved ejection fraction; HF_pEF, heart failure with preserved ejection fraction; HF_rEF, heart failure with reduced ejection fraction; LA, left atrium; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; NP, natriuretic peptide; and NT-proBNP, N-terminal pro-B-type natriuretic peptide.

from the index admission (median: 245 days, IQR 191–311 days) and 1191 (56.6%) patients had follow-up echocardiography >1 year from the index

admission (median 627 days, IQR 456–955 days). The changes in LVEF were similar in both groups (Figure S1).

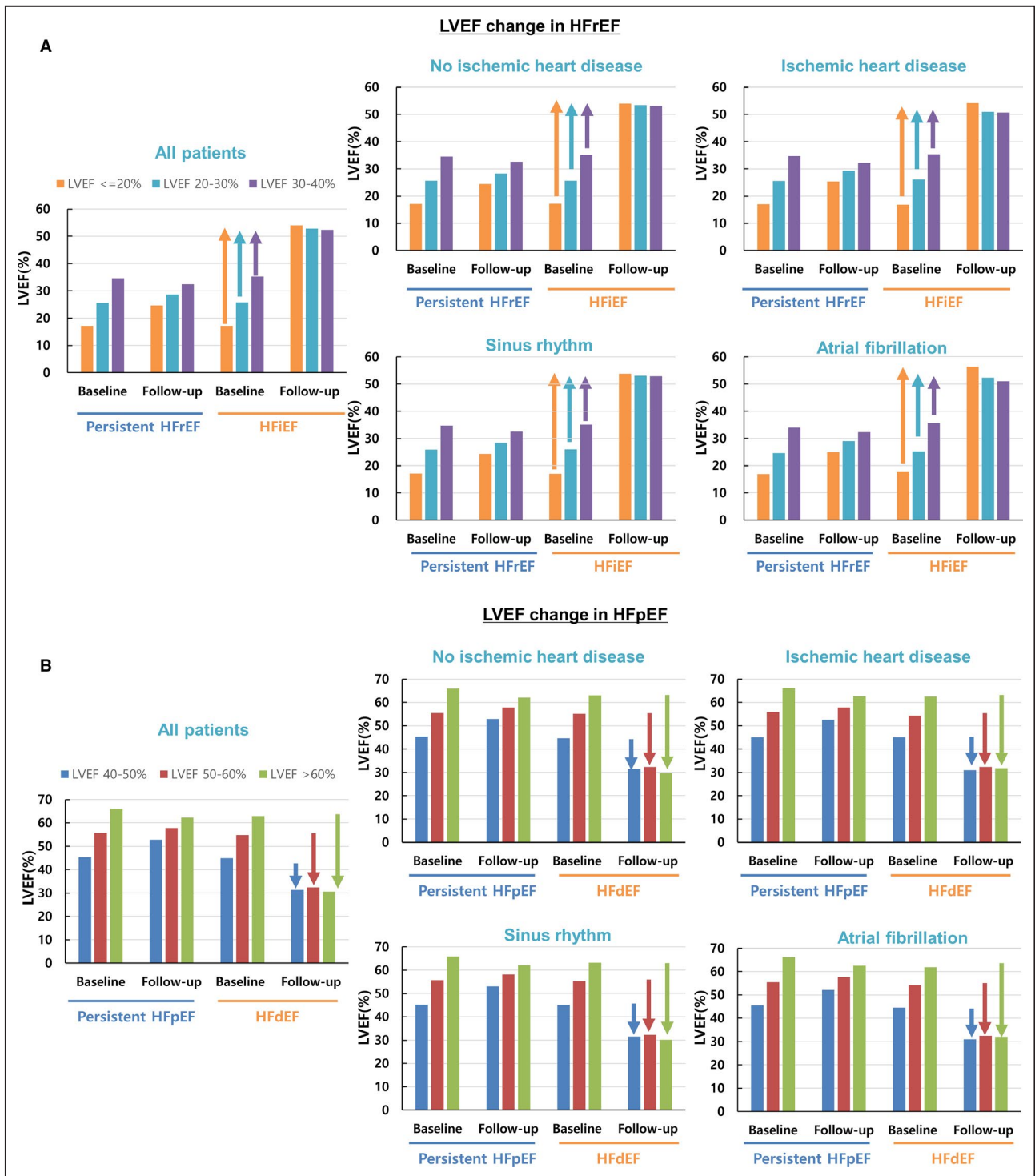


Figure 2. Longitudinal changes in ejection fraction according to heart failure phenotypes and baseline ejection fraction. **A**, In patients with heart failure with improved ejection fraction (HF iEF), the left ventricular ejection fraction (LVEF) improved to >50% in mildly (LVEF: 30–40%), moderately (LVEF: 20–30%), and severely (LVEF ≤20%) depressed LVEF; whereas the change in LVEF was minimal among patients with persistent heart failure with reduced ejection fraction (HF rEF). **B**, In patients with heart failure with declined ejection fraction (HF dEF), the LVEF decreased to <35% in all 3 groups (LVEF: 40–50%, 50–60%, or >60%); whereas the change in LVEF was minimal among patients with persistent heart failure with preserved ejection fraction (HF pEF).

When applying the European Society of Cardiology (ESC) classification (ie, HF rEF: EF <40%, HFmrEF: EF 40-49, HFpEF: EF ≥50%), there was no difference in

all-cause mortality between the 3 groups. However, under reclassification of patients by the follow-up LVEF, patients with LVEF ≥50% had the best, whereas those

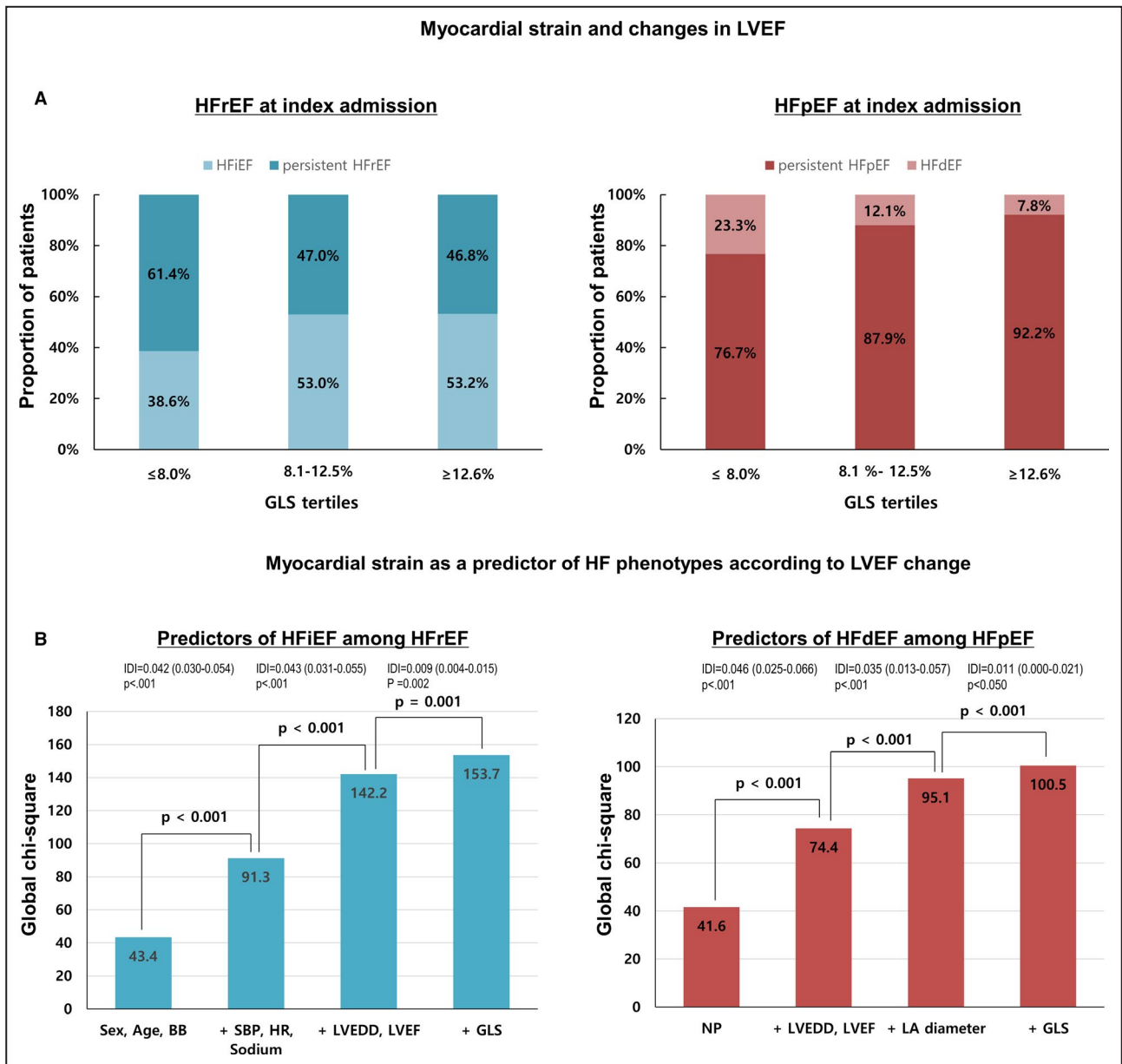


Figure 3. Myocardial strain and heart failure phenotypes according to changes in LVEF.

A. Patients were stratified according to GLS tertiles. The proportion of persistent HFReEF and that of HFdEF was highest in the lowest GLS tertile. **B.** Incremental prognostic value of predictors by binary logistic regression model presented as global χ^2 value. The addition of GLS offers a significant additional benefit over conventional parameters. BB indicates beta-blockers; GLS, global longitudinal strain; HFdEF, heart failure with declined ejection fraction; HFReEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFReEF, heart failure with reduced ejection fraction; HR, heart rate; IDI, integrated discrimination index; LA, left atrium; LVEDD, left ventricular end diastolic diameter; LVEF, left ventricular ejection fraction; NP, natriuretic peptide; and SBP, systolic blood pressure.

with LVEF <40% had the worst prognosis regardless of baseline LVEF (Figure S2).

DISCUSSION

In this comprehensive analysis of HF, we investigated the longitudinal changes in LVEF in a large cohort of patients with acute HF, and showed that nearly half of patients with HFReEF at the index admission developed

HFReEF, who had the best prognosis; whereas 11% of patients with HFpEF at the index admission developed HFdEF, who had the worst prognosis (Figure 5). We also showed that GLS was a significant predictor of both HFReEF and HFdEF, independent of LVEF. This study emphasized the importance of HF phenotyping according to LVEF change and illustrates the benefit of myocardial strain for the prediction of HF phenotypes for the first time.

Table 2. Predictors of Heart Failure Phenotypes

Variables	Univariate		95% CI	Multivariate		95% CI
	P Value	OR		P Value	OR	
Predictors of HFIEF						
Age (for each 1-y increase)	<0.001	0.98	0.97–0.99	<0.001	0.97	0.96–0.98
Men (vs female)	0.001	0.65	0.51–0.83	0.002	0.65	0.49–0.86
Body mass index, kg/m	0.035	1.03	1.00–1.06	<0.001	1.01	1.01–1.02
Ischemic heart disease	0.019	0.74	0.57–0.95
CKD	0.052	0.78	0.61–1.00
Systolic BP (for each 1 mm Hg increase)	<0.001	1.01	1.01–1.01
Heart rate (for each 1 beat/min increase)	<0.001	1.01	1.01–1.02	<0.001	1.01	1.01–1.02
Sodium, mmol/L	0.002	1.04	1.01–1.07	0.002	1.04	1.02–1.07
LA volume index, mL/m ²	0.002	0.99	0.99–1.00
LVEDD, mm	<0.001	0.95	0.94–0.96	<0.001	0.95	0.94–0.97
LVEF, %	<0.001	1.04	1.03–1.06
GLS, %	<0.001	1.08	1.04–1.12	<0.001	1.10	1.05–1.14
β-Blocker	0.006	1.44	1.11–1.88
Predictors of HFdEF						
Body mass index, kg/m	0.003	0.92	0.87–0.97
NP 100 percentiles	0.000	1.03	1.02–1.04	<0.001	1.02	1.01–1.03
CKD	0.011	1.74	1.13–2.66
LVEDD, mm	0.001	1.05	1.02–1.08	0.014	1.05	1.01–1.09
LA diameter, mm	0.003	0.97	0.94–0.99	<0.001	0.93	0.90–0.96
LA volume index, mL/m ²	0.151	1.00	0.99–1.00
LVEF, %	<0.001	0.91	0.88–0.94	0.001	0.93	0.89–0.97
GLS, %	<0.001	0.89	0.85–0.94	0.038	0.93	0.87–1.00
ACE inhibitor or ARB	0.025	1.76	1.07–2.88

ACE indicates, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor-blocker; BP, blood pressure; CKD, chronic kidney disease; GLS, global longitudinal strain; HFdEF, heart failure with declined ejection fraction, HFIEF, heart failure with improved ejection fraction, LA, left atrium; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; NP, natriuretic peptide; and OR, odds ratio.

LVEF Changes Occur According to Distinct Clinical Categories

In this study, 45% of the patients with HFrEF at the index admission had HFIEF during the follow-up. Interestingly, when their LVEF improved, it increased to >50% and was almost normalized regardless of the severity of baseline LV systolic dysfunction. By contrast, those with persistent HFrEF showed only marginal changes in LVEF during the follow-up. It appears that the improvement in LVEF occurs according to distinct clinical categories, and those whose LVEF improved (ie, HFIEF) versus those who did not (ie, persistent HFrEF) represented 2 very distinctive HF phenotypes. A similar phenomenon was observed in patients with HFpEF, but in the opposite direction; when patients with HFpEF experienced a decline in LVEF, the LVEF declined to <35% regardless of the patient's baseline LVEF. This phenomenon was also observed in patients with ischemic cause, atrial fibrillation, and short-term

follow-up duration. Nonetheless, the reason for the phenomenon is unclear.

Previous studies have reported improvements of LVEF during follow-up; nonetheless, those studies did not distinguish between patients whose LVEF improved versus those who did not.^{13,14} Our findings suggest that the longitudinal changes in LVEF occur according to distinct clinical categories, and the presence of patients with HF whose LVEF improves or declines. This new concept will need to be confirmed in other HF cohorts.

GLS as Predictors of LVEF Change

Identifying the predictors for LVEF change is clinically important. In this study, older age, male sex, and low body mass index were negative predictors of HFIEF. This is consistent with the findings from The Valsartan Heart Failure Trial substudy¹³ and CART 2 (Chronic Heart Failure Analysis and Registry in the

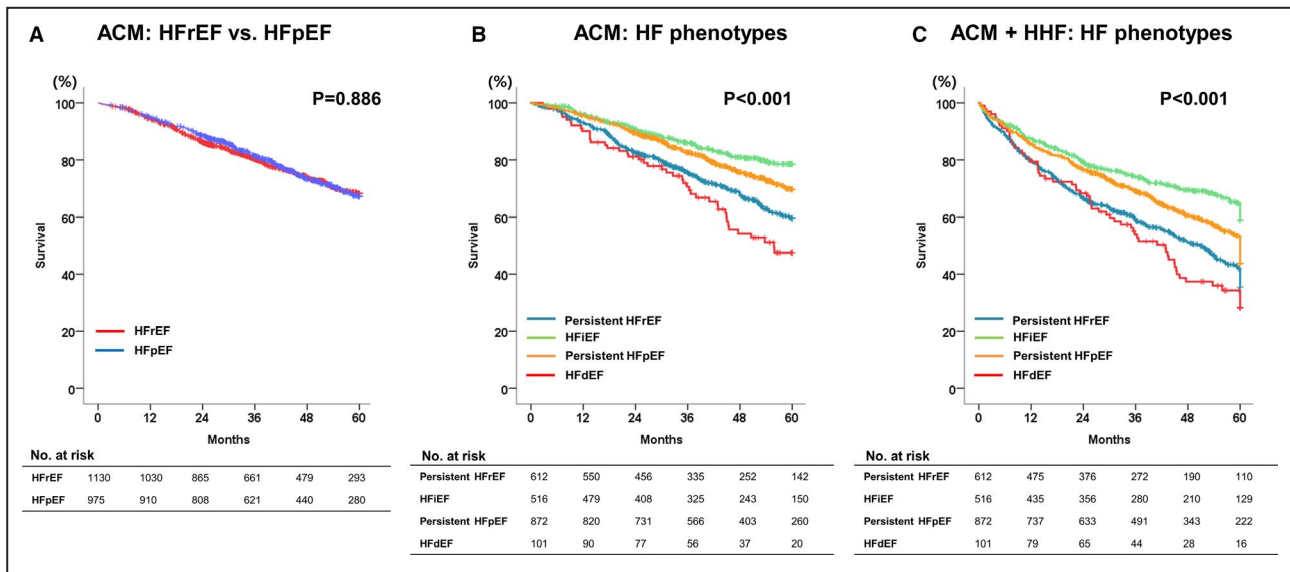


Figure 4. Five-year ACM and its composite and hospitalization according to HF phenotypes. **A**, ACM in HFrEF vs HFpEF. **B**, ACM according to HF phenotypes. HFIEF, heart failure with improved ejection fraction; **C**, The composite of ACM and hospitalization for HF according to HF phenotypes. ACM indicates all-cause mortality; HF, heart failure; HFdEF, heart failure with declined ejection fraction; HFIEF, heart failure with improved ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; and HHF, hospitalization for HF.

Tohoku District-2 Study).¹⁵ An important finding of this study was the predictive value of GLS for longitudinal LVEF change. In a small study with 166 patients with nonischemic cardiomyopathy, Swat et al showed that higher baseline absolute longitudinal strain was associated with recovered EF.¹⁶ In this large, confirmative study with 2105 patients, we showed that GLS was a significant predictor of both HFIEF and HFdEF: each 1% increase in GLS was associated with a 10% increased and 7% reduced odds for HFIEF and HFdEF, respectively. Interestingly, the baseline LVEF was not a predictor after adjustment.

GLS measures the contractility of the myocardium directly. There exists a significant correlation between LVEF and GLS; however, for a given LVEF, there was a wide distribution of GLS.⁸ This implies that patients with HFrEF have both preserved and reduced GLS. We hypothesized that some patients with HFrEF and preserved contractility (ie, high GLS) have the potential to improve their LVEF. The same is the case for patients with HFpEF, but in the opposite direction.

Regarding the medical treatment, neither β -blockers nor renin-angiotensin-system inhibitors were associated with HFIEF after adjustment. This contradicts the findings from previous reports including ours.¹³ However, when excluding GLS from the multivariate analysis, the use of β -blockers was associated with HFIEF (data not shown). There was also an interaction between β -blocker use and GLS for the prediction of HFIEF (P for interaction=0.087), possibly explaining the discrepancy between the studies.

Different Outcomes According to HF Phenotypes

The current guideline for HF divides patients with HF into 2 categories, ie, HFrEF and HFpEF, based on baseline echocardiography.¹ Although many patients experience changes in the LVEF during follow-up and have different outcomes, this was not adequately addressed in the current guidelines.^{1,12,17} Our principal finding is related to clinical outcomes according to HF phenotypes. First, there was no difference in mortality between HFrEF and HFpEF, which was consistent with previous findings.^{18,19} However, under stratification by the HF phenotypes according to LVEF change, the 5-year mortality was 2-fold higher in persistent HFrEF than HFIEF, which is in line with previous reports.²⁰ Because the proportion of patients with HFIEF and persistent HFrEF were comparable, the resulting overall survival of HFrEF was placed in the middle of both curves. Regarding HFpEF, HFdEF had a 2-fold higher mortality than persistent HFpEF. Nonetheless, the relatively small proportion of HFdEF (ie, 11%) among patients with HFpEF explains the low impact of HFdEF on the overall survival of HFpEF.

These results have important clinical implications. In contrast to the common assumption that HFrEF and HFpEF have similar outcomes, our study results emphasize the importance of reclassification of HF according to the longitudinal LVEF change, because the 4 HF phenotypes (ie, persistent HFrEF, HFIEF, persistent HFpEF, and HFdEF) have very distinctive prognoses. Therefore, an echocardiographic re-evaluation

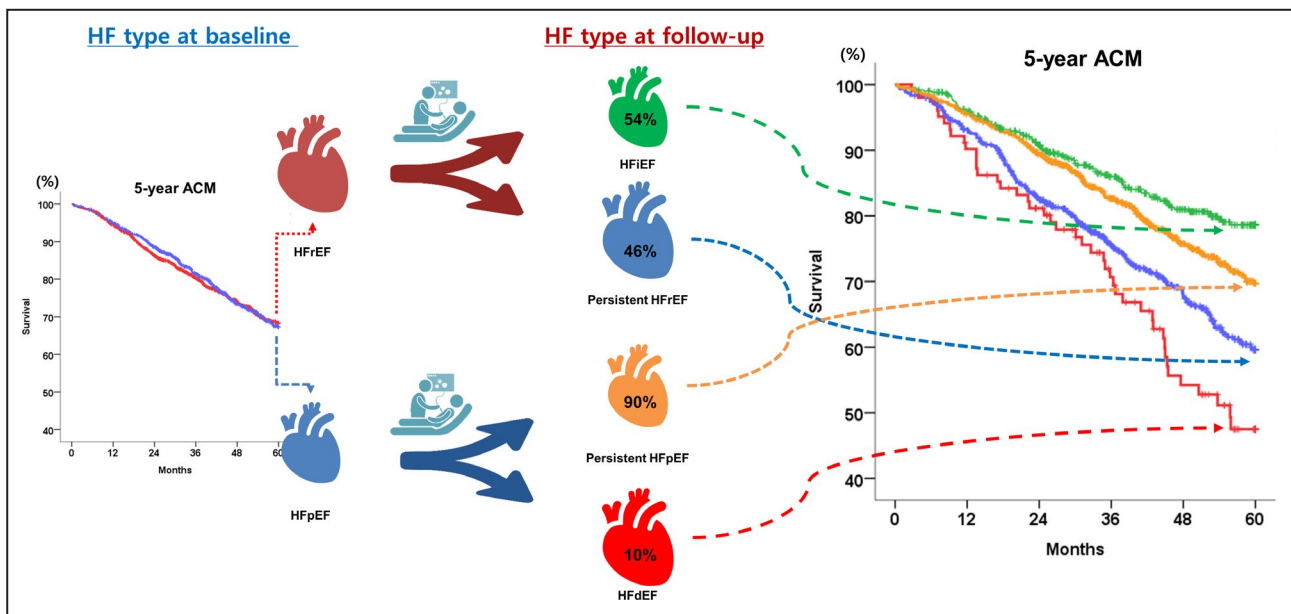


Figure 5. Longitudinal changes of HF phenotypes and outcomes.

Patients with HFpEF and HFrEF have a similar prognosis according to classification at baseline. LVEF is not static but changes during follow-up. Each HF phenotype according to the longitudinal LVEF change (ie, persistent HFrEF, HFIEF, persistent HFpEF, and HFdEF) has a distinct prognosis. HF indicates heart failure; HFdEF, heart failure with declined ejection fraction; HFIEF, heart failure with improved ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction, and LVEF, left ventricular ejection fraction.

of all patients with HF should be considered, instead of maintaining the initial diagnosis of index admission (ie, HFrEF versus HFpEF).

Strengths and Limitations of the Study

There have been several studies that investigated the changes of LVEF during follow-up. Those studies investigated only HFrEF,^{2,13,21} whereas our study evaluated changes in LVEF across the entire spectrum of patients with HF including those with HFpEF. Therefore, this study is the first study that compared the outcomes of various HF phenotypes according to LVEF changes. In addition, we also demonstrated that the incremental value of GLS can be used to predict the LVEF change in HF.

Nevertheless, this study had some limitations. First, this study was an analysis of a cohort study; therefore, there could be unmeasured confounding factors. Second, because we selected only patients who had at least 2 echocardiographic examinations, patients who died before the follow-up echocardiography were excluded. Although all Korean HF patients were encouraged to get a repeat echocardiogram, it is likely that compliance with this suggestion was greater for those with changed symptoms. This presents a significant selection bias, which is also reflected in the relatively low 5-year all-cause mortality of 26% in this substudy compared with the 5-year mortality of 40% in the original STRATS-AHF

cohort. The 5-year mortality rate of patients without follow-up echo was 55.4%, 59.9%, and 50.2% for all, HFrEF, and HFpEF, respectively. Specifically, the estimates of 54.2% remaining HFrEF and only 10.5% becoming HFdEF should not be assumed to represent all patients who were initially HFrEF or HFpEF, respectively. We do not have information on the use of angiotensin-receptor neprilysin-inhibitor or ivabradine, nor data on the onset and reversible causes of HF, which may have different characteristics and outcomes. In addition, whether the phenomenon that LVEF changes according to distinct clinical categories is a mathematical artifact caused by classification or a real physiologic phenomenon needs validation in future studies. Finally, because we enrolled only East Asian patients admitted for acute HF with echocardiography and considering changes in echocardiographic parameters during acute HF,¹⁴ it is unknown whether our findings can be extrapolated to patients with chronic stable HF or with other ethnicities.

In conclusion, in patients with HF, LVEF is not static but changes during the follow-up. Each HF phenotype according to the longitudinal LVEF change (ie, persistent HFrEF, HFIEF, persistent HFpEF, and HFdEF) has a distinct prognosis. These phenotypes may explain why HFrEF and HFpEF had a similar prognosis. GLS can be used to predict the HF phenotype. Therefore, we suggest repeated echocardiographic evaluations and measurements of GLS as the standard measurements in all patients with HF.

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Materials

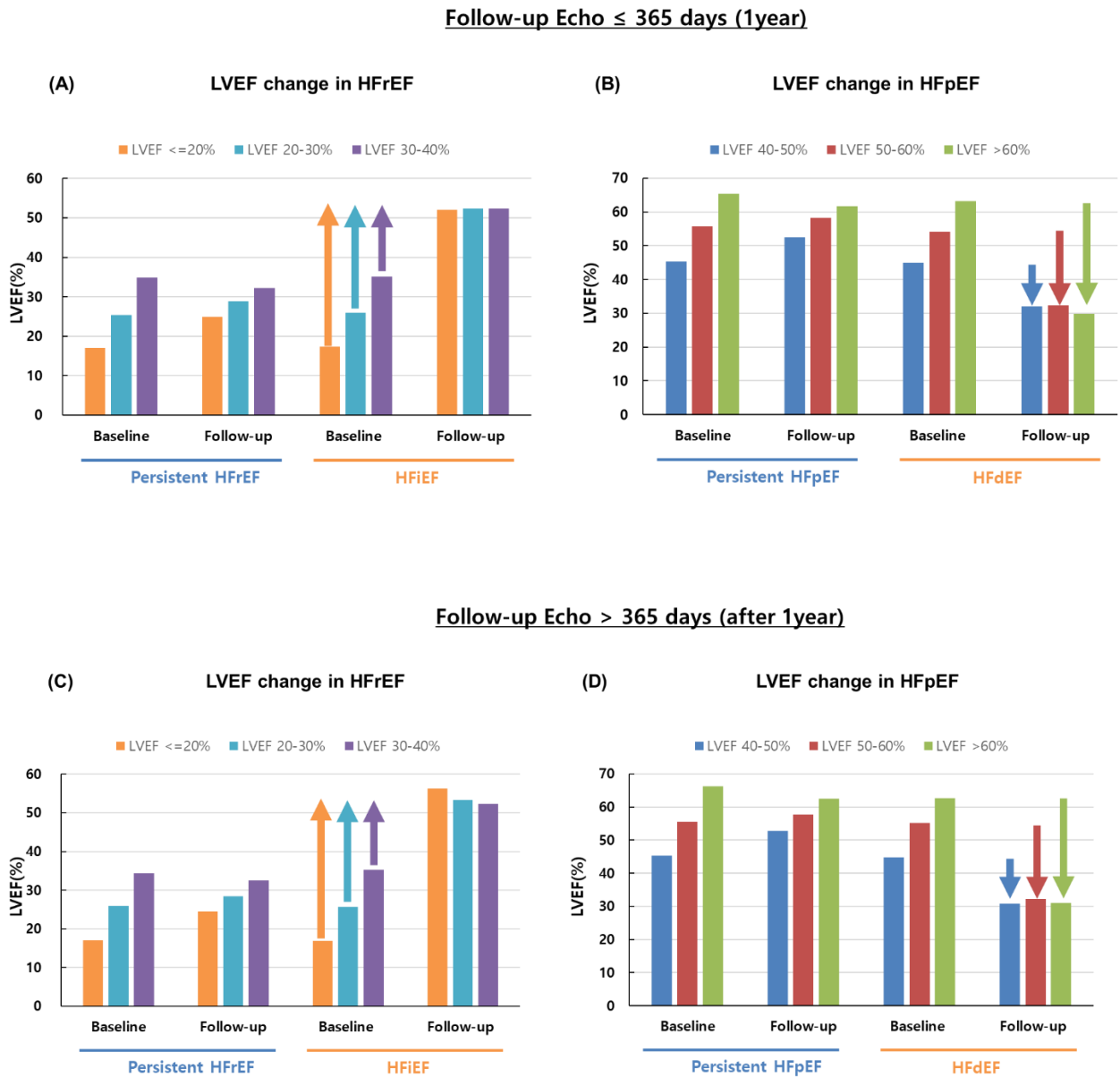
Figures S1–S2

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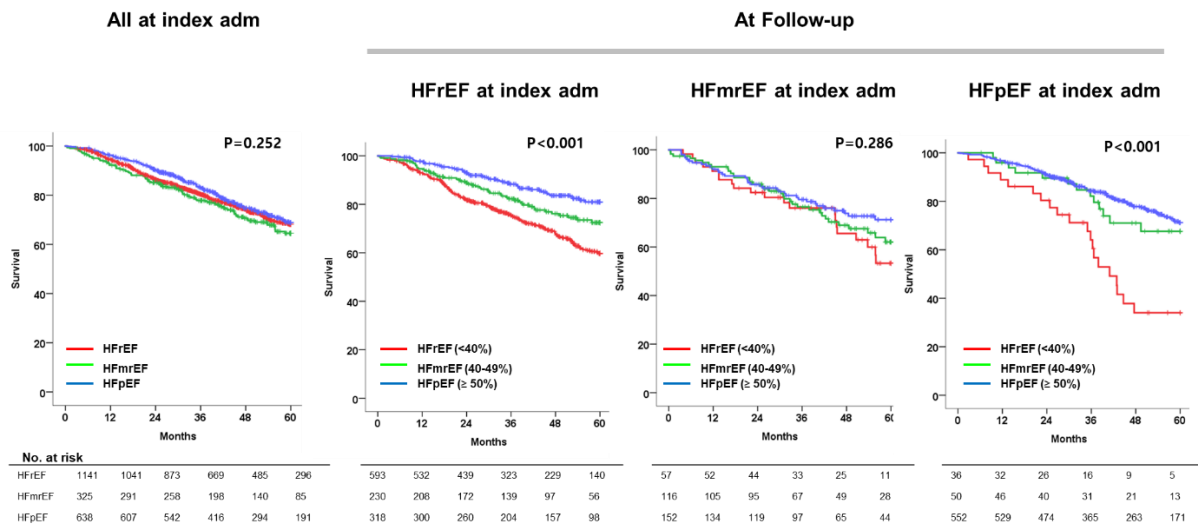
Supplemental Material

Figure S1. Stratification according to timing of echocardiography follow up.



Regarding the timing of echocardiography follow-up, 913 (43.4%) patients had follow-up echocardiography \leq 1 year from the index admission (median: 245 days, IQR 191-311 days) and 1191 (56.6%) patients follow-up echocardiography $>$ 1 year from the index admission (median 627 days, IQR 456-955 days). The changes in LVEF were similar in both groups.

Figure S2. Application of ESC HF classification.



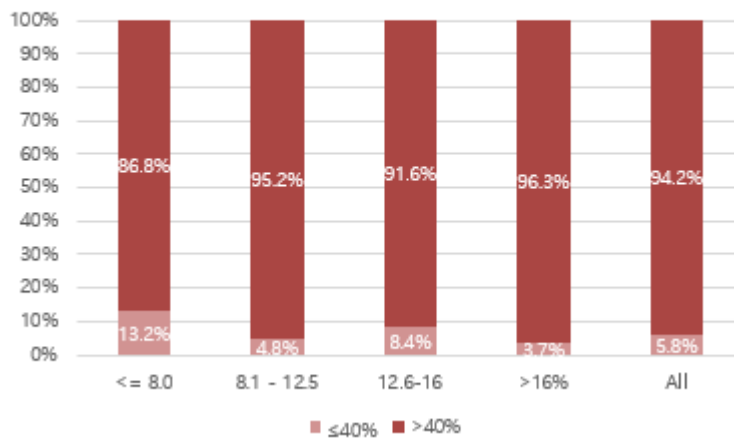
When applying the ESC classification, i.e. HFrEF EF <40%, HFmrEF EF 40-49, HFpEF ≥ 50%, there was no difference in all-cause mortality between the three groups. However, under reclassification of patients by the follow-up LVEF, patients with LVEF ≥50% had the best, whereas those with LVEF <40% had the worst prognosis regardless of baseline LVEF.

Change in LVEF during following according to HF classification according to ESC-guideline and GLS.

The ESC guideline categorized in HF into HFrEF, HFmrEF, and HFpEF. Using this HF classification, 1141, 325, and 638 patients HFrEF, HFmrEF, and HFpEF, respectively.

I- Patients with HFpEF [i.e LVEF > 50%]: differences in the rate of patients that changed to HFrEF [LVEF < 40%] at follow-up in patients with GLS < 8% vs. GLS 8-12.5% vs. GLS 12.5-16% and vs. GLS > 16%.

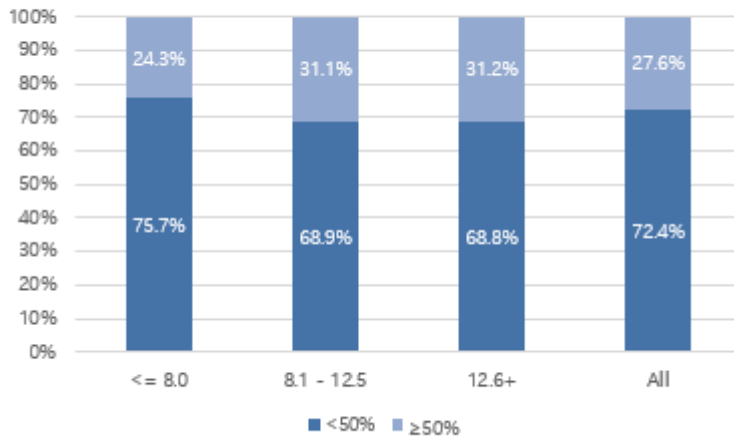
HFpEF at admission → HFrEF at F/U according to GLS



Among patients with HFpEF at the index admission, 5.8% experienced a decrease in LVEF to ≤40% during follow-up. When stratifying the patients according to GLS, 13.2% of patients with GLS ≤8% and 3.7% of patients with GLS >16% developed HFrEF, indicating that patients with low GLS were likely to experience a decrease in LVEF during follow-up.

II- Patients with HFrEF [i.e LVEF < 40%]: differences in the rate of patients that improved the LVEF (i.e. LVEF {greater than or equal to} 50%) at follow-up in patients with GLS < 8% vs. GLS 8-12.5% and vs. GLS > 12.5%.

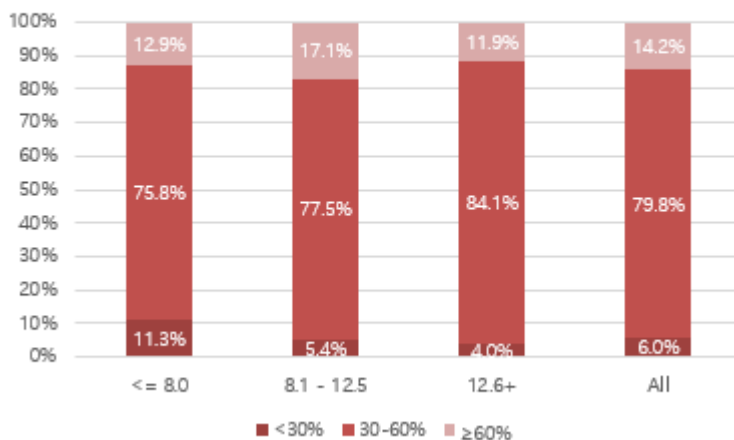
HFrEF at admission → F/U LVEF ≥50% according to GLS



Among patients with HFrEF at the index admission, 27.6% experienced an increase in LVEF to ≥50% during follow-up. Under stratification by GLS, 24.3% of patient with GLS ≤8% and 31% of patients with GLS > 8% experienced an increase in LVEF ≥ 50% during follow-up.

III- Patients with HFmrEF [i.e LVEF 40-50%]: - differences in the rate of patients that significantly improved the LVEF (i.e. LVEF {greater than or equal to} 60%) at 1 and 2 years of follow-up in patients with GLS < 8% vs. GLS 8-12.5% and vs. GLS > 12.5%; - differences in the rate of patients that significantly worsened the LVEF (i.e. LVEF < 30%) at follow-up in patients with GLS < 8% vs. GLS 8-12.5% and vs. GLS > 12.5%.

HFmrEF at admission → EF change according to GLS



For patients with HFmrEF, 14.2% experienced a decrease in LVEF to <30%, and 6%

experienced an increase in LVEF to $\geq 60\%$. When stratifying the patients according to GLS, among patients with $GLS \leq 8\%$, 11.3% experienced a decrease in LVEF to $< 30\%$, whereas 12.9% experienced an increase in LVEF to $\geq 60\%$. Among patients with $GLS > 12.6\%$, only 4% experienced a decline in LVEF to $< 30\%$.