ORIGINAL RESEARCH

Characteristics, Outcomes, and Treatment of Heart Failure With Improved Ejection Fraction

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***Background*—**Many patients with heart failure (HF) with reduced ejection fraction (HFrEF) experience improvement or recovery of left ventricular ejection fraction (LVEF). Data on clinical characteristics, outcomes, and medical therapy in patients with HF with improved ejection fraction (HFiEF) are scarce.

***Methods and Results*—**Of 5625 consecutive patients hospitalized for acute HF in the KorAHF (Registry [Prospective Cohort] for Heart Failure in Korea) study, 5103 patients had baseline echocardiography and 2302 patients had follow-up echocardiography at 12 months. HF phenotypes were defined as persistent HFrEF (LVEF ≤40% at baseline and at 1-year follow-up), HFiEF (LVEF ≤40% at baseline and improved up to 40% at 1-year follow-up), HF with midrange ejection fraction (LVEF between 40% and <50%), and HF with preserved ejection fraction (LVEF ≥50%). The primary outcome was 4-year all-cause mortality from the time of HFiEF diagnosis. Among 1509 HFrEF patients who had echocardiography 1 year after index hospitalization, 720 (31.3%) were diagnosed as having HFiEF. Younger age, female sex, de novo HF, hypertension, atrial fibrillation, and β-blocker use were positive predictors and diabetes mellitus and ischemic heart disease were negative predictors of HFiEF. During 4-year follow-up, patients with HFiEF showed lower mortality than those with persistent HFrEF in univariate, multivariate, and propensity-score–matched analyses. β-Blockers, but not renin–angiotensin system inhibitors or mineralocorticoid receptor antagonists, were associated with a reduced all-cause mortality risk (hazard ratio: 0.59; 95% CI, 0.40–0.87; *P*=0.007). Benefits for outcome seemed similar among patients receiving low- or high-dose β-blockers (log-rank, *P*=0.304).

***Conclusions*—**HFiEF is a distinct HF phenotype with better clinical outcomes than other phenotypes. The use of β-blockers may be beneficial for these patients.

***Clinical Trial Registration*—**URL: https://www.clinicaltrials.gov. Unique identifier: NCT01389843. **(*J Am Heart Assoc*. 2019;8: e011077. DOI: 10.1161/JAHA.118.011077.)**

Key Words: β-blockers • heart failure • improved ejection fraction • mortality

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Accompanying Tables S1 through S7 and Figures S1 through S9 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.118.011077

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Clinical Perspective

What Is New?

- Among patients with heart failure with reduced ejection fraction, left ventricular ejection fraction improves in a third. Patients with heart failure with improved ejection fraction (HFiEF) have better prognosis than other heart failure phenotypes.
- Younger age, female sex, de novo onset, hypertension, atrial fibrillation, and β-blocker prescription are positive predictors, whereas ischemic heart disease and diabetes mellitus are negative independent predictors of HFiEF.
- The use of β-blockers, but not renin–angiotensin system inhibitors or mineralocorticoid receptor antagonists, is associated with reduced all-cause mortality among patients with HFiEF.

What Are the Clinical Implications?

- HFiEF is a distinct heart failure phenotype with better clinical outcomes than other phenotypes.
- β-Blockers should be continued in HFiEF patients.

Heart failure (HF) is currently classified as HF with reduced ejection fraction (HFrEF), HF with midrange ejection fraction (HFmrEF), or HF with preserved ejection fraction (HFpEF) based on left ventricular ejection fraction (LVEF).[1] Although the prognoses for the various HF types appear to be similar, the level of neurohumoral activity and the response to medical therapy differ among HF types, suggesting differences in their underlying pathophysiology.[2]

Among patients with HFrEF, a subgroup experience the restoration of LVEF with goal-directed medical therapy (GDMT) and are classified as having HF with improved ejection fraction (HFiEF).[3–5] Data on demographics, etiology, and prognosis remain scarce, especially in Asian patients with HF.

Regarding treatment strategies, drugs targeting the sympathetic nervous system and neurohumoral activation have improved survival in patients with HFrEF[6–9] but not in those with HFpEF.[10–13] It is unknown whether HFiEF would behave like HFrEF or HFpEF in terms of response to GDMT.

KorAHF (Registry [Prospective Cohort] for Heart Failure in Korea) is a prospective, nationwide, multicenter cohort study that consecutively enrolled patients with acute HF (AHF), and every patient was scheduled to undergo echocardiography at baseline and at 1 year after the index admission. Using this registry, we sought to comprehensively investigate the clinical characteristics, outcomes, and response to medical therapy of patients with HFiEF.

Methods

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

Study Population and Data Collection

KorAHF was a prospective, multicenter cohort study, and the design and preliminary results have been described elsewhere (ClinicalTrial.gov identifier NCT01389843).[14,15] Briefly, 5625 consecutive patients hospitalized for AHF in 10 tertiary university hospitals in the Republic of Korea were enrolled between March 2011 and December 2014. Patients who had signs or symptoms of HF and lung congestion, objective findings of left ventricular systolic dysfunction, or structural heart disease were included in this study. There were no exclusion criteria.

Each patient was scheduled for follow-up at least 5 years after the index hospitalization. The mortality data of patients who were lost to follow-up were collected from National Insurance data or National Death Records.

The institutional review board or ethics committee at each participating hospital approved the study protocol and waived the need for written informed consent. This study complied with the Declaration of Helsinki principles.

Study Variables and Definitions

All echocardiographic studies were performed by cardiologists who were certified by the Korean Society of Echocardiography, using a standard ultrasound machine with a 2.5-MHz probe. Standard techniques were adopted to obtain M-mode, 2-dimensional, and Doppler measurements, in accordance with the American Society of Echocardiography's guidelines.[16] LVEF was measured using the Simpson biplane method, unless the Simpson method was not possible. Based on the echocardiography findings at the index AHF hospitalization, patients were classified into those with HFrEF (LVEF ≤40%), HFmrEF (LVEF between 40% and <50%), and HFpEF (LVEF ≥50%). All patients were encouraged to undergo follow-up echocardiography at 1 year after the index hospitalization. Among patients with HFrEF at the index hospitalization, those whose LVEF improved to >40% were considered to have HFiEF, whereas those with LVEF ≤40% were considered to have persistent HFrEF (Figure 1A).

In terms of medication, the use of β-blockers for HF treatment was defined as a prescription for carvedilol, metoprolol, bisoprolol, or nebivolol, according to the recommendation of the current guidelines.[1,4] Use of renin–angiotensin system (RAS) inhibitors was defined as the administration of either an angiotensin-converting enzyme inhibitor or an angiotensin II receptor blocker. The β-blocker name and dose were evaluated in the year following diagnosis of HFiEF. Low- and high-dose β-blockers were defined as those with 1% to 49% and ≥50% of the target dose, respectively.

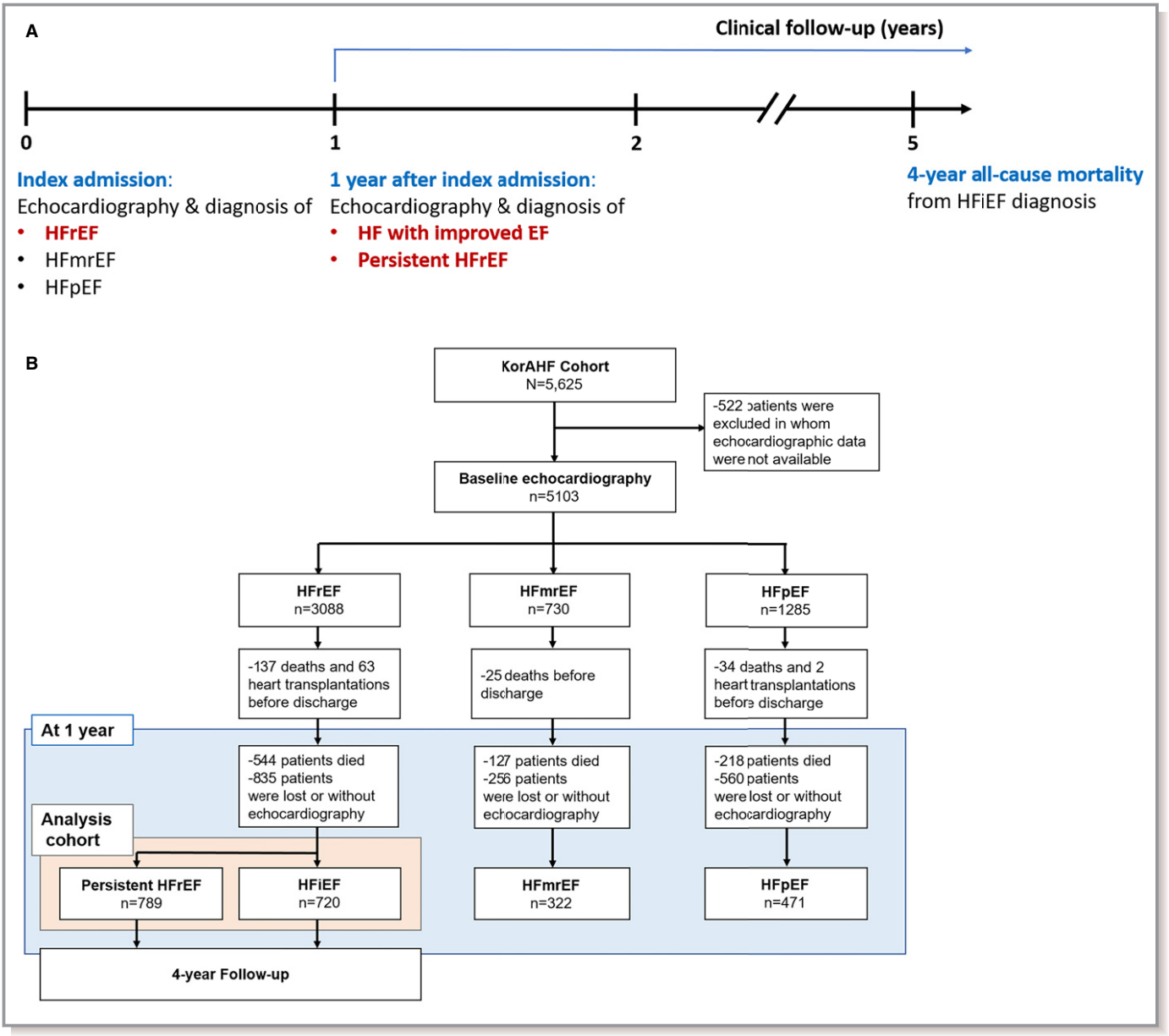

Figure 1. Study population. **A**, Flowchart of the study. **B**, Patients demographics according to the flowchart. EF indicates ejection fraction; HF, heart failure; HFiEF, heart failure with improved ejection fraction; HFmrEF, heart failure with midrange ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; KorAHF, Registry (Prospective Cohort) for Heart Failure in Korea.

The target dose of the β-blockers was based on the clinical guideline.[1,17] Medication history at admission, during admission, at discharge, and during follow-up (at 1, 3, 6, and 12 months) was recorded in the KorAHF registry.

The primary outcome was 4-year all-cause mortality from time of HFiEF diagnosis.

Statistical Analysis

The data are presented as number and frequency for categorical variables and as mean±SD for continuous variables. For comparison between groups, the χ^2 test (or Fisher exact test when any expected cell count was <5 for a 2×2 table) was used for categorical variables and the unpaired Student *t* test was used for continuous variables. The chronological trends of the outcomes were expressed as Kaplan–Meier estimates and compared by β-blocker use. The log-rank test was performed for comparison of the differences in the clinical outcomes. A multivariable Cox proportional hazards regression model was used to determine the independent predictors of all-cause mortality. Variables associated with mortality with a $P<0.05$ were included as confounding variables in the multivariate analysis. As a sensitivity analysis, we performed both propensity-score–

matched (PSM) and inverse-probability treatment-weighted (IPTW) analysis. The propensity score was calculated using multivariable logistic regression analysis, and the PSM population was created using the nearest neighbor method without replacement in a 1:1 ratio (the following variables were included for matching: age, sex, body mass index, previous history of heart failure, hypertension, diabetes mellitus, ischemic heart disease, valvular heart disease, chronic obstructive pulmonary disease, cerebrovascular disease, atrial fibrillation, malignancy, New York Heart Association functional class, and medication history of β-blockers, renin–angiotensin system inhibitors, and mineralocorticoid receptor antagonists). Considering reduction of participants during PSM analysis, the IPTW analysis was also performed to account for confounders. Success of PSM and IPTW analyses was assessed by calculating standardized differences in the baseline characteristics (Tables S1 and S2). We used the "MatchIt" package for R programming for PSM analysis and the "Twang" package for IPTW analysis.

A 2-sided $P<0.05$ was considered statistically significant. The statistical tests were performed using IBM SPSS v23 (IBM Corp) and R v3.1.0 (R Foundation for Statistical Computing).

Results

Demographic and Clinical Characteristics

Among 5625 patients included in the KorAHF registry, 5103 patients underwent baseline echocardiographic evaluation. Based on LVEF, 3088 (61%) patients were classified as having HFrEF, 730 (14%) as having HFmrEF, and 1285 (25%) as having HFpEF. During the following year, 889 had died and 1651 were either lost to follow-up or did not undergo 1-year follow-up echocardiography; therefore, the data of 2302 patients were available for this analysis. Of these patients, 789 (34%) were finally diagnosed with persistent HFrEF, 720 (31%) with HFiEF, 322 (14%) with HFmrEF, and 471 (20%) with HFpEF (Figure 1B).

Tables 1 and 2 present clinical characteristics of patients with HFrEF at the index admission and at 1 year after index admission. In brief, patients with HFiEF had more favorable baseline characteristics: they were younger, showed a preponderance of de novo HF, and had less hypertension, diabetes mellitus, ischemic heart disease, and chronic obstructive lung disease. Change of LVEF from index admission to 1-year follow-up was 13.7±15.1% in all, 2.7±7.6% in persistent HFrEF, and 25.7±11.6% in HFiEF. The clinical information of other HF phenotypes is presented in Table S3.

Predictors of HFiEF

The etiology and aggravating factors for AHF by HF phenotype are presented in Figure 2A and 2C. Compared with patients with persistent HFrEF, patients with HFiEF had less ischemic but more tachycardia-induced cardiomyopathy.

We investigated independent predictors of HFiEF in patients who were initially diagnosed as having HFrEF at baseline (Table 3). In the multivariable analysis, younger age, female sex, de novo HF, hypertension, atrial fibrillation, and use of β-blockers were positive independent predictors. In contrast, diabetes mellitus, ischemic heart disease, and mineralocorticoid receptor antagonist (MRA) prescription at discharge were inversely associated with an HFiEF diagnosis.

Clinical Outcomes

The treatment and outcomes during the index hospitalization are displayed in Table S4.

During 4-year follow-up, 116 (16%) patients with HFiEF died, all of whom had more unfavorable characteristics, as expected (Table S5). Patients with HFiEF showed better prognosis (log-rank, $P<0.001$) than those with persistent HFrEF in crude, PSM, and IPTW cohorts (Figure 3, Tables S1 and S2). Clinical outcomes of other HF phenotypes are presented in Figure S1. Briefly, those with HFiEF had the lowest mortality (116 deaths, 16.1%) compared with those with persistent HFrEF (270 deaths, 34.2%), HFmrEF (214 deaths, 33.5%), and HFpEF (149 deaths, 31.6%).

GDMT in HFiEF

Regarding the effect of GDMT in HFiEF, patients with β-blockers had lower 4-year all-cause mortality in crude, PSM and IPTW populations (Figure 4, Table S6, Figure S2).

In multivariate analysis, only the use of β-blockers was associated with a 41% reduced risk of mortality (hazard ratio: 0.59; 95% CI, 0.40–0.87; $P=0.007$), whereas the effect of RAS inhibitor and MRA use on mortality appeared to be neutral (Table 4).

Effect of the Dose and Timing of Initiation of β-Blockers

Among patients with HFiEF who took β-blockers, most received carvedilol (216 patients, 48.8%) or bisoprolol (201 patients, 45.4%) whereas nebivolol (24 patients, 5.4%) and metoprolol (2 patients, 0.5%) were rarely used. There was no difference between carvedilol and bisoprolol; however, because of the small number of patients taking metoprolol and nebivolol, a definite conclusion could not be drawn. Stratified by β-blocker dose, patients who received either high- or low-dose β-blockers at the time of diagnosis of HFiEF showed better 4-year mortality than those who did not; however, there was no difference between the patients who received low- and high-dose β-blockers (log-rank, $P=0.304$; Figure S3).

Table 1. Clinical Characteristics According to HF Phenotypes at the Index Admission

	All HFrEF (n=1509)	Persistent HFrEF (n=789)	HFiEF (n=720)	*P* Value
Demographic data				
Age, y	62.4±15.2	65.0±14.1	59.5±15.8	<0.001
Men	937 (62.1)	516 (65.4)	421 (58.5)	<0.001
BMI, kg/m^2	23.7±3.8	23.6±3.5	23.7±4.1	0.507
De novo HF	833 (55.2)	354 (44.9)	479 (66.5)	<0.001
Past medical history				
Hypertension	757 (50.2)	409 (51.8)	348 (48.3)	<0.001
Diabetes mellitus	495 (32.8)	319 (40.4)	176 (24.4)	<0.001
Ischemic heart disease	378 (25.0)	267 (33.9)	111 (15.4)	<0.001
Valvular heart disease	131 (8.7)	60 (7.6)	71 (9.9)	0.120
COPD	127 (8.4)	72 (9.1)	55 (7.6)	0.008
Cerebrovascular disease	167 (11.1)	100 (12.7)	67 (9.3)	0.037
Atrial fibrillation	326 (21.6)	163 (20.7)	163 (22.6)	<0.001
Malignancy	123 (8.2)	55 (7.0)	68 (9.4)	0.079
Current smoking	341 (22.6)	176 (22.3)	165 (22.9)	0.777
NYHA functional class				
II	240 (15.9)	124 (15.7)	116 (16.1)	0.532
III	595 (39.4)	302 (38.3)	293 (40.7)	
IV	674 (44.7)	363 (46.0)	311 (43.2)	
Physical examination				
SBP, mm Hg	127.7±28.2	125.4±25.7	130.3±30.5	0.001
DBP, mm Hg	80.1±18.8	77.6±16.4	82.8±20.7	<0.001
HR, beats/min	94.7±24.7	92.5±23.5	97.1±25.7	<0.001
Laboratory examination				
Hemoglobin, mg/dL	13.1±2.3	13.0±2.2	13.2±2.3	0.032
Sodium, mmol/L	137.9±4.5	137.9±4.4	137.9±4.5	0.772
Potassium, mmol/L	4.4±0.6	4.4±0.6	4.3±0.6	0.021
BUN, mg/dL	24.5±14.8	25.6±15.2	23.2±14.2	0.002
Creatinine, mg/dL	1.4±1.4	1.4±1.3	1.4±1.5	0.692
BNP, pg/mL	980.5 (533.3–1856.5)	927.0 (508.5–1685.0)	1063.0 (545.0–2078.0)	0.090
NT-proBNP, pg/mL	4688.0 (2363.5–10 491.2)	4785.0 (2419.0–11 784.0)	4453.0 (2336.0–9531.5)	0.221
Troponin I, ng/mL	0.06 (0.04–0.20)	0.06 (0.04–0.18)	0.06 (0.03–0.24)	0.198
Echocardiography				
LAD, mm	47.7±9.0	48.3±8.7	47.0±9.3	0.004
LVEDD, mm	62.3±9.1	64.5±9.0	60.0±8.7	<0.001
LVESD, mm	53.0±9.9	55.3±9.8	50.5±9.5	<0.001
E/e′	21.8±11.1	22.8±11.7	20.6±10.3	0.001
RVSP, mm Hg	43.4±14.3	44.1±14.8	42.5±13.6	0.083
LVEF, %	26.2±7.4	25.3±7.1	27.3±7.6	<0.001
Medication				
B-Blocker	906 (60.0)	453 (57.4)	453 (62.9)	0.029
RASi	1186 (78.6)	622 (78.8)	564 (78.3)	0.813
MRA	840 (55.7)	472 (59.8)	368 (51.1)	0.001

Data are shown as n (%), mean±SD, or median (interquartile range). BMI indicates body mass index; BNP, B-type natriuretic peptide; BUN, blood urea nitrogen; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; HF, heart failure; HFiEF, heart failure with improved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, heart rate; LAD, left atrial diameter; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal proB-type natriuretic peptide; NYHA, New York Heart Association; RASi, renin-angiotensin system inhibitor; RVSP, right ventricular systolic pressure; SBP, systolic blood pressure.

Table 2. Clinical Characteristics According to HF Phenotypes 1 Year After Index Admission (ie, at HFiEF diagnosis)

	All HFrEF	Persistent HFrEF (n=789)	HFiEF (n=720)	*P* Value
Physical examination				
SBP, mm Hg	118.2±18.7	114.7±17.9	121.8±18.9	<0.001
DBP, mm Hg	70.6±12.7	68.4±12.0	72.8±12.9	<0.001
HR, bpm	78.2±15.6	78.4±16.1	78.1±15.2	0.767
Laboratory examination				
Hemoglobin, mg/dL	12.7±2.1	12.8±2.1	12.7±2.0	0.371
Sodium, mmol/L	139.1±3.3	138.8±3.2	139.4±3.5	0.006
Potassium, mmol/L	4.5±0.5	4.5±0.5	4.5±0.5	0.072
BUN, mg/dL	24.5±14.5	25.9±15.2	22.8±13.5	0.001
Creatinine, mg/dL	1.5±1.6	1.6±1.5	1.5±1.6	0.423
Echocardiography				
LAD, mm	44.4±8.8	46.9±8.4	41.6±8.4	<0.001
LVEDD, mm	57.7±10.0	63.6±8.8	51.2±6.7	<0.001
LVESD, mm	44.8±12.3	53.6±9.6	35.6±7.0	<0.001
E/e′	16.7±10.2	19.8±11.4	13.5±7.5	<0.001
RVSP, mm Hg	36.8±31.6	40.3±24.2	32.3±38.6	<0.001
LVEF, %	39.9±14.8	28.0±7.4	53.0±8.4	<0.001
ΔLVEF from index admission, %	13.7±15.1	2.7±7.6	25.7±11.6	<0.001
Medications				
B-Blocker	878 (63.3)	443 (60.9)	443 (65.8)	0.058
RASi	981 (70.7)	535 (74.9)	446 (66.3)	<0.001
MRA	612 (44.1)	373 (52.2)	239 (35.5)	<0.001

Data are shown as n (%) or mean±SD. BUN indicates blood urea nitrogen; DBP, diastolic blood pressure; E/e′, the ratio between early mitral inflow velocity and mitral annular early diastolic velocity; HF, heart failure; HFiEF, heart failure with improved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, heart rate; LAD, left atrial diameter; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; MRA, mineralocorticoid receptor antagonist; RAS, renin-angiotensin system inhibitor; RVSP, right ventricular systolic pressure; SBP, systolic blood pressure.

Because the status of β-blocker prescription changed between discharge from the index hospitalization and the time of HFiEF diagnosis, we further categorized the patients into 4 groups according to β-blocker use at discharge and at HFiEF diagnosis. In the Kaplan–Meier analysis, patients who were on β-blockers at the time of HFiEF diagnosis had similar prognoses, regardless of β-blocker use at discharge from the index hospitalization (log-rank, *P*=0.497; Figure S3).

Subgroup Analysis

We performed exploratory subgroup analyses that included age, sex, ischemic versus nonischemic etiology, HF onset (de novo versus acute decompensated HF [ADHF]), chronic kidney disease, diabetes mellitus, RAS inhibitor use, MRA use, and changes in LVEF. There was no significant interaction between the β-blocker effect and subgroups, and β-blocker use was consistently associated with reduced risk for 4-year all-cause mortality across all subgroups (Figure S4).

Next, we stratified the patients by rhythm. Patients with a β-blocker had better survival than patients without among those with sinus rhythm but not among those with atrial fibrillation (Figure S5).

Regarding the onset of HF, 55% of the patients had de novo HF and 45% had ADHF. Patients with HFiEF had better survival than those with persistent HFrEF among both de novo HF and ADHF patients (Figure S6). Regarding GDMT, β-blocker use was associated with improved survival of both de novo HF and ADHF patients. In Kaplan–Meier analysis, β-blockers showed a therapeutic implication for de novo HF (log-rank, *P*=0.016) but attenuated improvement in ADHF (log-rank, *P*=0.089). After adjusting for covariates, both de novo HFiEF (hazard ratio: 0.73; 95% CI, 0.54–1.00; *P*=0.049) and acute decompensated HFiEF (hazard ratio: 0.57; 95% CI, 0.33–0.98, *P*=0.041) showed a benefit of β-blockers. In contrast, the effect of RAS inhibitors and MRAs appeared to be neutral in both de novo HF and ADHF patients (Figures S7 and S8).

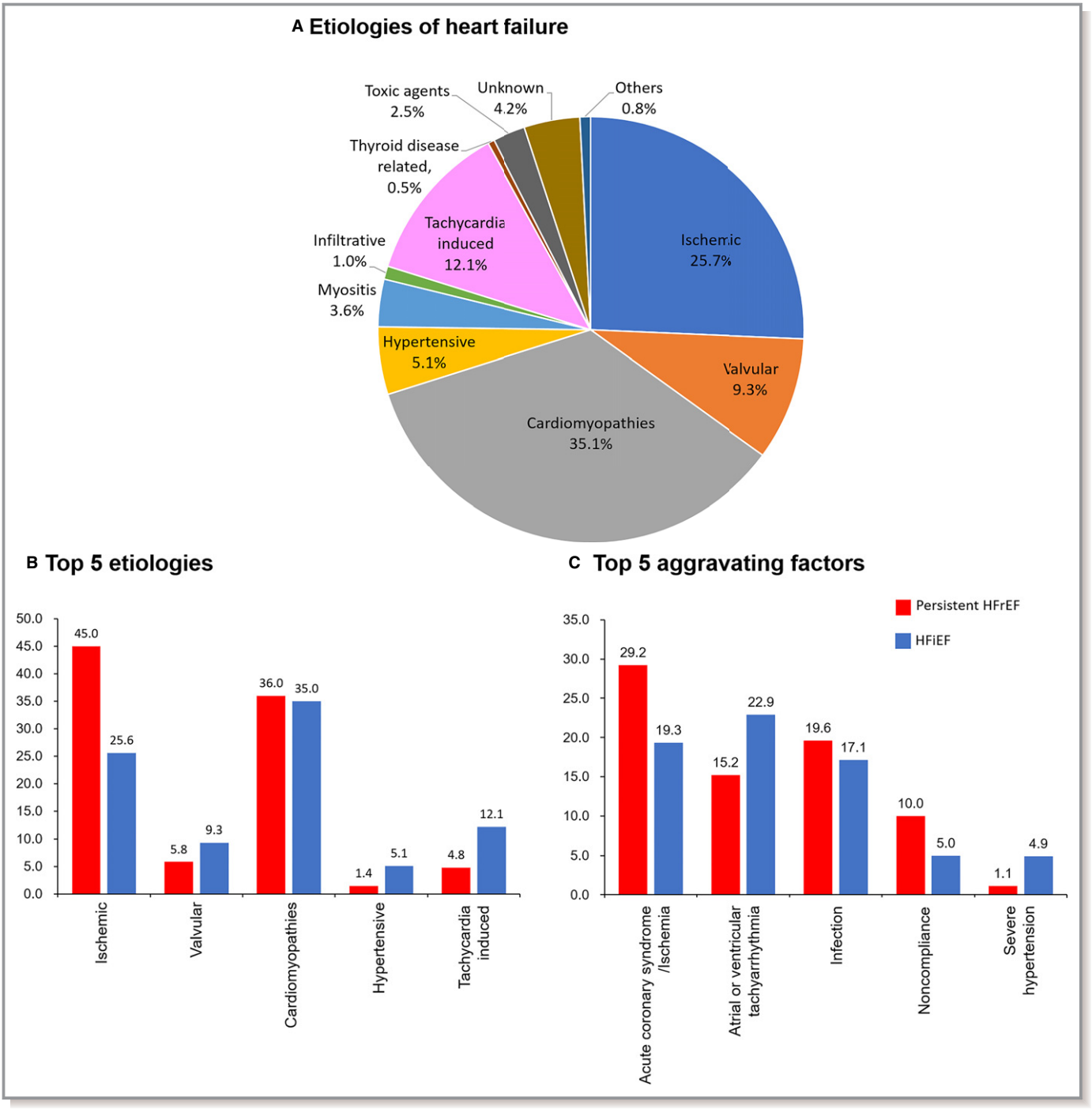

Figure 2. Etiology and aggravating factors according to HF phenotypes. **A**, Proportion of HF etiology. **B**, Top 5 etiologic causes according to the HF phenotypes. **C**, Five most common aggravating factors of acute HF according to the HF phenotypes. HF indicates heart failure; HFiEF, heart failure with improved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

Discussion

In this comprehensive analysis of HFiEF, we investigated the clinical characteristics, predictors, and prognostic outcomes of patients with HFiEF in comparison with persistent HFrEF. Younger age, de novo onset, and β-blocker prescription were positive predictors; in contrast, ischemic heart disease and diabetes mellitus were negative independent predictors of HFiEF among patients with HFrEF at index admission. Compared with persistent HFrEF, patients with HFiEF had better prognosis, and the use of β-blockers was associated with improved survival in these patients.

Table 3. Independent Predictors of HFiEF Among Patients With HFrEF at the Index Admission

	OR	95% CI	*P* Value
Age	0.98	0.97–0.99	<0.001
Male	0.65	0.52–0.81	<0.001
De novo onset	2.23	1.77–2.80	<0.001
Hypertension	1.31	1.05–1.65	0.020
Diabetes mellitus	0.55	0.43–0.70	<0.001
Ischemic heart disease	0.58	0.45–0.76	<0.001
Atrial fibrillation	1.77	1.36–2.32	<0.001
B-Blocker at discharge	1.28	1.03–1.59	0.024
MRA at discharge	0.59	0.47–0.73	<0.001

ORs have been adjusted for age, sex, de novo heart failure, previous history of hypertension, diabetes mellitus, ischemic heart disease, chronic obstructive pulmonary disease, cerebrovascular accident, atrial fibrillation and malignancy, New York Heart Association functional class, β-blocker at discharge, renin–angiotensin system inhibitor at discharge, and MRA at discharge. HFiEF indicates heart failure with improved ejection fraction; HFrEF, heart failure with reduced ejection fraction; MRA, mineralocorticoid receptor antagonist; OR, odds ratio.

Clinical Characteristics and Predictors of HFiEF

Understanding the clinical characteristics and predictors of HFiEF provides important information and can be used for risk stratification and guidance of therapy in patients with HF. In this study, we showed that younger age and de novo HF were independent predictors of HFiEF. Previous studies also found patients with LVEF improvement to be younger.[18] Conversely, ischemic heart disease was a strong negative predictor, in accordance with a report indicating that patients with HFiEF had less coronary artery disease.[6] Patients with ischemic cardiomyopathy have been found to have less viable myocardium and more scarring; in addition, owing to its irreversible nature, the extent of the myocardial scar was found to correlate inversely with LVEF improvement.[19,20]

Prognosis of Patients With HFiEF

The principal finding of this study pertains to mortality, and patients with HFiEF had better prognosis compared not only with HFpEF but also with other HF phenotypes (Figure 3, Figure S1), with a remarkably reduced risk of 4-year all-cause mortality. Our findings are consistent with previous studies reporting the superior long-term clinical prognosis of patients with HFiEF compared with the other HF phenotypes.[3,5]

Notably, patients with HFiEF required more catecholamines and mechanical circulatory support device assistance during the index admission, indicating a more serious in-hospital course in contrast to the ultimately favorable long-term outcomes. This implies that in patients with HFrEF who survive the first year, the more serious in-hospital course does not necessarily equate to grave long-term postdischarge outcomes.

GDMT in HFiEF

Another principal finding was related to the effect of GDMT in patients with HFiEF. We found that the use of β-blockers,

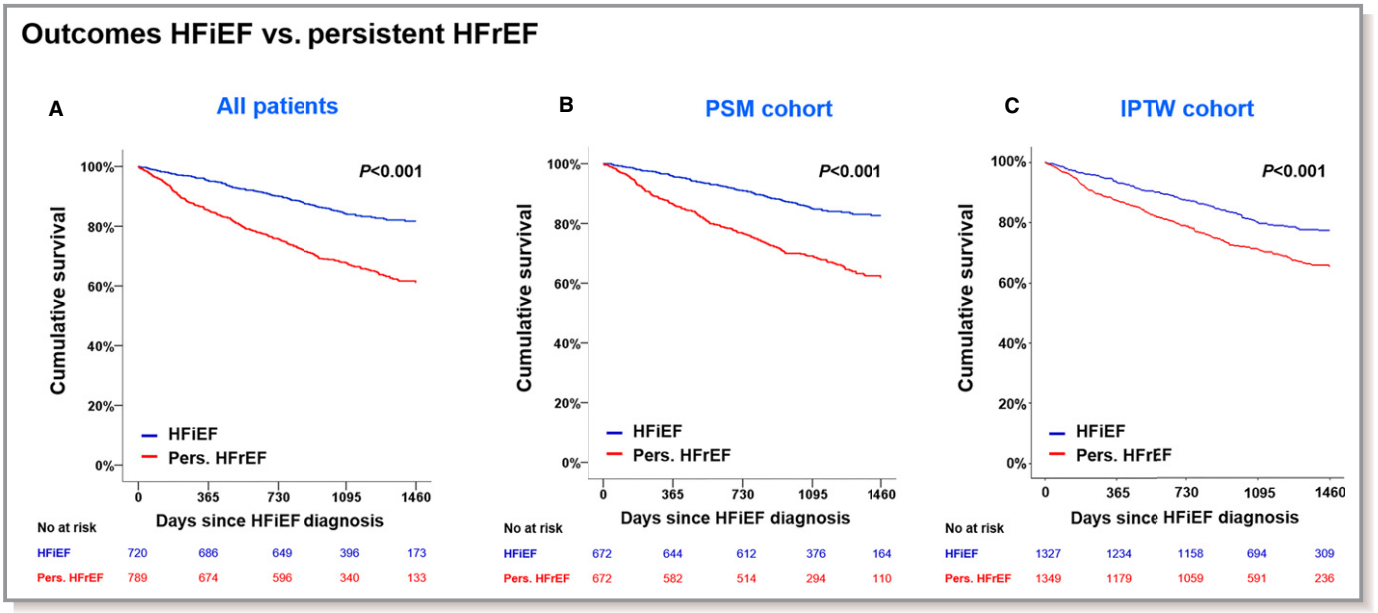

Figure 3. Clinical outcomes according to HFiEF and persistent HFrEF. **A**, Kaplan–Meier survival curves for 4-year mortality according to HF phenotypes. As sensitivity analyses, the PSM cohort (**B**) and the IPTW cohort (**C**) were also analyzed. The curves are left-truncated at 4 years after index admission. HFiEF, heart failure with improved ejection fraction; HFrEF, heart failure with reduced ejection fraction; IPTW, inverse-probability treatment weighted; PSM, propensity score matching.

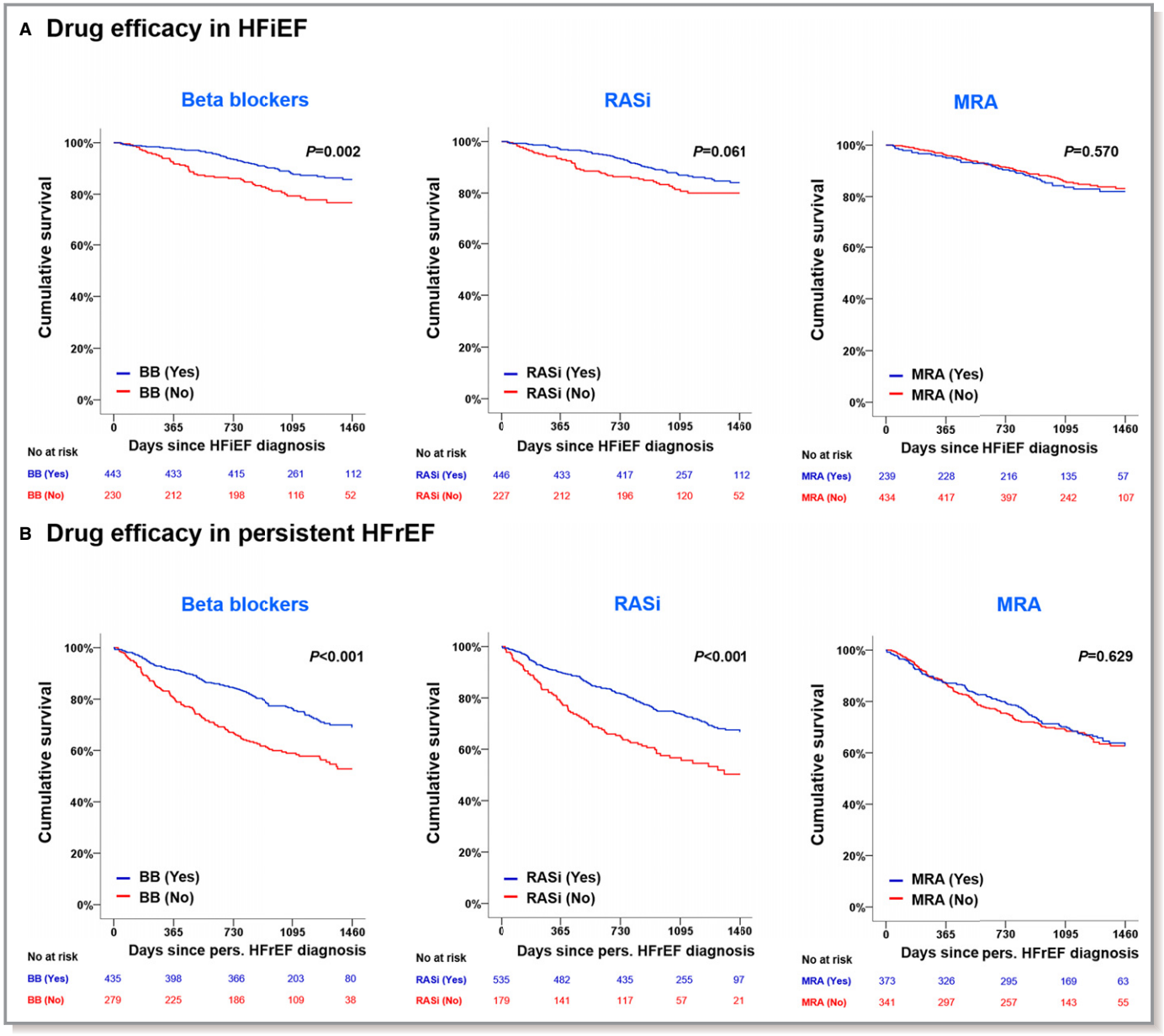

Figure 4. Impact of GDMT on 4-year mortality in HFiEF patients (**A**) and persistent HFpEF patients (**B**). GDMT indicates goal-directed medical therapy; HFrEF, heart failure with reduced ejection fraction; HFiEF, heart failure with improved ejection fraction; MRA, mineralocorticoid receptor antagonists; RASi, renin–angiotensin system inhibitor.

but not the use of RAS inhibitors or MRAs, was associated with improved survival. This finding is crucial and has important clinical implications: In patients with HFrEF, β-blockers should be continued even after the restoration of LVEF. Interestingly, there was no difference in mortality between the patients with high- and low-dose β-blockers in our study. Considering the similar prognoses for those taking low- or high-dose β-blockers, careful dose reduction of β-blockers may be possible for patients with HFiEF who do not tolerate β-blockers well. Furthermore, we showed that β-blocker use at HFiEF diagnosis was associated with improved survival regardless of the prescription of β-blockers at hospital discharge. This finding suggests that all patients with HFiEF could benefit from β-blocker use. The reasons for the lack of effect of RAS inhibitors and MRAs are not clear.

Strengths and Limitations

This study has several limitations. First, because this study is a post hoc analysis of a prospective cohort study, albeit a large one, as opposed to a randomized controlled trial, there could be unmeasured confounding factors. Second, we enrolled only patients who underwent echocardiographic assessment at

Table 4. Cox Regression Analysis for 4-Year Mortality From HFiEF Diagnosis

	Unadjusted			Adjusted		
	Hazard Ratio	95% CI	*P* Value	Hazard Ratio	95% CI	*P* Value
Age	1.06	1.04–1.07	<0.001	1.05	1.03–1.06	<0.001
Male	1.28	0.88–1.87	0.198			
De novo onset	0.41	0.28–0.59	<0.001	0.53	0.35–0.79	0.002
Hypertension	1.99	1.36–2.90	<0.001	0.96	0.60–1.52	0.852
Diabetes mellitus	2.41	1.67–3.48	<0.001	1.39	0.90–2.16	0.140
Ischemic heart disease	2.93	1.98–4.33	<0.001	1.56	0.99–2.46	0.055
COPD	1.01	0.51–2.00	0.971			
Cerebrovascular disease	3.21	2.07–4.96	<0.001	2.09	1.29–3.38	0.003
Atrial fibrillation	0.78	0.52–1.18	0.234			
Malignancy	1.52	0.88–2.62	0.130			
NYHA functional class						
II	1	Reference	0.079			
III	1.22	0.67–2.24				
IV	1.74	0.97–3.10				
B-Blocker at HFiEF diagnosis	0.54	0.37–0.80	0.002	0.59	0.40–0.87	0.007
RASi at HFiEF diagnosis	0.69	0.46–1.02	0.063			
MRA at HFiEF diagnosis	1.12	0.75–1.67	0.570			

Adjusted hazard ratios were adjusted for variables that showed $P<0.05$ in univariate analysis. COPD indicates chronic obstructive pulmonary disease; HFiEF, heart failure with improved ejection fraction; MRA, mineralocorticoid antagonist; NYHA, New York Heart Association; RASi, renin–angiotensin system inhibitor.

1 year after index admission, and this approach may have led to selection and lead-time biases, possibly favoring less ill patients or those with better compliance, in this substudy (Table S7). Third, because the participants comprise only East Asian patients, it is unknown whether the results can be extrapolated to other ethnicities and countries. In addition, we assessed left ventricular systolic function by LVEF, but even patients with "normal" LVEF might have impaired left ventricular systolic function.[21] In addition, β-blocker, RAS inhibitor, and MRA administration may have been altered, and other factors could be related to medication during the follow-up period. Although we evaluated the therapeutic implications of GDMT including β-blockers, RAS inhibitors, and MRAs, further studies are necessary to validate the prognostic value of sacubitril or valsartan in patients with HFiEF. Digoxin and loop diuretics have been prevalently prescribed to manage patients with AHF, but these patients did not show significant prognostic improvement (Figure S9). In addition, we defined de novo HF based on medical history of HF.[22–24] Last, we did not perform core laboratory analysis of the echocardiographic measurement of LVEF.

This study also has specific strengths. The KorAHF registry is a well-designed, nationwide, prospective cohort study in which every patient was scheduled to undergo echocardiography at baseline and 1 year after index admission and to be followed up for at least 5 years after index hospitalization. This design facilitates a definitive diagnosis of HFiEF, the identification of predictors, and the demonstration of its natural history; thanks to the prospective design and follow-up schedule, the KorAHF registry could identify more patients with HFiEF than previously reported.[3,5,25] Furthermore, we were also able to investigate the effect of GDMT in patients with HFiEF for the first time. Considering that LVEF improvement by GDMT was often observed between 6 and 12 months after the initiation of therapy,[26,27] echocardiographic assessment of LVEF at 1 year may be the appropriate timing for the detection of HFiEF. To minimize bias by indication, we performed several sensitivity analyses, and the protective relationship between β-blocker use and clinical outcomes was consistent in the univariate, multivariate, PSM and IPTW analyses. Despite the strengths of this study, a randomized clinical trial is necessary to rigorously evaluate the effect of GDMT in patients with HFiEF.

Conclusions

HFiEF is a unique disease entity that has superior clinical outcomes. Younger age, de novo HF, nonischemic heart disease, and a β-blocker prescription are independent predictors of HFiEF.

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Disclosures

None.

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Supplemental Material

Characteristics of matched population

Table S1. Clinical characteristics in propensity score-matched population

N=1344	HFiEF (n=672)	Persistent HFrEF (n=672)	Absolute mean difference	p-value
Demographic data				
Age (years)	59.6±15.7	65.3±13.7	4.844	<0.001
Men (%)	400 (59.5)	448 (66.7)	0.060	0.008
Body mass index (kg/m^2)	23.8±4.2	23.5±3.5	0.141	0.252
De novo heart failure (%)	441 (65.6)	291 (43.3)	0.176	<0.001
Past Medical History				
Hypertension	327 (48.7)	333 (49.6)	0.025	0.743
Diabetes mellitus	165 (24.6)	286 (42.6)	0.152	<0.001
Ischemic Heart Disease	105 (15.6)	237 (35.3)	0.150	<0.001
Valvular Heart Disease	70 (10.4)	49 (7.3)	0.022	0.044
COPD	54 (8.0)	63 (9.4)	0.012	0.384
Cerebrovascular disease	59 (8.8)	87 (12.9)	0.033	0.014
Atrial fibrillation	155 (23.1)	131 (19.5)	0.021	0.110
Malignancy	67 (10.0)	42 (6.3)	0.030	0.012
Current Smoking	159 (23.7)	146 (21.7)	0.010	0.397
NYHA functional class (%)			0.042	0.528
II	111 (16.5)	102 (15.2)		
III	273 (40.6)	262 (39.0)		
IV	288 (42.9)	308 (45.8)		
Beta-blocker (%)				
at discharge	422 (62.8)	385 (57.3)	0.034	0.039
at HFiEF diagnosis	442 (65.8)	400 (59.5)	0.027	0.018
RAS-inhibitor (%)				
at discharge	529 (78.7)	522 (77.7)	0.153	0.644
at HFiEF diagnosis	445 (66.2)	510 (75.9)	0.006	<0.001
MRA (%)				
at discharge	348 (51.8)	411 (61.2)	0.042	0.001
at HFiEF diagnosis	238 (35.4)	367 (54.6)	0.073	<0.001

COPD, chronic obstructive pulmonary disease; HFiEF, heart failure with improved ejection fraction; MRA, Mineralocorticoid receptor antagonist; NYHA, New York Heart Association; RAS-inhibitor, renin-angiotensin-system inhibitor

Table S2. Clinical characteristics in inverse probability treatment weight-adjusted population

N=2,676	HFiEF (n=1327)	Persistent HFrEF (n=1349)	Absolute mean difference	p-value
Demographic data				
Age (years)	61.9±15.2	63.2±14.7	0.089	0.112
Men (%)	818 (61.6)	864 (64.1)	0.051	0.360
Body mass index (kg/m^2)	23.7±3.8	23.6±3.6	0.022	0.690
De novo heart failure (%)	787 (59.3)	721 (53.5)	0.118	0.038
Past Medical History				
Hypertension	684 (51.5)	688 (51.0)	0.010	0.859
Diabetes mellitus	415 (31.3)	477 (35.4)	0.087	0.123
Ischemic Heart Disease	310 (23.4)	362 (26.9)	0.083	0.157
Valvular Heart Disease	120 (9.1)	106 (7.9)	0.043	0.436
COPD	110 (8.3)	113 (8.4)	0.003	0.951
Cerebrovascular disease	139 (10.4)	158 (11.7)	0.040	0.476
Atrial fibrillation	298 (22.5)	282 (20.9)	0.039	0.958
Malignancy	117 (8.8)	101 (7.5)	0.048	0.391
Current Smoking	302 (22.7)	305 (22.6)	0.003	0.478
NYHA functional class (%)			0.005	0.958
II	205 (15.5)	219 (16.2)		
III	529 (39.9)	512 (38.0)		
IV	593 (44.7)	618 (45.8)		
Beta-blocker (%)				
at discharge	826 (62.3)	802 (59.5)	0.057	0.305
at HFiEF diagnosis	813 (66.1)	786 (63.6)	0.052	0.370
RAS-inhibitor				
at discharge	1048 (79.0)	1055 (78.2)	0.018	0.157
at HFiEF diagnosis	865 (70.3)	913 (73.4)	0.082	0.490
MRA				
at discharge	726 (54.7)	777 (57.6)	0.076	0.300
at HFiEF diagnosis	522 (42.4)	571 (46.1)	0.038	0.194

* Abbreviations as in Supplemental Table 1

Patients with HFrEF, HFmrEF, and HFpEF

In this study 2,302 patients in the KorAHF registry had echocardiography both at baseline and 1 year after index admission. The patients were stratified according to HF types.

Table S3. Clinical characteristics according to HF phenotypes at the index admission

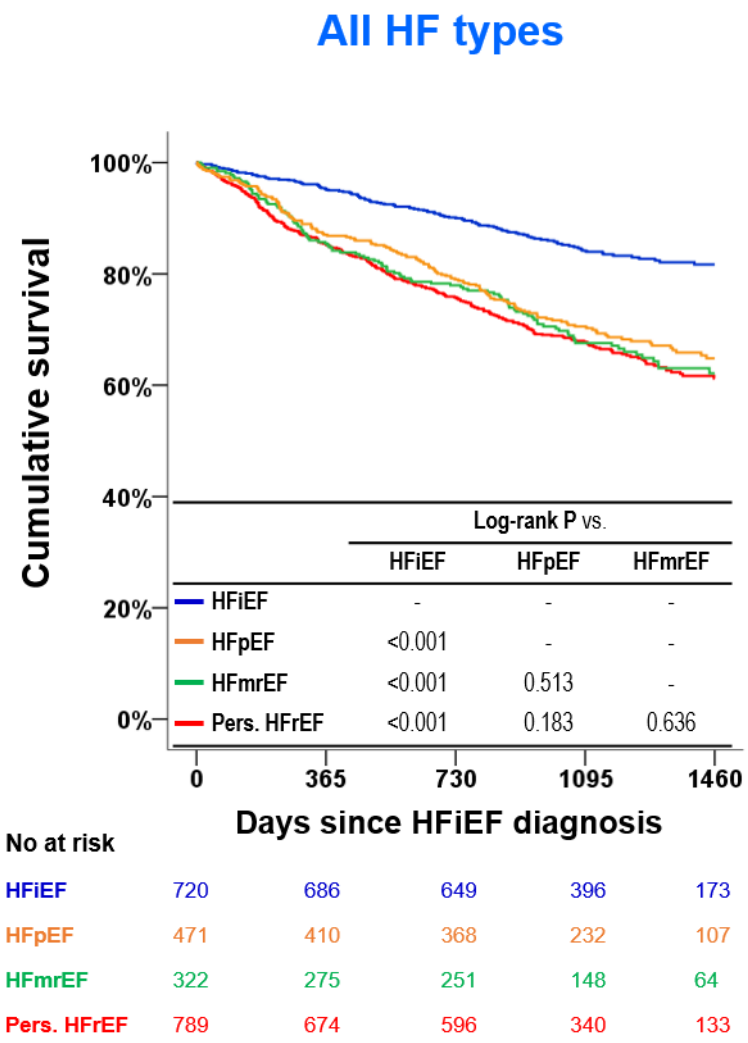
	Persistent HFrEF (n=789)	HFiEF (n=720)	HFmrEF (n=322)	HFpEF (n=471)	p-value
Demographic data					
Age (years)	65.0±14.1	59.5±15.8	67.7±14.2	69.3±13.9	<0.001
Men (%)	516 (65.4)	421 (58.5)	152 (47.2)	189 (40.1)	<0.001
BMI (kg/m^2)	23.6±3.5	23.7±4.1	23.8±3.8	24.2±4.1	0.045
De novo HF (%)	354 (44.9)	479 (66.5)	187 (58.1)	242 (51.4)	<0.001
Past Medical History (%)					
Hypertension	409 (51.8)	348 (48.3)	195 (60.6)	287 (60.9)	<0.001
Diabetes mellitus	319 (40.4)	176 (24.4)	111 (34.5)	144 (30.6)	<0.001
Ischemic heart disease	267 (33.9)	111 (15.4)	87 (27.0)	107 (22.7)	<0.001
Valvular heart disease	60 (7.6)	71 (9.9)	54 (16.8)	152 (32.3)	<0.001
COPD	72 (9.1)	55 (7.6)	36 (11.2)	63 (13.4)	0.008
Cerebrovascular disease	100 (12.7)	67 (9.3)	46 (14.3)	59 (12.5)	0.071
Atrial fibrillation	163 (20.7)	163 (22.6)	89 (27.6)	181 (38.5)	<0.001
Malignancy	55 (7.0)	68 (9.4)	28 (8.7)	27 (5.7)	0.084
Current Smoking	176 (22.3)	165 (22.9)	45 (14.0)	54 (11.5)	<0.001
NYHA functional class (%)					0.382

II	124 (15.7)	116 (16.1)	52 (16.1)	92 (19.5)	
III	302 (38.3)	293 (40.7)	128 (39.8)	192 (40.8)	
IV	363 (46.0)	311 (43.2)	142 (44.1)	187 (39.7)	
Physical exam at index admission					
SBP (mmHg)	125.4±25.7	130.3±30.5	137.3±31.7	134.3±29.3	<0.001
DBP (mmHg)	77.6±16.4	82.8±20.7	79.2±20.3	76.4±18.3	<0.001
HR (beats per min)	92.5±23.5	97.1±25.7	89.1±22.8	84.3±24.4	<0.001
Laboratory exam at index admission					
Hemoglobin (mg/dL)	13.0±2.2	13.2±2.3	12.2±2.4	12.1±2.1	<0.001
Sodium (mmol/L)	137.9±4.4	137.9±4.5	138.2±4.3	137.9±4.7	0.670
Potassium (mmol/L)	4.4±0.6	4.3±0.6	4.4±0.6	4.3±0.7	0.020
BUN (mg/dL)	25.6±15.2	23.2±14.2	24.0±13.3	23.1±13.1	0.004
Creatinine (mg/dL)	1.4±1.3	1.4±1.5	1.4±1.3	1.2±1.0	0.042
BNP (pg/mL)	927.0 (508.5-1685.0)	1063.0 (545.0-2078.0)	763.5 (410.3-1403.5)	529.0 (203.5-904.8)	<0.001
NT-proBNP (pg/mL)	4785.0 (2419.0-11784.0)	4453.0 (2336.0-9531.5)	4356.0 (1960.0-11457.0)	2438.5 (1059.8-4204.0)	<0.001
Troponin I (ng/mL)	0.06 (0.04-0.18)	0.06 (0.03-0.24)	0.10 (0.04-0.73)	0.04 (0.02-0.09)	<0.001
Echocardiography at index admission					
LAD (mm)	48.3±8.7	47.0±9.3	47.9±9.9	50.3±11.9	<0.001

LVEDD (mm)	64.5±9.0	60.0±8.7	54.6±7.3	50.4±7.5	<0.001
LVESD (mm)	55.3±9.8	50.5±9.5	40.8±6.8	32.7±6.1	<0.001
E/e’	22.8±11.7	20.6±10.3	19.7±10.8	20.2±12.1	<0.001
RVSP (mmHg)	44.1±14.8	42.5±13.6	41.2±13.9	44.6±16.9	0.020
LVEF (%)	25.3±7.1	27.3±7.6	44.3±2.9	59.2±6.2	<0.001
Medication (%)					
Beta-blocker	453 (57.4)	453 (62.9)	181 (56.2)	153 (32.5)	<0.001
RAS-inhibitor	622 (78.8)	564 (78.3)	223 (69.3)	246 (52.2)	<0.001
MRA	472 (59.8)	368 (51.1)	128 (39.8)	192 (40.8)	<0.001

BMI, body mass index; BNP, B-type natriuretic peptide; BUN, blood urea nitrogen; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; HF, heart failure; HFiEF, heart failure with improved ejection fraction; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, heart rate; LAD, left atrial diameter; LVEDD, left ventricular end diastolic dimension; LVEF, left ventricular ejection fraction; LVESD, left ventricular end systolic diameter; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal proB-type natriuretic peptide; NYHA, New York Heart Association; RAS, renin-angiotensin system; RVSP, right ventricular systolic pressure; SBP, systolic blood pressure

Figure S1 Clinical outcomes according to HF phenotypes



HFiEF, heart failure with improved ejection fraction; HFmrEF, heart failure with midrange ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction

HFrEF: HFiEF versus persistent HFrEF

Table S4. In-hospital treatment during index hospitalization according to HF phenotypes

	Persistent HFrEF (n=789)	**HFiEF (n=720)**	**p-value**
Total hospital (day)	12.2±10.5	16.2±19.4	<0.001
ICU admission (%)	365 (46.3)	387 (53.8)	0.004
ICU duration (days)	2.0±4.6	2.9±6.8	0.006
Pharmacological treatments			
Parenteral medication (%)			
Nitroglycerin	283 (35.9)	289 (40.1)	0.088
Nitroprusside	4 (0.5)	18 (2.5)	0.001
Norepinephrine	49 (6.2)	64 (8.9)	0.048
Milrinone	14 (1.8)	29 (4.0)	0.009
Dopamine	110 (13.9)	142 (19.7)	0.003
Dobutamine	219 (27.8)	189 (26.3)	0.510
Diuretics	589 (74.7)	522 (72.5)	0.343
Oral medication (%)			
Nitrates	431 (54.6)	399 (55.4)	0.758
Hydralazine	12 (1.5)	26 (3.6)	0.010
Loop diuretics	756 (95.8)	667 (92.6)	0.008
Thiazide	110 (13.9)	105 (14.6)	0.722
Amiodarone	125 (15.8)	131 (18.2)	0.224
Digoxin	294 (37.3)	293 (40.7)	0.172
Heparin/LWMH	332 (42.1)	359 (49.9)	0.002
Warfarin	230 (29.2)	278 (38.6)	<0.001
Aspirin	567 (71.9)	410 (56.9)	<0.001
Non-pharmacological treatments (%)			
Blood transfusion	104 (13.2)	142 (19.7)	0.001
Mechanical ventilation	84 (10.6)	112 (15.6)	0.005
CRT	18 (2.3)	8 (1.1)	0.081
ICD	23 (2.9)	9 (1.3)	0.025
PCI	94 (11.9)	71 (9.9)	0.202
CABG	30 (3.8)	21 (2.9)	0.342
Valve operation	15 (1.9)	24 (3.3)	0.080

ECMO/PCPS	19 (2.4)	23 (3.2)	0.354

CABG, coronary artery bypass graft; CRT, cardiac resynchronization therapy; ECMO, extracorporeal membrane oxygenation; HFiEF, heart failure with improved ejection fraction; HFmrEF, heart failure with midrange ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; IABP, intraaortic balloon pump; ICD, intracardiac defibrillator; ICU, intensive care unit; LMWH, low molecular heparin; PCI, percutaneous coronary intervention; PCPS, percutaneous cardiopulmonary support

Table S5. Clinical characteristics of patients with HFiEF according to 4-year all-cause mortality from HFiEF diagnosis

	Alive (n=604)	**Deceased (n=116)**	**p-value**
Demographic data			
Age (years)	57.5±15.4	69.8±13.4	<0.001
Men (%)	347 (57.5)	74 (63.8)	0.204
BMI (kg/m^2)	24.0±4.2	22.4±3.3	<0.001
De novo HF (%)	424 (70.2)	55 (47.4)	<0.001
Past Medical History (%)			
Hypertension	274 (45.4)	74 (63.8)	<0.001
Diabetes mellitus	127 (21.0)	49 (42.2)	<0.001
Ischemic heart disease	74 (12.3)	37 (31.9)	<0.001
Valvular heart disease	63 (10.4)	8 (6.9)	0.242
COPD	46 (7.6)	9 (7.8)	0.958
Cerebrovascular disease	41 (6.8)	26 (22.4)	<0.001
Atrial fibrillation	132 (21.9)	31 (26.7)	0.251
Malignancy	53 (8.8)	15 (12.9)	0.161
Current Smoking	145 (24.0)	20 (17.2)	0.112
NYHA functional class (%)			0.074
II	102 (16.9)	14 (12.1)	
III	252 (41.7)	41 (35.3)	
IV	250 (41.4)	61 (52.6)	
Physical exam at index admission			
SBP (mmHg)	129.6±30.7	133.6±29.5	0.206
DBP (mmHg)	83.0±21.0	81.7±18.8	0.531
HR (beats per min)	97.5±26.2	95.0±23.3	0.301
Physical exam at 1 year follow-up			
SBP (mmHg)	121.9±18.5	121.1±21.3	0.727
DBP(mmHg)	73.4±12.9	68.9±11.9	0.003
HR (beats per min)	77.5±14.9	81.3±16.7	0.055
Laboratory exam at index admission			

Hemoglobin (mg/dL)	13.4±2.3	12.4±2.2	<0.001
Sodium (mmol/L)	137.9±4.5	137.8±4.8	0.958
Potassium (mmol/L)	4.3±0.6	4.4±0.7	0.128
BUN (mg/dL)	22.4±13.6	27.7±16.1	0.001
Creatinine (mg/dL)	1.3±1.4	1.9±2.1	0.004
BNP (pg/mL)	1060.0 (533.0-1918.0)	1501.5 (668.0-3090.5)	0.084
NT-proBNP (pg/mL)	3982.0 (2201.5-8133.5)	7623.0 (3247.0-15893.0)	0.004
Troponin I (ng/mL)	0.05 (0.03-0.23)	0.08 (0.04-0.29)	0.136
Laboratory exam at 1 year follow-up			
Hemoglobin (mg/dL)	12.8±2.1	12.1±1.9	0.011
Sodium (mmol/L)	139.7±3.2	138.2±4.6	0.015
Potassium (mmol/L)	4.5±0.5	4.4±0.7	0.360
BUN (mg/dL)	22.0±12.8	26.9±16.1	0.018
Creatinine (mg/dL)	1.4±1.5	1.9±2.1	0.075
Echocardiography at index admission			
LAD (mm)	46.9±8.9	47.7±11.2	0.386
LVEDD (mm)	60.3±8.8	58.5±8.5	0.045
LVESD (mm)	51.0±9.5	48.0±9.2	0.002
E/e’	20.3±10.2	22.0±10.5	0.131
RVSP (mmHg)	42.6±13.6	42.4±14.0	0.896
LVEF (%)	26.8±7.5	29.9±7.2	<0.001
Echocardiography at 1 year follow-up			
LAD (mm)	41.3±8.1	43.5±9.3	0.017
LVEDD (mm)	51.1±6.5	51.7±7.8	0.408
LVESD (mm)	35.3±6.9	37.0±7.6	0.020
E/e’	13.2±0.8	15.2±0.7	0.013
RVSP (mmHg)	29.2±13.6	45.7±87.1	0.095
LVEF (%)	53.7±8.3	49.5±8.1	<0.001
Δ LVEF (%)	26.9±11.2	19.6±11.9	<0.001
Beta-blocker (%)			

at discharge	388 (64.2)	65 (56.0)	0.094
at 1 year follow-up	389 (68.1)	54 (52.9)	0.003
RAS-inhibitor (%)			
at discharge	481 (79.6)	83 (71.6)	0.053
at 1year follow-up	386 (67.6)	60 (58.8)	0.084
MRA (%)			
at discharge	307 (50.8)	61 (52.6)	0.729
at 1year follow-up	200 (35.0)	39 (38.2)	0.533

BMI, body mass index; BNP, B-type natriuretic peptide; BUN, blood urea nitrogen; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; HF, heart failure; HFiEF, heart failure with improved ejection fraction; HFmrEF, heart failure with midrange ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, heart rate; LAD, left atrial diameter; LVEDD, left ventricular end diastolic dimension; LVEF, left ventricular ejection fraction; LVESD, left ventricular end systolic diameter; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal proB-type natriuretic peptide; NYHA, New York Heart Association; RAS, renin-angiotensin system; RVSP, right ventricular systolic pressure; SBP, systolic blood pressure;

Effect of beta-blockers in patients with HFiEF

Because beta blockers appear to be effective in patients with HFiEF on long-term outcomes, we performed additional analyses.

The baseline characteristics according to beta-blocker use are summarized in **Table S6**. In brief, the patients who received beta-blockers were more likely to be men and have a higher incidence of de-novo HF but a lower incidence of valvular heart disease and atrial fibrillation, at the time of diagnosis of HFiEF. There was no difference in the blood pressure between the groups; however, the heart rate was lower in the patients who received beta-blockers. Regarding medical therapy, patients who received beta-blockers were administered renin-angiotensin system (RAS) inhibitors and mineralocorticoid antagonists (MRAs) more frequently also at the time of diagnosis of HFiEF.

Table S6. Baseline characteristics according to beta-blocker medication at the diagnosis of HFiEF

	Without Beta-blocker (n=230)	With Beta-blocker (n=443)	p-value
Demographic data			
Age (years)	59.6±16.8	59.6±15.1	0.985
Men (%)	122 (53.0)	279 (63.0)	0.013
Body mass index (kg/m^2)	22.8±3.7	24.3±4.3	<0.001
De novo heart failure (%)	132 (57.4%)	309 (69.8%)	0.001
Past Medical History (%)			
Hypertension	104 (45.2)	104 (45.2)	0.207
Diabetes mellitus	56 (24.3)	109 (24.6)	0.941
Ischemic Heart Disease	39 (17.0)	66 (14.9)	0.485
Valvular Heart Disease	34 (14.8)	36 (8.1)	0.007
COPD	19 (8.3)	35 (7.9)	0.870
Cerebrovascular disease	25 (10.9)	34 (7.7)	0.165
Atrial fibrillation	66 (28.7)	89 (20.1)	0.012
NYHA functional class (%)			0.755
II	40 (18.4)	71 (16.0)	
III	96 (41.7)	178 (40.2)	
IV	94 (40.9)	194 (43.8)	
Physical exam at discharge			
Systolic blood pressure (mmHg)	112.7±17.9	114.7±16.7	0.153
Diastolic blood pressure (mmHg)	67.8±11.4	69.4±11.8	0.085
Heart rate (beats per min)	78.8±14.4	77.0±13.0	0.115
Physical exam at HFiEF diagnosis			
Systolic blood pressure (mmHg)	120.4±18.4	122.5±19.1	0.204
Diastolic blood pressure (mmHg)	72.5±12.0	72.9±13.3	0.721
Heart rate (beats per min)	83.5±16.9	75.6±13.7	<0.001
Echocardiography at index admission			
Left atrial diameter (mm)	47.2±10.7	47.1±8.3	0.894
LVEDD (mm)	59.3±9.7	60.8±8.0	0.040
LVESD (mm)	49.7±10.4	51.4±8.7	0.043

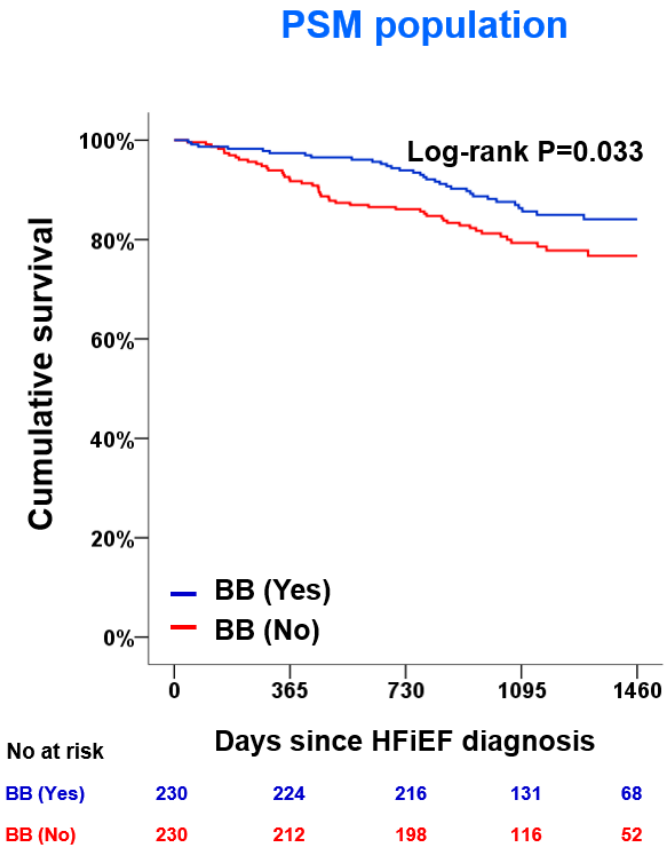
E/e’	21.2±11.8	20.3±9.1	0.388
LVEF (%)	28.2±7.5	26.7±7.5	0.015
Echocardiography at HFiEF diagnosis			
Left atrial diameter (mm)	41.6±9.7	41.8±7.7	0.774
LVEDD (mm)	49.6±7.0	52.1±6.4	<0.001
LVESD (mm)	33.7±7.3	36.7±6.7	<0.001
E/e’	13.7±7.8	13.3±6.4	0.527
LVEF (%)	54.7±8.9	52.1±8.0	<0.001
Δ LVEF (%)	26.5±13.4	25.4±10.9	0.272
Beta blocker (%)			
at discharge	59 (25.7)	364 (82.2)	<0.001
RAS-inhibitor (%)			
at discharge	155 (67.4)	375 (84.7)	<0.001
at HFiEF diagnosis	103 (44.8)	343 (77.4)	<0.001
MRA (%)			
at discharge	101 (43.9)	248 (56.0)	0.003
at HFiEF diagnosis	49 (21.3)	190 (42.9)	<0.001

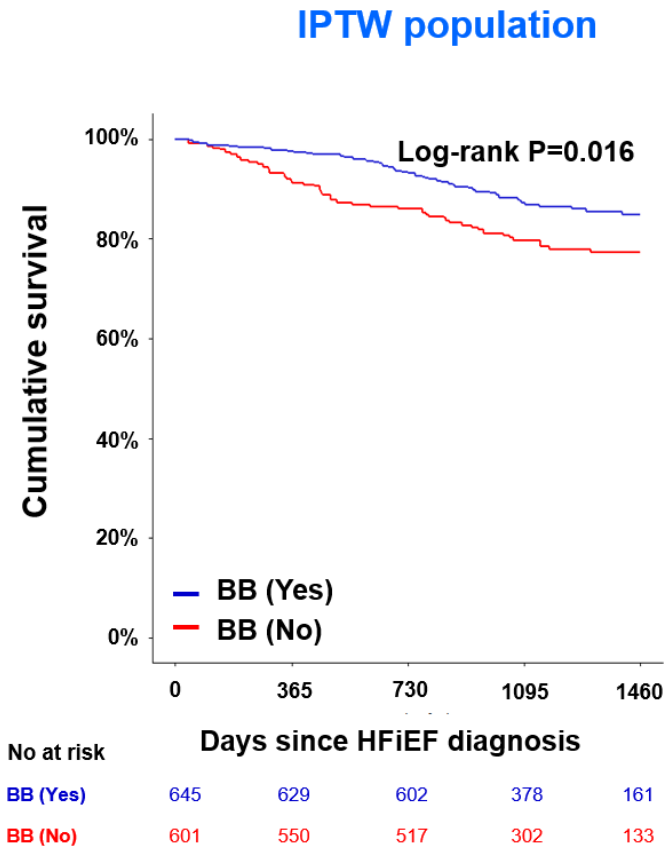
COPD, chronic obstructive pulmonary disease; HFiEF, heart failure with improved ejection fraction; LVEDD, left ventricular end diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end systolic diameter; MRA, Mineralocorticoid receptor antagonist; NYHA, New York Heart Association; RAS-inhibitor, renin-angiotensin system inhibitor

Propensity-score matching and inverse-probability treatment weighted analyses

In crude population, patients with beta-blockers had better 4-year all-cause mortality from HFiEF diagnosis. To minimize the bias by indication, we performed propensity-score matching (PSM) and inverse-probability treatment weighted (IPTW) analyses as sensitivity analyses. A total of 460 patients were 1:1-matched based on their propensity score. The baseline characteristics of the cohort after matching were well balanced, except for medication. In both analyses, beta-blocker use was associated with reduced 4-year all-cause mortality from HFiEF diagnosis (**Figure S2**).

Figure S2 Beta-blockers in HFiEF after adjustment





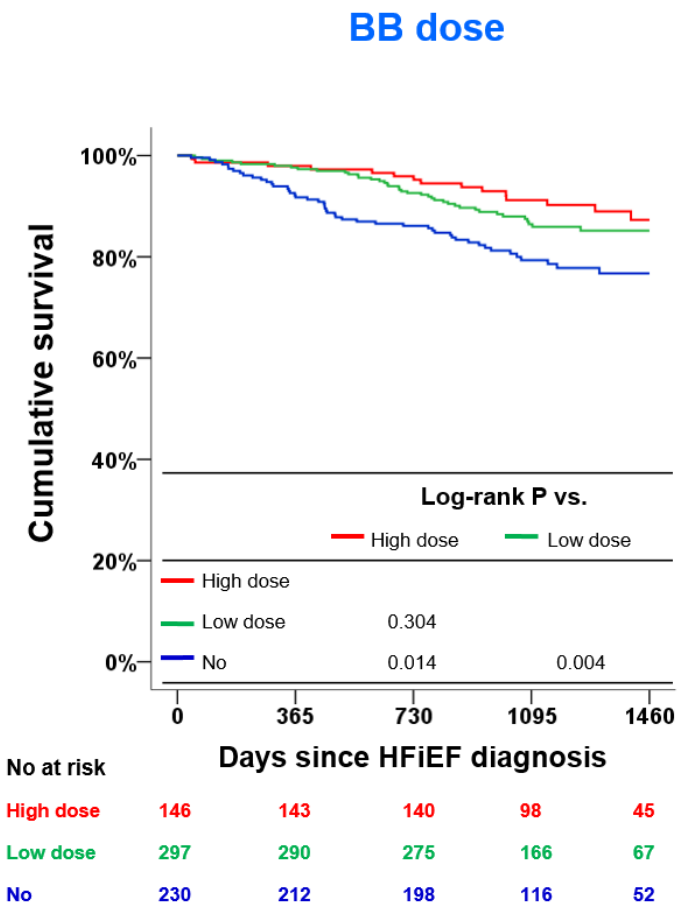
Following variables were included for: age, sex, body mass index, previous history of heart failure, hypertension, diabetes mellitus, ischemic heart disease, valvular heart disease, chronic obstructive pulmonary disease, cerebrovascular disease, atrial fibrillation, malignancy, and New York Heart Association functional class.

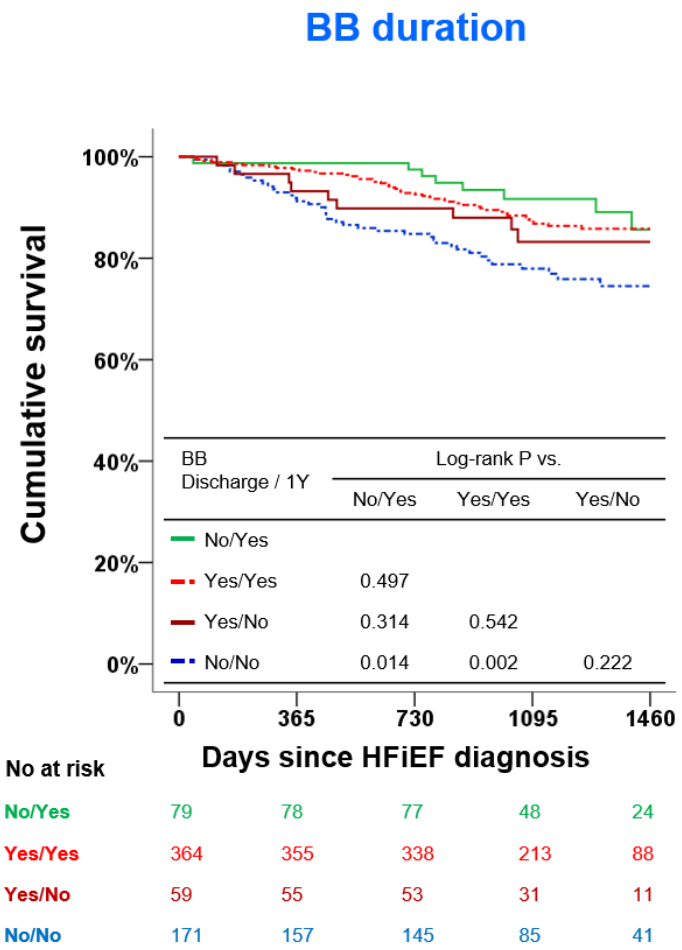
Clinical outcomes according to beta-blocker dose and administration duration

When the subjects were stratified according to the beta-blocker dose, patients who received either high- or low-dose beta-blockers at the time of diagnosis of HFiEF showed better 4-year mortality than those who did not (log-rank P=0.014 and log-rank P=0.004, respectively); however, there was no difference between the patients who received low- and high-dose beta-blockers (log-rank P=0.846) (**Figure S3**).

Because the status of beta-blocker prescription changed between discharge from the index hospitalization and the time of HFiEF diagnosis, we further categorized the patients into four groups according to beta-blocker use at discharge and at HFiEF diagnosis. In the Kaplan-Meier analysis, patients who were on beta-blockers at the time of HFiEF diagnosis had a similar prognosis, regardless of beta-blocker use or not at discharge from the index hospitalization (log-rank P=0.014).

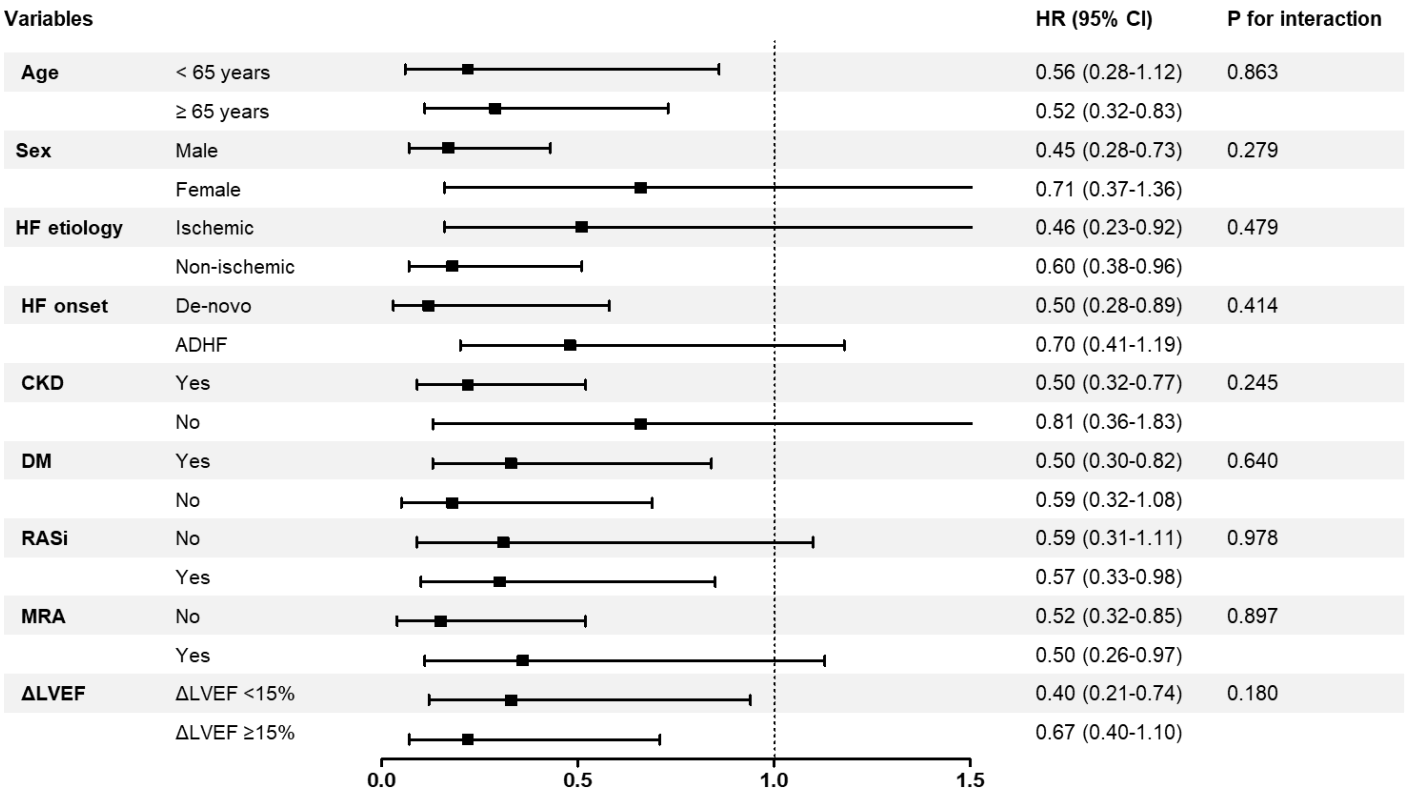
Figure S3 Beta-blockers in HFiEF according to dose and duration





Subgroup analysis

Figure S4 Association between the 4-year all-cause mortality and beta-blocker use in the subgroups of patients with HFiEF



In the exploratory subgroup analysis, the effect of beta-blockers was consistent across all subgroups.

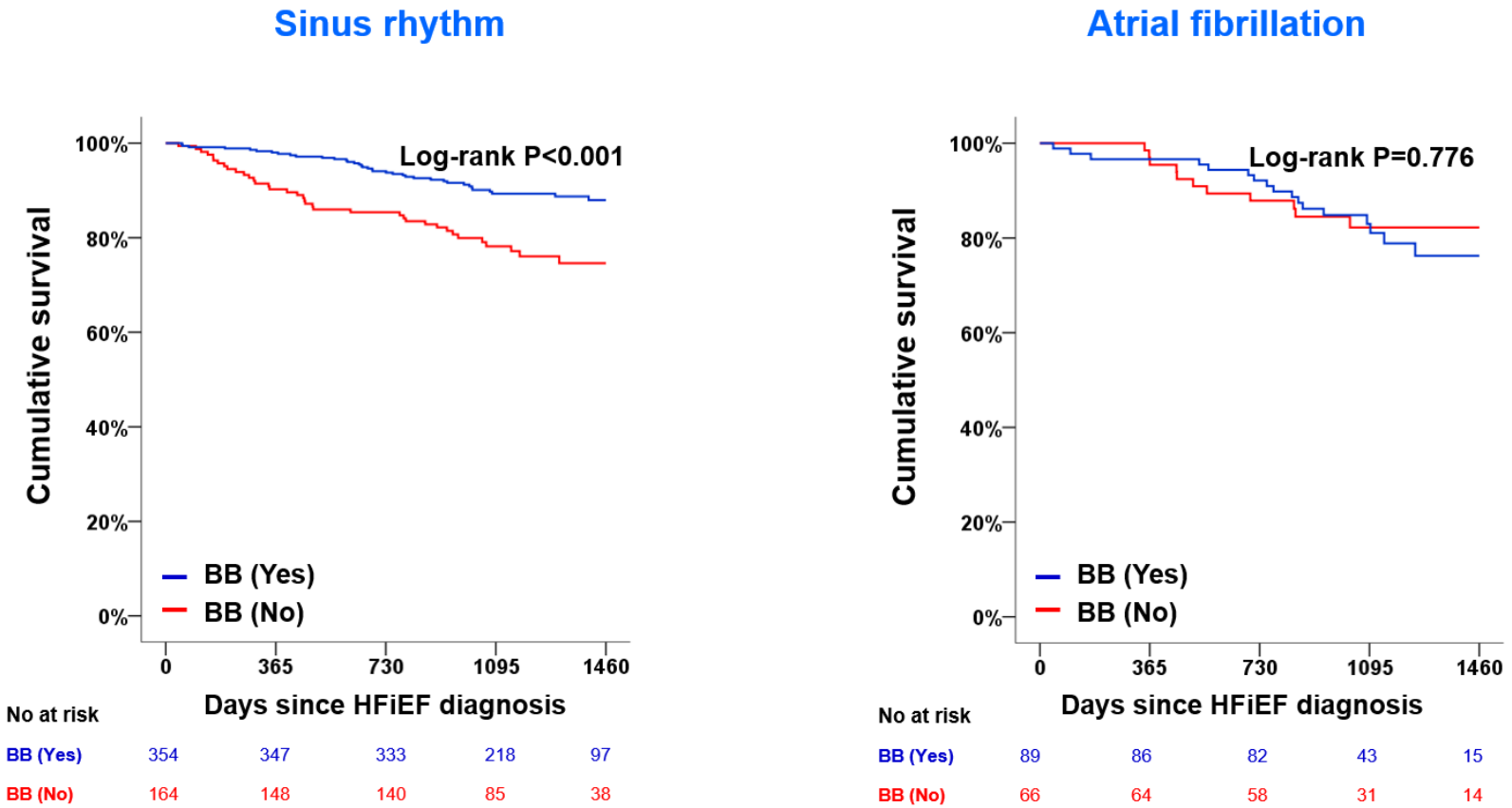
The squares with horizontal lines indicate the HRs and corresponding 95% CIs.

CI, confidence interval; CKD, chronic kidney disease; DM, diabetes mellitus; HF, heart failure; HFiEF, heart failure with improved ejection fraction; HR, hazard ratio; IHD, ischemic heart disease; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; RASi, renin-angiotensin system inhibitor

Clinical outcomes according to rhythm: sinus rhythm versus atrial fibrillation

We stratified the patients according to rhythm. In patients with sinus rhythm, patients with beta-blockers had better survival than those without beta-blockers. By contrast, in patients with atrial fibrillation there was no difference between those with and without beta-blockers (**Figure S5**).

Figure S5 Beta blockers in HFiEF according to rhythm

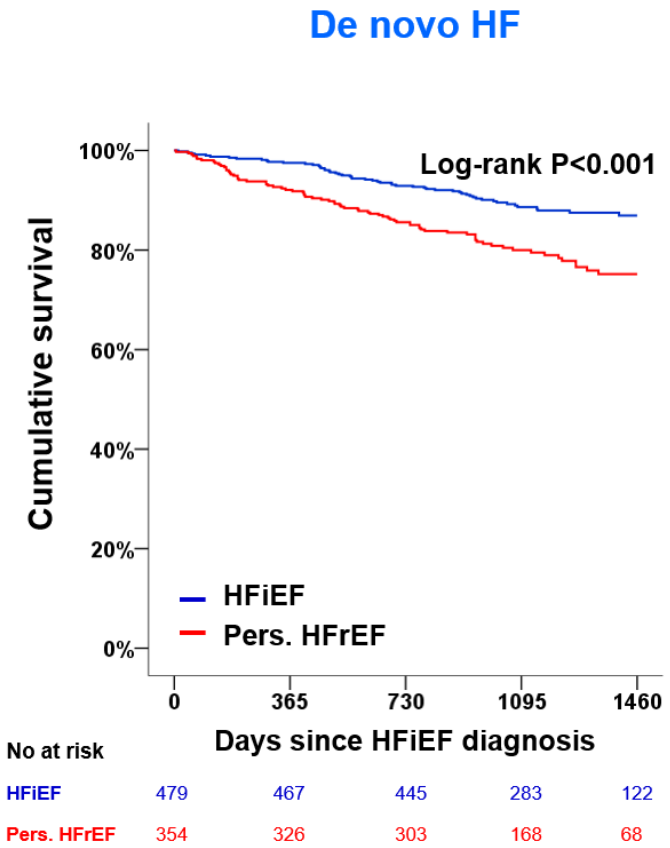


VI. Stratification according to onset of heart failure

Regarding the onset of heart failure, 55% and 45% of the patients had de-novo and acutely-decompensated heart failure (ADHF), respectively. Overall, patients with de-novo onset had better outcomes than those with ADHF. Patients with HFiEF had better survival than those with persistent HFrEF in both de-novo HF and ADHF (**Figure S6**).

Regarding drug efficacy, patients with beta-blocker had lower mortality than those without beta-blocker in de-novo HF. Similarly, patients with beta-blockers had better survival in ADHF with a marginal significance. The effect of RAS inhibitors and MRA appeared to be neutral in both de-novo and ADHF patients (**Figure S7 and Figure S8**).

Figure S6 Outcomes according to onset of HF



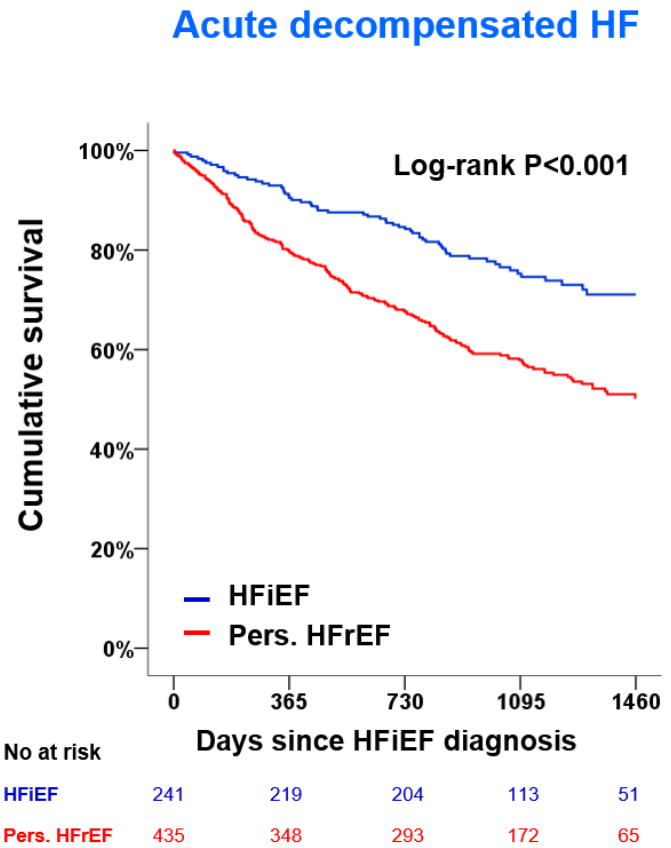


Figure S7 Drug efficacy in de-novo HFiEF

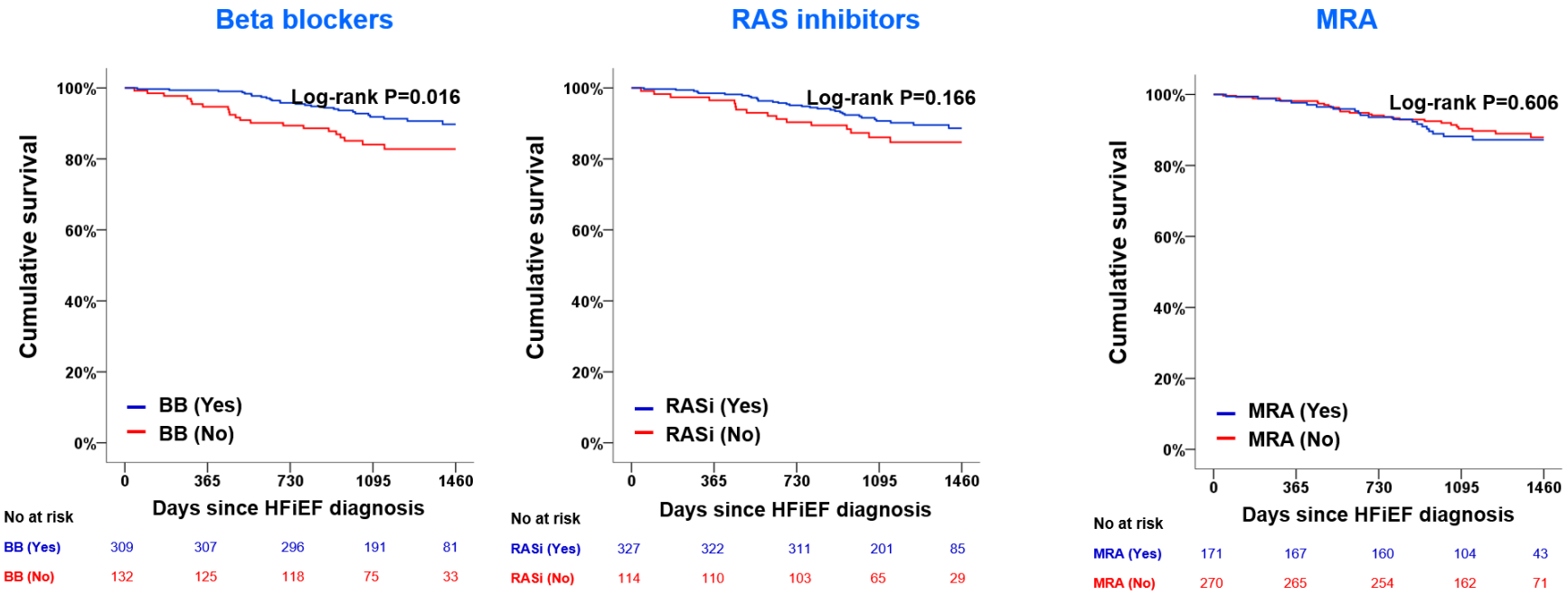


Figure S8 Drug efficacy in acutely-decompensated HFiEF

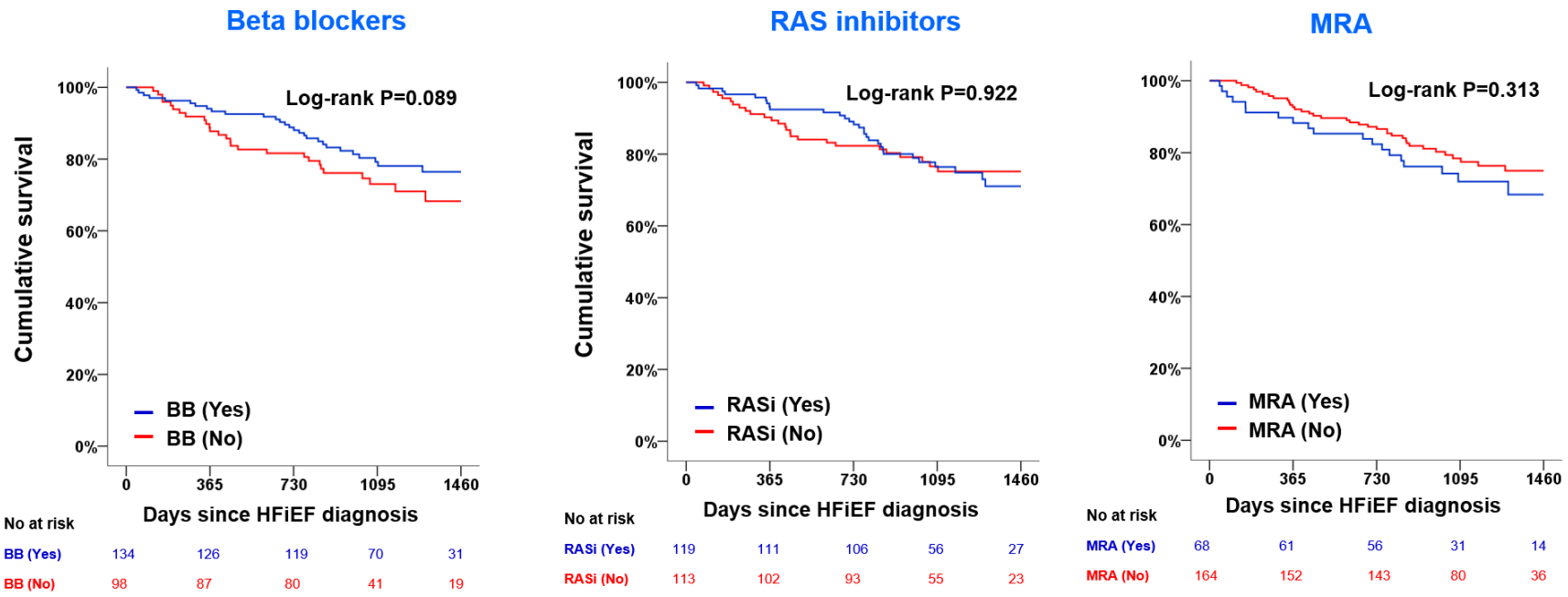
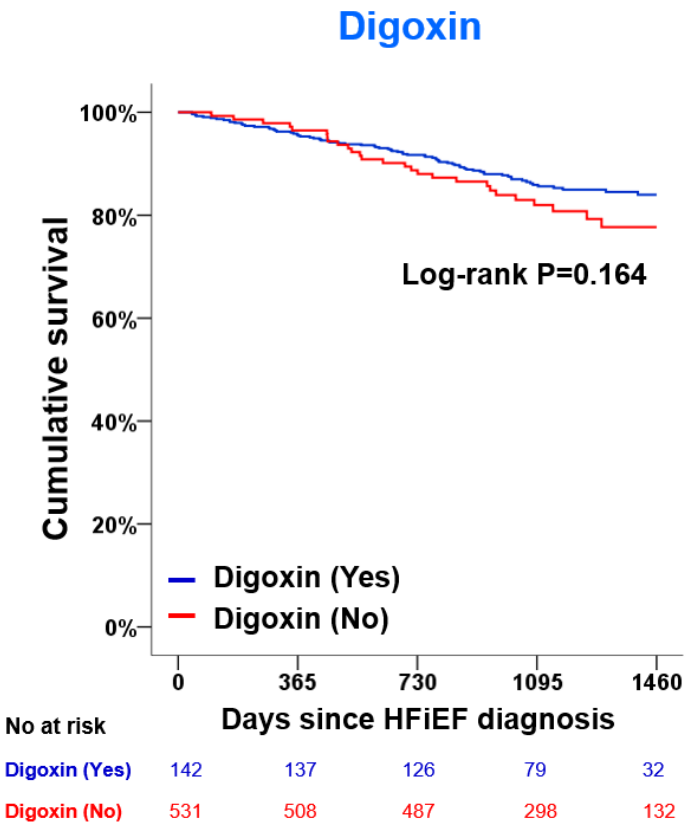
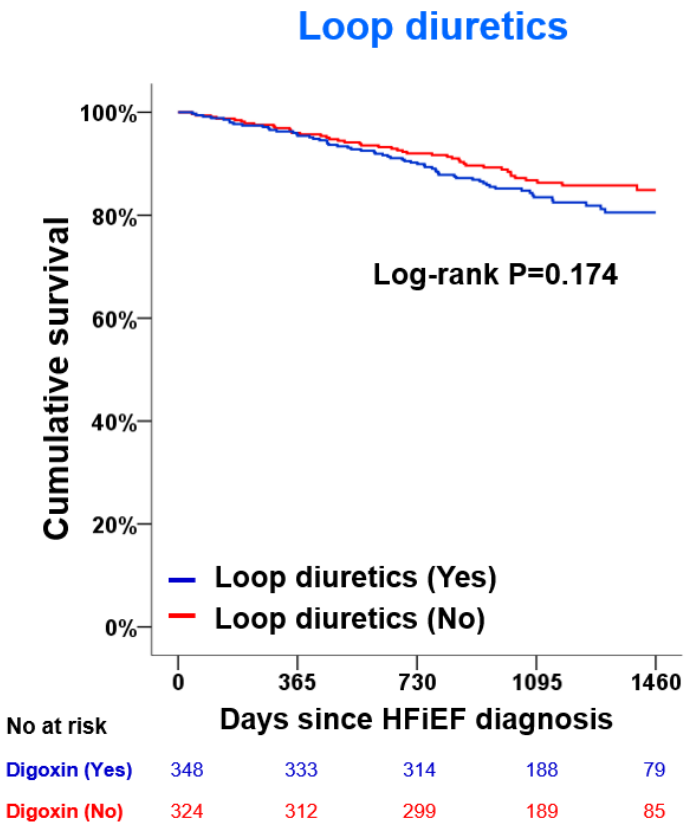


Figure S9 Impact of digoxin and loop diuretics on 4-year mortality in HFiEF patients





Patients with and without follow-up echocardiography

Table S7 Clinical characteristics of patients with HFrEF according to presence of 1 year follow up echocardiography

N=2,319	Without echocardiography (n=810)	With echocardiography (n=1,509)	p-value
Demographic data			
Age (years)	67.9±13.9	62.4±15.2	<0.001
Men (%)	477 (58.9)	937 (62.1)	0.131
Body mass index (kg/m^2)			
De novo heart failure (%)	430 (53.1)	833 (55.2)	0.329
Past Medical History			
Hypertension	473 (58.4)	757 (50.2)	<0.001
Diabetes mellitus	310 (38.3)	495 (32.8)	0.008
Ischemic Heart Disease	242 (29.9)	378 (25.1)	0.013
Valvular Heart Disease	56 (6.9)	131 (8.7)	0.136
COPD	85 (10.5)	127 (8.4)	0.098
Cerebrovascular disease	92 (11.4)	170 (11.3)	0.947
Atrial fibrillation	201 (24.8)	326 (21.6)	0.079
NYHA functional class (%)			0.050
II	109 (13.5)	240 (15.9)	
III	298 (36.8)	595 (39.4)	
IV	403 (49.8)	674 (44.7)	
Physical exam at discharge			
Systolic blood pressure (mmHg)	133.8±29.9	127.7±28.2	<0.001
Diastolic blood pressure (mmHg)	81.9±18.9	80.1±18.8	0.031
Heart rate (beats per min)	97.6±25.4	94.7±24.7	0.008
Echocardiography at index admission			
Left atrial diameter (mm)	48.1±8.4	47.7±9.0	0.310
Left ventricular end diastolic diameter (mm)	61.3±8.7	62.3±9.1	0.009
Left ventricular end systolic diameter (mm)	51.4±9.2	53.0±9.9	<0.001
E/e’	22.0±10.3	21.8±11.1	0.666

Left ventricular ejection fraction (%)	27.9±7.1	26.2±7.4	<0.001
Medication at discharge			
Beta-blocker	444 (54.8)	906 (60.0)	0.015
RAS-inhibitor	642 (79.3)	1186 (78.6)	0.709
MRA	413 (51.0)	840 (55.7)	0.031

COPD, chronic obstructive pulmonary disease; HFrEF, heart failure with reduced ejection fraction; MRA, Mineralocorticoid receptor antagonist; NYHA, New York Heart Association; RAS-inhibitor, renin-angiotensin-system inhibitor