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ORIGINAL RESEARCH ARTICLE

# Frequency, predictors, and prognosis of heart failure with improved left ventricular ejection fraction: a single-centre retrospective observational cohort study

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## Abstract

**Aims** An improved left ventricular ejection fraction (HFiEF) was observed across heart failure (HF) patients with a reduced or mid-range ejection fraction (HFrEF or HFmrEF, respectively). We postulated that HFiEF patients are clinically distinct from non-HFiEF patients.

**Methods and results** A total of 447 patients hospitalized due to a clinical diagnosis of HF (LVEF <50% at baseline) were enrolled from September 2017 to September 2019. Echocardiogram re-evaluation was conducted repeatedly over 6 months of follow-up after discharge. The primary endpoint included the composite of HF hospitalization and all-cause mortality. Subjects ($n$ = 184) with HFiEF (defined as an absolute LVEF improvement≥10%) were compared with 263 non-HFiEF (defined by <10% improvement in LVEF) subjects. Multivariable Cox regression was performed and identified younger age, smaller left ventricular end diastolic dimension (LVEDD), beta-blocker use, AF ablation and cardiac resynchronization therapy (CRT) as independent predictors of HFiEF. According to Kaplan–Meier analysis, HFiEF subjects had lower cardiac composite outcomes ($P$ = 0.002) and all-cause mortality ($P$ = 0.003) than non-HFiEF subjects. Multivariate Cox survival analysis revealed that non-HFiEF (compared with HFiEF) was an independent predictor of both the primary endpoints (HR = 0.679, 95% CI: 0.451–0.907, $P$ = 0.012), which was driven by all-cause mortality (HR = 0.504, 95% CI: 0.256–0.991, $P$ = 0.047).

**Conclusions** These data confirm that compared with non-HFiEF, HFiEF is a distinct HF phenotype with favourable clinical outcomes.

**Keywords** Predictors; Prognosis; Heart failure; Left ventricular ejection fraction

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## Introduction

Definitions for patients with heart failure (HF) vary, but LVEF is the most commonly used surrogate parameter of left ventricular (LV) systolic function in the current HF classification. Recent studies have reported that improvement in LVEF is systematically linked to lower HF-rehospitalization rates and mortality. However, data regarding the clinical characteristics, outcomes, and medical therapy for patients with HF with improved LVEF are scarce, especially among Asian patients. Moreover, no study to date has investigated HF patients with both reduced and mid-range ejection fraction (HFrEF and HFmrEF). Thus, the objective of this research is to establish independent predictors of LVEF improvement in a broader spectrum (LVEF <50%) of HF patients and to investigate the clinical outcomes of HFiEF (defined as an absolute LVEF improvement ≥10%) subjects compared with those of non-HFiEF patients in real-world clinical practice.

# Methods

## Data sources and cohort

The study was a single-centre retrospective observational cohort study of Asian adult patients admitted to Fuwai Yunnan Cardiovascular Hospital, China with a diagnosis of HF (ICD 10 code I50.x) between 1 September 2017 and 31 September 2019. Demographic data, echocardiograms and blood samples were obtained from all patients at the first hospitalization. All patients were encouraged to undergo echocardiography periodically to assess LV function. Patients who completed the 6 month re-examination echocardiograms were selected for this research. The first echocardiogram during the 6 month interval was defined as the re-examination echocardiogram to classify EF improvement. Absolute LVEF improvement ≥10% within 6 months was considered to be indicative of HFiEF. The exclusion criteria were as follows: (a) a lack of quantified clinical data; (b) no re-examination over 6 months; and (c) a history of congenital or valvular heart disease correction (*Figure 1*).

## Measurement of parameters and laboratory data

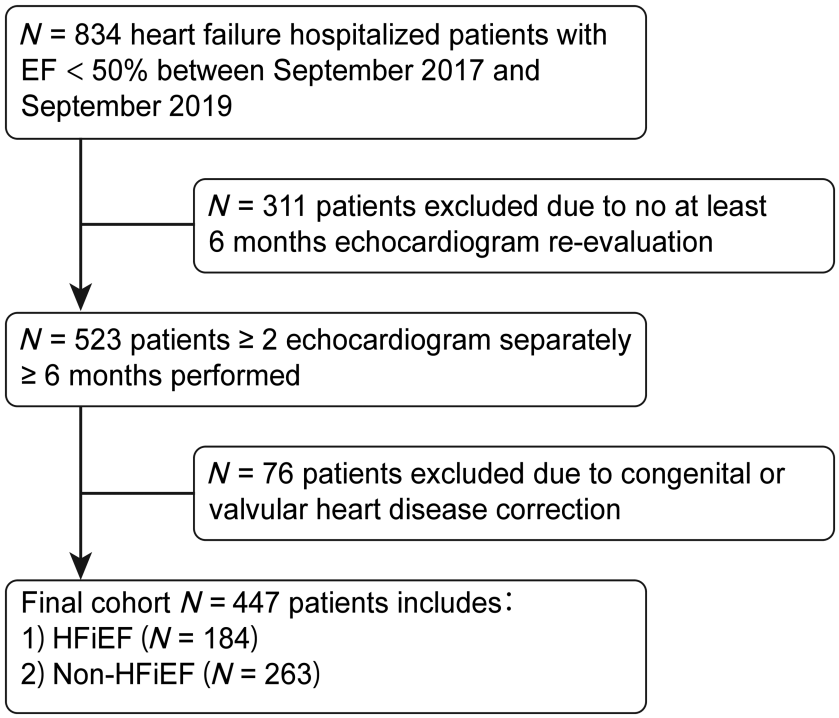
At the first hospitalization, clinical information collected from the patients consisted of demographic data, co-morbidities, physical exam and blood analysis results at baseline. In terms of medication, the use of beta-blockers, angiotensin converting enzyme inhibitor (ACEi), angiotensin receptor blockade (ARB) or aldosterone antagonists for HF treatment was defined as a prescription after discharge according to the recommendation of current guidelines.[1]

All patient echocardiographs were performed independently by two experienced technicians. Two-dimensional, targeted M-mode echocardiographs, and Doppler ultrasound measurements were obtained by using standard techniques in accordance with the American Society of Echocardiography and the European Association of Cardiovascular Imaging's guidelines.[2] LVEF assessment was based on two-dimensional echocardiography using the quantitative two-dimensional biplane volumetric Simpson method from 4- and 2-chamber views.

## Outcomes

For this study, the primary endpoint included composite outcomes of hospitalization for HF decompensation and all-cause mortality. The secondary endpoint was all-cause mortality. Time zero was set at the diagnosis of HFiEF or non-HFiEF according to the data from the second echocardiogram (≥6 months), and composite endpoints occurring after this time point were included in our analyses. The patients

**Figure 1** Derivation of the cohort. HF patients with first hospitalization with two echocardiograms separated over 6 months between September 2017 and September 2019 were identified. In total, 447 patients were used for this cohort after exclusion criteria were applied.



were followed up until May 2020. Status and dates of death were obtained from the patients' medical records. If these data were unavailable, patient status was ascertained by a telephone call to the physician at the referring hospital. We were able to follow up on all patients.

### Statistical analysis

Categorical variables are expressed as numbers and percentages. Parametric variables are presented as the mean ± SD, and non-parametric variables (e.g., NT-proBNP and hs-troponin I) are presented as the median and interquartile range. Statistical analyses were conducted using Student's *t* test, a $\chi^2$ test, or the log-rank test between HFiEF and non-HFiEF groups. All variables with statistically significant differences between the two groups, as shown in *Table 1*, were considered candidate variables. Multivariable Cox regression was applied to identify each possible independent predictor of HFiEF. A Cox proportional hazards regression model was used to determine the independent association of improvement in LVEF with a survival benefit. Cardiac composite outcomes and all-cause mortality in the HFiEF and non-HFiEF groups were compared using cumulative incidence curve Kaplan–Meier analysis and the log rank test. In addition, we used propensity score matching (PSM) to perform a sensitivity analysis. The PSM population was created using the nearest neighbour method without replacement in a 1:1 ratio. The variables included for matching were age, male sex, body mass index, history of hypertension, diabetes, hyperlipidaemia, ischaemic heart disease (IHD), cardiomyopathy, valvular heart disease, atrial fibrillation, stroke or transient ischaemic attack (TIA), NYHA class III or IV, medication history of β blocker, ACEi or ARB, and optimal medical therapy (OMT). After success matching, these variables were statistically comparable between the two groups. The *P* value considered for statistical significance was 0.05. Data were stored and analysed using SPSS software (IBM Corp, Armonk, NY, version 23.0).

## Results

### Baseline characteristics of the study population

A total of 447 patients (mean age 57.1 ± 13.7, 337 men) were included in the analysis. The clinical characteristics of the patients and their treatments at hospital discharge are presented in *Table 1*. Age, level of NT-proBNP, uric acid, and creatinine were lower in the HFiEF group than in the non-HFiEF group, whereas the rate of male sex and level of albumin were higher. In addition, the prevalence of IHD, diabetes mellitus, hyperlipidaemia, NYHA Class III or IV, antiplatelet agent use, hypolipidaemic drug use, ICD implantation and PCI or CABG was lower in the HFiEF group than in the non-HFiEF group. The rate of ACEi or ARB and beta-blocker use and the rate of AF ablation or CRT implantation were higher in the HFiEF group than in the non-HFiEF group. In contrast, other parameters, including blood pressure, heart rate, haemoglobin, hs-troponin I, sodium, and potassium, time between two echocardiographs, and cases of *de novo* HF and HFrEF or HFmrEF, among others, did not differ significantly between the two groups. The aetiology for HF is presented in *Figure 2*.

### Predictors of heart failure patients with improved ejection fraction

According to the echocardiography re-evaluation over 6 months, 184 patients were identified as HFiEF, while 263 patients were classified into the non-HFiEF group. Univariate analysis indicated younger age, IHD, smaller baseline LVEDD, more severe NYHA class, use of hypolipidaemic drugs, ACEi or ARB and beta-blocker, AF ablation and CRT implantation were potential predictors of HFiEF; however, in multivariable Cox regression analysis, younger age, smaller baseline LVEDD, beta-blocker use, AF ablation and CRT implantation were independent predictors for HFiEF (*Table 2*).

### Predictors of the outcomes

During a median follow-up of 11 months (range 6–16 months), 200 events occurred, including 149 composite outcomes (HFiEF *n* = 46 vs. non-HFiEF *n* = 103) and 51 deaths (HFiEF *n* = 11 vs. non-HFiEF *n* = 40). In Kaplan–Meier analysis, HFiEF was associated with lower cardiac composite outcomes (*P* = 0.002) and all-cause mortality (*P* = 0.003) than non-HFiEF (*Figure 3*). In multivariable Cox proportional hazard analyses, HFiEF (vs. non-HFiEF) was an independent predictor of both cardiac composite outcomes HR = 0.679, 95% CI: 0.451–0.907, *P* = 0.012 and all-cause mortality HR = 0.504, 95% CI: 0.256–0.991, *P* = 0.047 (*Tables 3* and *4*).

### Sensitivity analysis

A 1:1 PSM was used in sensitivity analyses. After PSM, a cohort of 276 patients was identified, which included 138 patients in the HFiEF group and 138 patients in the non-HFiEF group. The rates of composite outcomes and all-cause mortality in the HFiEF group were 29.7% and 7.9%, respectively, which were lower than those in the non-HFiEF group (52.5%, log-rank *P* = 0.001, and 18.8%, log rank *P* = 0.016) (*Figure 4*).

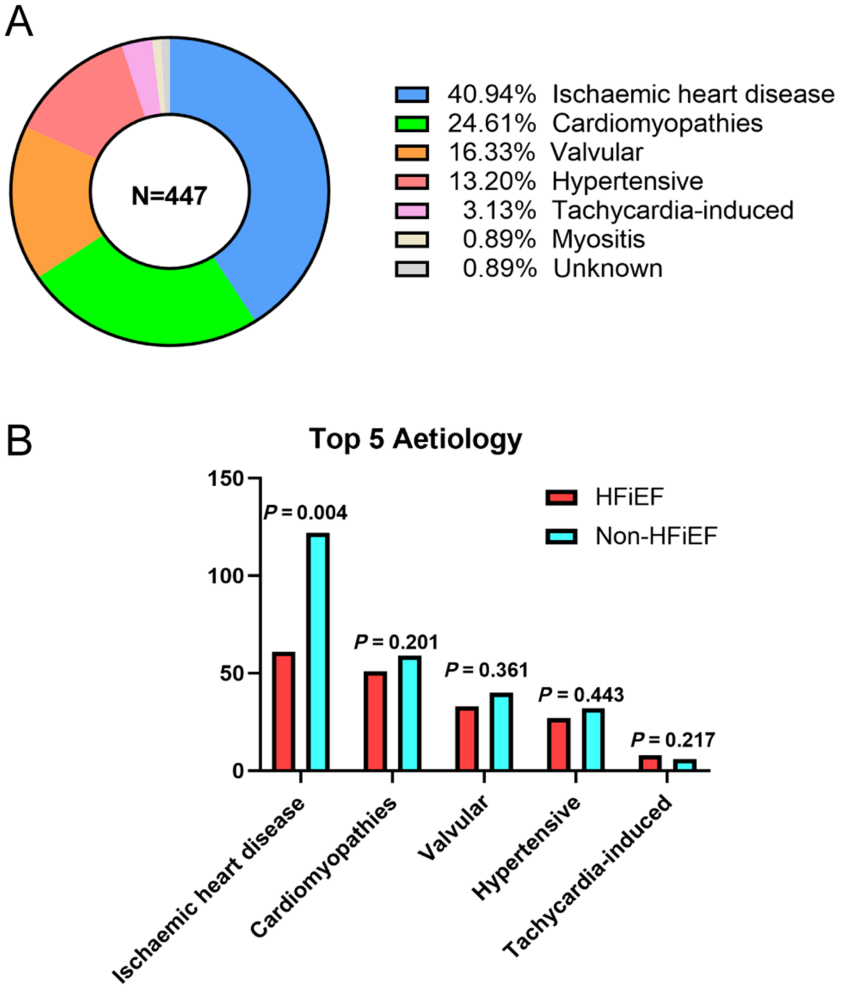
A bias analysis of LVEF measurement using the Bland and Altman method was performed. Inter-observer agreement and intra-observer agreement were assessed among 30

**Table 1** Baseline demographics and clinical characteristics of patients with HFiEF and non-HFiEF

| | Overall $N = 447$ | HFiEF $N = 184$ | Non-HFiEF $N = 263$ | *P*-value |
|---|---|---|---|---|
| Demographic data | | | | |
| Age (years) | 57.1 ± 13.7 | 54.1 ± 15.2 | 59.2 ± 12.1 | 0.001 |
| Male (%) | 337 (75.3) | 128 (69.5) | 209 (79.4) | 0.011 |
| BMI (kg/m$^2$) | 24.0 | 23.9 ± 3.5 | 24.1 ± 3.3 | 0.619 |
| Past medical history | | | | |
| *De novo* HF (%) | 192 (42.9) | 82 (44.5) | 110 (41.8) | 0.564 |
| HFrEF (%) | 194 (43.4) | 71 (38.5) | 123 (46.7) | |
| HFmrEF (%) | 253 (56.5) | 113 (61.5) | 140 (53.2) | 0.085 |
| Atrial fibrillation (%) | 106 (23.7) | 53 (28.8) | 53 (20.2) | 0.055 |
| Ischaemic heart disease (%) | 183 (40.9) | 61 (33.2) | 122 (46.4) | 0.004 |
| Diabetes mellitus (%) | 106 (23.7) | 35 (19.0) | 71 (27.0) | 0.043 |
| Hypertension (%) | 202 (45.1) | 82 (44.6) | 120 (45.6) | 0.773 |
| Hyperlipidaemia (%) | 171 (38.2) | 55 (29.9) | 116 (44.1) | 0.012 |
| Prior stroke or TIA (%) | 30 (6.7) | 10 (5.4) | 20 (7.6) | 0.444 |
| Physical exam | | | | |
| SBP (mmHg) | 119.3 ± 17.9 | 120.3 ± 17.9 | 118.7 ± 17.9 | 0.353 |
| DBP (mmHg) | 77.3 ± 14.0 | 76.7 ± 16.6 | 77.8 ± 12.7 | 0.490 |
| HR (b.p.m.) | 80.3 ± 16.6 | 80.3 ± 13.6 | 80.3 ± 18.5 | 0.943 |
| NYHA Class III or IV (%) | 245 (53.8) | 77 (41.8) | 168 (63.8) | <0.001 |
| Laboratory exam | | | | |
| Haemoglobin (g/L) | 129.3 ± 21.2 | 129.1 ± 25.6 | 129.4 ± 17.4 | 0.897 |
| Uric acid (μmol/L) | 417.7 ± 150.3 | 391.3 ± 15.1 | 436.2 ± 14.7 | 0.002 |
| Creatinine (μmol/L) | 97.6 ± 30.4 | 91.8 ± 28.2 | 101.71 ± 31.2 | 0.004 |
| eGFR (mL/min/1.73 m$^2$) | 71.2 ± 25.6 | 75.8 ± 25.7 | 67.9 ± 25.0 | 0.001 |
| Sodium (mmol/L) | 136.3 ± 3.1 | 136.1 ± 5.2 | 136.5 ± 3.1 | 0.175 |
| Potassium (mmol/L) | 4.1 ± 0.3 | 4.1 ± 0.4 | 4.1 ± 0.3 | 0.392 |
| Hs-troponin I (ng/mL) | 0.04 (0.01, 0.25) | 0.05 (0.01, 0.41) | 0.05 (0.01, 0.46) | 0.137 |
| NT-proBNP (pg/mL) | 1226.0 (557.9, 2451.2) | 993.2 (459.0, 1815.2) | 1455.0 (708.1, 2776.0) | 0.006 |
| LDL-C (mmol/L) | 2.4 ± 0.7 | 2.4 ± 0.7 | 2.4 ± 0.8 | 0.857 |
| Albumin (g/L) | 38.0 ± 3.6 | 38.4 ± 3.9 | 37.7 ± 3.2 | 0.045 |
| Baseline echo | | | | |
| LAD (mm) | 41.5 ± 8.5 | 39.9 ± 9.3 | 42.6 ± 7.8 | 0.001 |
| LVEDD (mm) | 58.7 ± 10.6 | 55.3 ± 10.6 | 61.2 ± 9.9 | <0.001 |
| LVEF (%) | 39.0 ± 8.8 | 39.8 ± 8.5 | 38.5 ± 9.1 | 0.147 |
| Second echo | | | | |
| LAD (mm) | 40.5 ± 8.4 | 37.5 ± 7.5 | 42.6 ± 8.4 | <0.001 |
| LVEDD (mm) | 56.8 ± 10.8 | 50.3 ± 8.1 | 61.3 ± 10.1 | <0.001 |
| LVEF (%) | 46.7 ± 13.5 | 57.8 ± 8.5 | 39.0 ± 10.6 | <0.001 |
| Time between two echocardiograms (days) | 251 (208,353) | 244 (206,329) | 259 (209,365) | 0.083 |
| Medications at discharge | | | | |
| Beta-blockers (%) | 118 (26.4) | 70 (38.0) | 48 (18.3) | <0.001 |
| ACEi or ARB (%) | 178 (39.8) | 98 (53.3) | 80 (30.4) | <0.001 |
| Aldosterone antagonists (%) | 347 (77.6) | 136 (73.9) | 211 (80.2) | 0.069 |
| CCB (%) | 51 (11.4) | 26 (14.1) | 25 (9.5) | 0.134 |
| Digitalis (%) | 104 (23.3) | 36 (19.6) | 68 (25.9) | 0.113 |
| Diuretics (%) | 277 (62.0) | 116 (63.0) | 161 (61.2) | 0.767 |
| Antiplatelet agents (%) | 259 (57.9) | 92 (50.0) | 167 (63.5) | 0.003 |
| Hypolipidaemic drugs (%) | 238 (53.2) | 83 (45.1) | 155 (58.9) | 0.003 |
| Anticoagulants (%) | 139 (31.1) | 58 (31.5) | 81 (30.8) | 0.521 |
| Nitrates (%) | 56 (12.5) | 28 (15.2) | 28 (10.6) | 0.111 |
| Amiodarone (%) | 39 (8.7) | 19 (10.3) | 20 (7.6) | 0.395 |
| OMT (%) | 103 (23.0) | 46 (25.0) | 57 (21.6) | 0.411 |
| Treatment | | | | |
| ICD (%) | 48 (10.7) | 12 (6.5) | 36 (13.7) | 0.014 |
| CRT (%) | 44 (9.8) | 28 (15.2) | 16 (6.1) | 0.002 |
| PCI or CABG (%) | 55 (12.3) | 16 (8.7) | 39 (14.8) | 0.057 |
| AF ablation (%) | 26 (5.8) | 17 (9.4) | 9 (3.4) | 0.013 |

ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass grafting; CCB, calcium channel blocker; CRT, cardiac resynchronization therapy; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HR, heart rate; ICD, implantable cardioverter defibrillator; LAD, left atrial diameter; LDL-D, low-density lipoprotein; LVEDD, left ventricular end diastolic dimension; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; OMT, optimal medical therapy; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; TIA, transient ischaemic attack.

**Figure 2** Top five aetiologic causes according to the HF phenotypes.




randomly selected patients and were evaluated using Bland–Altman plots with the mean difference and 95% limit of agreement (Supporting Information, *Figure S1*). No significant difference was found (intra-observer: −3.065 to 2.931, $P = 0.813$; inter-observer: −3.432 to 2.366, $P = 0.579$, respectively). Six (1.3%) patients were treated using targeted M-mode due to poor quality, and follow-up measurements for each individual were made using the same technique as their original study.

## Discussion

This is the first study to focus on absolute LVEF improvement and to examine mortality and hospitalization for HF decompensation patients with both reduced and mid-range EF (HFrEF or HFmrEF) in an Asian population, which has not been documented previously to our knowledge. The study populations in previous related studies predominantly included non-Asian subjects, and although HF patients with a mid-range EF experience absolute LVEF improvement, these subgroups have usually been excluded. Our main findings are that younger age, smaller LVEDD, beta-blocker use, AF ablation and CRT implantation are independent predictors of HFiEF. Furthermore, subjects with HFiEF had significantly lower all-cause mortality and fewer hospitalizations for HF decompensation than those with non-HFiEF.

### Definitions and frequency of heart failure patients with improved ejection fraction

The true frequency of patients with improved or recovered LVEF has not been established, partly because a consensus definition has not been reached (Supporting Information, *Table S1*). A commonly used definition of HFiEF is based on an absolute improvement in LVEF.[3–5] In the IMPROVE HF


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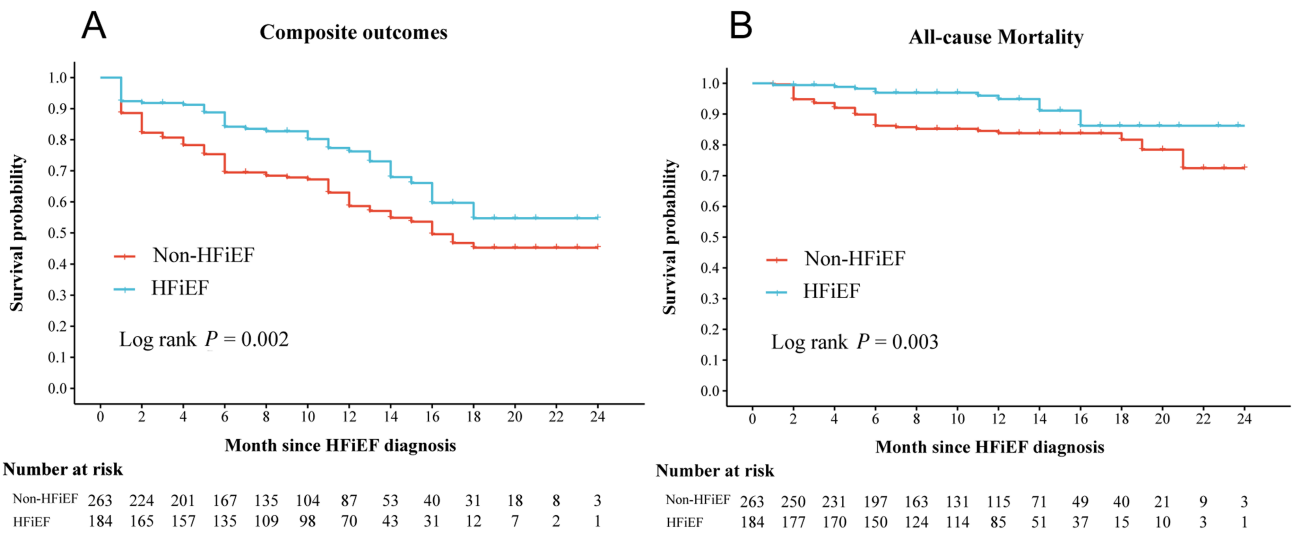
**Table 2** Cox analysis of identifying predictors of HFiEF

| | HR | 95% CI | *a* value | aHR | 95% CI | *P* value |
|---|---|---|---|---|---|---|
| Age (years) | 0.737 | 0.576–0.943 | 0.015 | 0.664 | 0.512–0.816 | 0.002 |
| Male | 1.123 | 0.830–1.519 | 0.453 | | | |
| Ischaemic heart disease | 1.389 | 1.087–1.776 | 0.009 | | | |
| Diabetes mellitus | 0.945 | 0.718–1.244 | 0.687 | | | |
| Hyperlipidaemia | 1.084 | 0.848–1.385 | 0.217 | | | |
| NYHA Class III or IV | 1.362 | 1.062–1.748 | 0.015 | | | |
| eGFR (mL/min/1.73 $m^2$) | 0.995 | 0.990–1.000 | 0.060 | | | |
| Albumin (pg/mL) | 0.994 | 0.974–1.016 | 0.606 | | | |
| NT-proBNP (pg/mL) | 1.088 | 0.852–1.390 | 0.498 | | | |
| Baseline LAD (mm) | 1.006 | 0.993–1.019 | 0.399 | | | |
| Baseline LVEDD (mm) | 1.019 | 1.007–1.031 | 0.002 | 1.013 | 1.001–1.028 | 0.037 |
| ACEi or ARB | 0.625 | 0.479–0.814 | 0.001 | | | |
| Beta-blocker | 0.543 | 0.396–0.744 | 0.001 | 0.585 | 0.425–0.805 | 0.001 |
| Antiplatelet agents | 1.160 | 0.901–1.494 | 0.251 | | | |
| Hypolipidaemic drugs | 1.319 | 1.030–1.689 | 0.028 | | | |
| ICD | 1.093 | 0.763–1.564 | 0.629 | | | |
| CRT | 0.434 | 0.261–0.722 | 0.001 | 0.575 | 0.343–0.964 | 0.036 |
| AF ablation | 0.416 | 0.205–0.844 | 0.015 | 0.336 | 0.163–0.696 | 0.003 |
| PCI or CABG | 1.386 | 0.985–1.949 | 0.061 | | | |

aHR have been adjusted for age, previous history of ischaemic heart disease, New York Heart Association class, baseline LAD, LVEDD, ACEi or ARB, beta-blocker, hypolipidaemic drugs at discharge and CRT, AF ablation.
ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; aHR, adjusted hazard ratio; ARB, angiotensin receptor blocker; CABG, coronary artery bypass grafting; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; HR, hazard ratio; ICD, implantable cardioverter defibrillator; LAD, left atrial diameter; LVEDD, left ventricular end diastolic dimension; NYHA, New York Heart Association; PCI, percutaneous coronary intervention.

**Figure 3** Kaplan–Meier curves showing the composite outcomes of hospitalization for HF decompensation and all-cause death (A) and all-cause death (B).




population,[3] a baseline echocardiographic LVEF ≤35% and an absolute improvement in the LVEF of at least 10% were defined as HFiEF. In the study by Florea *et al*,[5] 3519 patients with a baseline LVEF <35% and 321 (9.1%) patients with an LVEF >40% after 12 months were defined as the HFiEF subgroup. In an echocardiogram-based registry, an EF ≤40% at baseline with an absolute EF improvement ≥10% was regarded as HFiEF, and 37.6% of patients had HFiEF. Other investigators have defined HFiEF as improvement of a reduced LVEF to a normal LVEF (usually >50%) rather than an absolute improvement in LVEF. Abe *et al*.[6] reported that 44% of these patients recovered to EF >50% at the 2nd examination. Basuray *et al*.[7] found that 176 (9.6%) HF patients with a baseline LVEF <50% improved to an LVEF ≥50%. In the A-HeFT trial,[8] HFiEF patients were defined as those with an LVEF <35% at baseline and an LVEF >40% at the 6 month

**Table 3** Hazard ratios (95% CI) for baseline and HFiEF in relation to the composite endpoint

| | HR | 95% CI | *P* value | aHR | 95% CI | *P* value |
|---|---|---|---|---|---|---|
| Age ≥65 (years) | 1.399 | 1.015–1.930 | 0.041 | 0.664 | 0.512–0.816 | 0.002 |
| Male | 1.144 | 0.780–1.678 | 0.490 | | | |
| Ischaemic heart disease | 1.201 | 0.867–1.662 | 0.271 | | | |
| Diabetes mellitus | 1.200 | 0.830–1.736 | 0.332 | | | |
| Hyperlipidaemia | 0.996 | 0.713–1.391 | 0.980 | | | |
| NYHA Class III or IV | 1.669 | 1.194–2.333 | 0.003 | | | |
| eGFR (mL/min/1.73 $m^2$) | 0.991 | 0.984–0.997 | 0.007 | | | |
| Albumin (pg/mL) | 0.982 | 0.681–1.415 | 0.922 | | | |
| NT-proBNP (pg/mL) | 2.085 | 1.403–2.931 | 0.001 | 1.966 | 1.393–2.763 | 0.001 |
| Baseline LAD (mm) | 1.015 | 0.997–1.034 | 0.105 | | | |
| Baseline LVEDD (mm) | 1.019 | 1.004–1.034 | 0.012 | | | |
| ACEi or ARB | 0.979 | 0.963–0.996 | 0.013 | | | |
| Beta-blocker | 0.968 | 0.942–0.994 | 0.018 | 0.973 | 0.947–0.999 | 0.041 |
| Antiplatelet agents | 1.295 | 0.928–1.806 | 0.128 | | | |
| Hypolipidaemic drugs | 1.214 | 0.878–1.680 | 0.242 | | | |
| ICD | 1.706 | 1.710–2.622 | 0.015 | | | |
| CRT | 1.308 | 0.799–2.141 | 0.286 | | | |
| AF ablation | 1.284 | 0.654–2.524 | 0.468 | | | |
| PCI or CABG | 1.104 | 0.674–1.807 | 0.694 | | | |
| HFiEF | 0.592 | 0.418–0.839 | 0.003 | 0.679 | 0.451–0.907 | 0.012 |

aHR have been adjusted for age, NYHA Class III or IV, eGFR, baseline level of NT-proBNP, LVEDD, ACEi or ARB use, beta-blocker use, ICD implantation and HFiEF.
ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; aHR, adjusted hazard ratio; ARB, angiotensin receptor blocker; CABG, coronary artery bypass grafting; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; HR, hazard ratio; ICD, implantable cardioverter defibrillator; LAD, left atrial diameter; LVEDD, left ventricular end diastolic dimension; NYHA, New York Heart Association; PCI, percutaneous coronary intervention.

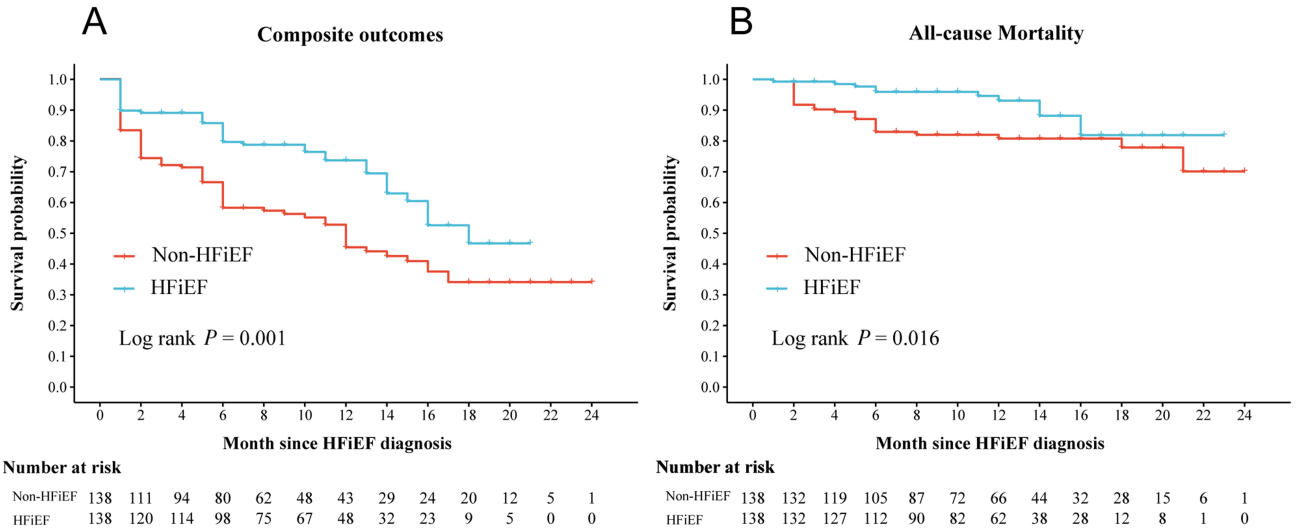
**Table 4** Hazard ratios (95% CI) for baseline and HFiEF in relation to all-cause death

| | HR | 95% CI | *P* value | aHR | 95% CI | *P* value |
|---|---|---|---|---|---|---|
| Age ≥65 (years) | 1.025 | 0.590–1.781 | 0.929 | | | |
| Male | 1.483 | 0.722–3.049 | 0.283 | | | |
| Ischaemic heart disease | 0.932 | 0.582–1.627 | 0.810 | | | |
| Diabetes mellitus | 1.910 | 1.075–3.395 | 0.027 | | | |
| Hyperlipidaemia | 1.258 | 0.720–2.199 | 0.420 | | | |
| NYHA Class III or IV | 2.419 | 1.321–4.428 | 0.004 | | | |
| eGFR (mL/min/1.73 $m^2$) | 1.000 | 1.989–1.001 | 0.062 | | | |
| Albumin (pg/mL) | 1.006 | 0.961–1.052 | 0.807 | | | |
| NT-proBNP (pg/mL) | 3.220 | 1.685–6.150 | 0.001 | 2.633 | 1.362–5.091 | 0.004 |
| Baseline LAD (mm) | 1.049 | 1.023–1.076 | 0.001 | | | |
| Baseline LVEDD (mm) | 1.050 | 1.024–1.076 | 0.001 | 1.037 | 1.011–1.064 | 0.005 |
| ACEi or ARB | 0.863 | 0.432–1.649 | 0.656 | | | |
| Beta-blocker | 0.514 | 0.269–0.983 | 0.044 | | | |
| Antiplatelet agents | 1.008 | 0.812–1.251 | 0.945 | | | |
| Hypolipidaemic drugs | 1.067 | 0.875–1.301 | 0.524 | | | |
| ICD | 0.849 | 0.385–1.232 | 0.389 | | | |
| CRTP or CRTD | 0.654 | 0.778–3.527 | 0.191 | | | |
| AF ablation | 0.903 | 0.640–1.272 | 0.559 | | | |
| PCI or CABG | 1.161 | 0.860–1.569 | 0.329 | | | |
| HFiEF | 0.381 | 0.195–0.743 | 0.005 | 0.504 | 0.256–0.991 | 0.047 |

aHR have been adjusted for diabetes mellitus, NYHA Class III or IV, baseline level of NT-proBNP, baseline LAD, LVEDD, beta-blocker use and HFiEF.
ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; aHR, adjusted hazard ratio; ARB, angiotensin receptor blocker; CABG, coronary artery bypass grafting; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; HR, hazard ratio; ICD, implantable cardioverter defibrillator; LAD, left atrial diameter; LVEDD, left ventricular end diastolic dimension; NYHA, New York Heart Association; PCI, percutaneous coronary intervention.

echocardiographic re-evaluation. In the prospective cohort KorAHF study,[9] HFiEF was defined as an LVEF ≤40% at baseline, with improvement up to 40% after 1 year of follow-up, and 720 (31.3%) subjects were regarded as having HFiEF. A comprehensive review of the literature by Gulati and Udelson[10] documented rates of improved LVEF (to LVEF >50%) ranging from 9% to 72% considering that the frequency of HFiEF is variable because of the heterogeneity of

**Figure 4** Association between the composite outcomes (A) and all-cause death (B) with HFiEF in PSM population.




study populations with regard to differing definitions, HF origins and underlying medical therapy. In our patient population, 184 (41.4%) subjects with a baseline LVEF <50% showed improvement in their LVEF by 10% according to the recent ACC Scientific Expert Panel.[11] HFmrEF accounts for 38% (71/184) of HFiEF cases. If we changed the definition with a baseline LVEF <50% improved to an LVEF ≥50%, there were 231 (51.6%) HF patients with HFiEF or HFrecEF. Regardless of the definition of HFiEF, the clinical outcomes of HFiEF patients were improved compared with those of patients with non-HFiEF with respect to the primary endpoint (Supporting Information, *Figure S2*). We prefer the 'improved' LVEF to the 'recovered' LVEF to define the subgroup because the underlying structural cardiomyopathic process does not completely recover with LVEF improvement.

## Factors that predict heart failure with improved ejection fraction

Although HFiEF definitions vary, several clinical characteristics are consistently considered to be candidate predictors of improved LVEF. Compared with previous studies, subjects with HFiEF tend to be younger,[6,9] female,[9,12] have a better NYHA class,[6,9,12] have AF[6,8,12] and have a smaller LVEDD.[6] However, there are conflicting data regarding higher[8] or lower baseline EF.[12] In our study, patients with HFiEF exhibited the following: a lower rate of male sex, IHD, diabetes mellitus, and hyperlipidaemia; a higher level of albumin; a lower level of uric acid and creatinine; lower LAD and LVEDD; higher use of ACEi or ARB and beta-blockers; reduced use of antiplatelet agents and hypolipidaemic drugs; higher rates of CRT implantation and AF ablation; and lower rates of ICD implantation.

Our study identified five variables that independently correlated with HFiEF: younger age, smaller LVEDD, beta-blocker use, AF ablation, and CRT implantation were positive predictors. The result was consistent with a few other studies: our subjects with HFiEF were more likely to be younger[6,9] and treated with a beta-blocker[9] and CRT implantation.[13] Moreover, smaller LVEDD was an independent factor that predicted a greater likelihood of LVEF improvement. Otherwise, the novel findings of this study are that patients with AF ablation had greater odds of being in the HFiEF group. It is understandable that LV remodelling can also be reduced by atrial fibrillation, and electrophysiological processes play an important role in LV reverse remodelling.[14] We also found that cardioversion to sinus rhythm in AF subgroup patients (Supporting Information, *Figure S3A*) undergoing radiofrequency catheter ablation and CRT implantation in the device subgroup led to greater improvement in the LVEF (Supporting Information, *Figure S3B*). Of note, there was significantly more IHD in the non-HFiEF group, Consistent with our data, several investigations[3,5,8] have implicated non-ischaemic aetiology is associated with a higher likelihood of LVEF improvement as IHD might respond differently to treatment.

## Outcomes in heart failure patients with improved ejection fraction

Recent studies have described HFiEF as a distinct entity for those cases systematically linked to lower hospitalization for HF decompensation rates and mortality. HFiEF patients seem to have more favourable clinical outcomes than non-HFiEF patients in different cohort studies. The study by Ghimire

*et al*.[12] also confirmed a non-significant trend towards reductions in mortality (HR = 0.16, 95% CI: 0.02–1.15 $P = 0.068$) and fewer recurrent hospitalizations for HF (HR = 0.41, 95% CI: 0.24–0.68, $P < 0.001$). In the Park *et al*.[9] study cohort, the proportion of surviving patients was significantly higher in the HFiEF group (log-rank $P$ value = 0.005). The mortality rate was found to be approximately 2.9 cases per 100 person-years (95% CI: 1.8–4.5, $P < 0.05$) in the HFiEF group and 5.8 cases per 100 person-years (95% CI: 5.3–6.4, $P < 0.05$) in the continued HFrEF group. In the study of Basuray *et al*.[7] according to multivariate Cox regression models, HFiEF (vs. HFrEF) independently predicted both the adverse cardiovascular event rate (HR = 0.668, 95% CI: 0.450–0.994, $P = 0.046$) and mortality (HR = 0.655, 95% CI: 0.459–0.934, $P = 0.019$). Similar conclusions were reached in a recent European cohort.[12] The HFiEF subgroup demonstrated lower rates of mortality (aHR = 0.70) and fewer hospitalizations (aHR = 0.87) and emergency room visits (aHR = 0.88) than patients with persistent HFrEF. Consistent with these conclusions, our study confirmed that HFiEF as a distinct clinical entity is associated with a more favourable prognosis than non-HFiEF. Based on Kaplan–Meier analysis, HFiEF was associated with lower composite outcomes ($P = 0.002$) and all-cause mortality ($P = 0.003$) than non-HFiEF. Further, multivariate Cox regression analyses demonstrated that HFiEF (vs. non-HFiEF) was an independent predictor of both cardiac composite outcomes and all-cause mortality.

### Management of heart failure patients with improved ejection fraction

The optimal clinical management of HFiEF patients remains unclear due to a lack of robust prospective data. In fact, there has only been one randomized controlled clinical trial (TRED-HF) in 50 patients with non-ischaemic HFiEF to assess the safety of weaning guideline-directed medical therapy in HFiEF patients.[15] The results of some prospective studies supported that the use of beta-blockers is beneficial for Asian HFiEF patients, this outcome was reported in a Japanese cohort[16] and a multicentre cohort study in South Korea.[8] Our research also showed that beta-blocker use was associated with improved composite outcomes (aHR = 0.973, 95% CI: 0.947–0.999, $P = 0.041$). Until recently, guideline-directed medical care for patients with HFiEF was recommended to be continued indefinitely according to the recent ACC Scientific Expert Panel.[11]

### Limitations and directions

We may have overestimated LVEF improvement because we did not include subjects who died before the second cardiogram could be conducted. This may have affected the non-HFiEF group in particular, as death before the second echocardiograph occurred more often in the non-HFiEF group than in the HFiEF group, which could be a source of bias. Moreover, echocardiographic data were collected from summary reports in routine clinical practice rather than with a prospective standardized protocol. Finally, many unknown clinical factors associated with a higher likelihood of LVEF improvement still need to be elucidated before these data can be used as predictive or prognostic tools for individual patients.

## Conclusions

We describe the frequency, predictors, and prognosis of HFiEF patients. In our study, younger age, smaller LVEDD, beta-blocker use, AF ablation and CRT implantation were independent predictors of HFiEF. Furthermore, subjects with HFiEF had significantly less all-cause mortality and fewer hospitalizations for HF decompensation than those with non-HFiEF. The natural history can be further characterized, and optimal management strategies can be better established in HFiEF patients only through ongoing studies.

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## Conflict of interest

None declared.

## Supporting information

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

**Table S1.** Definitions of HFiEF.
**Figure S1.** Inter-observer agreement and intra-observer agreement analysis of Bland and Altman method.
**Figure S2.** Association between the composite outcomes (A) and all-cause death (B) with HFiEF in redefined HFiEF population. HFiEF was redefined as a baseline LVEF <50% improved to an LVEF ≥50%.
**Figure S3.** Kaplan–Meier curves showing the composite outcomes with HFiEF in the subgroup of AF patients (A) and device patients (B).

## References


1. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016; **37**: 2129–2200.
2. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2015; **28**: 1–39 e14.
3. Wilcox JE, Fonarow GC, Yancy CW, Albert NM, Curtis AB, Heywood JT, Inge PJ, McBride ML, Mehra MR, O'Connor CM, Reynolds D, Walsh MN, Gheorghiade M. Factors associated with improvement in ejection fraction in clinical practice among patients with heart failure: findings from IMPROVE HF. *Am Heart J* 2012; **163**: 49–56 e42.
4. Punnoose LR, Givertz MM, Lewis EF, Pratibhu P, Stevenson LW, Desai AS. Heart failure with recovered ejection fraction: a distinct clinical entity. *J Card Fail* 2011; **17**: 527–532.
5. Florea VG, Rector TS, Anand IS, Cohn JN. Heart failure with improved ejection fraction: clinical characteristics, correlates of recovery, and survival: results from the valsartan heart failure trial. *Circ Heart Fail* 2016; **9**: e003123.
6. Abe S, Yoshihisa A, Ichijo Y, Sato Y, Kanno Y, Takiguchi M, Yokokawa T, Misaka T, Sato T, Oikawa M, Kobayashi A, Yamaki T, Kunii H, Takeishi Y. Recovered left ventricular ejection fraction and its prognostic impacts in hospitalized heart failure patients with reduced ejection fraction. *Int Heart J* 2020; **61**: 281–288.
7. Basuray A, French B, Ky B, Vorovich E, Olt C, Sweitzer NK, Cappola TP, Fang JC. Heart failure with recovered ejection fraction: clinical description, biomarkers, and outcomes. *Circulation* 2014; **129**: 2380–2387.
8. Chang KW, Beri N, Nguyen NH, Arbit B, Fox S, Mojaver S, Clopton P, Tam SW, Taylor AL, Cohn JN, Maisel AS, Anand IS. Heart failure with recovered ejection fraction in African Americans: results from the African-American heart failure trial. *J Card Fail* 2018; **24**: 303–309.
9. Park CS, Park JJ, Mebazaa A, Oh IY, Park HA, Cho HJ, Lee HY, Kim KH, Yoo BS, Kang SM, Baek SH, Jeon ES, Kim JJ, Cho MC, Chae SC, Oh BH, Choi DJ. Characteristics, outcomes, and treatment of heart failure with improved ejection fraction. *J Am Heart Assoc* 2019; **8**: e011077.
10. Gulati G, Udelson JE. Heart failure with improved ejection fraction: is it possible to escape one's past? *JACC Heart Fail* 2018; **6**: 725–733.
11. Wilcox JE, Fang JC, Margulies KB, Mann DL. Heart failure with recovered left ventricular ejection fraction: JACC scientific expert panel. *J Am Coll Cardiol* 2020; **76**: 719–734.
12. Ghimire A, Fine N, Ezekowitz JA, Howlett J, Youngson E, McAlister FA. Frequency, predictors, and prognosis of ejection fraction improvement in heart failure: an echocardiogram-based registry study. *Eur Heart J* 2019; **40**: 2110–2117.
13. Zhang N, Cai M, Hua W, Hu Y, Niu H, Cai C, Gu M, Zhang S. Prognostic effects of longitudinal changes in left ventricular ejection fraction with cardiac resynchronization therapy. *ESC Heart Fail* 2021; **8**: 368–379.
14. Hunter RJ, Berriman TJ, Diab I, Kamdar R, Richmond L, Baker V, Goromonzi F, Sawhney V, Duncan E, Page SP, Ullah W, Unsworth B, Mayet J, Dhinoja M, Earley MJ, Sporton S, Schilling RJ. A randomized controlled trial of catheter ablation versus medical treatment of atrial fibrillation in heart failure (the CAMTAF trial). *Circ Arrhythm Electrophysiol* 2014; **7**: 31–38.
15. Halliday BP, Wassall R, Lota AS, Khalique Z, Gregson J, Newsome S, Jackson R, Rahneva T, Wage R, Smith G, Venneri L, Tayal U, Auger D, Midwinter W, Whiffin N, Rajani R, Dungu JN, Pantazis A, Cook SA, Ware JS, Baksi AJ, Pennell DJ, Rosen SD, Cowie MR, Cleland JGF, Prasad SK. Withdrawal of pharmacological treatment for heart failure in patients with recovered dilated cardiomyopathy (TRED-HF): an open-label, pilot, randomised trial. *Lancet* 2019; **393**: 61–73.
16. Waagstein F, Caidahl K, Wallentin I, Bergh CH, Hjalmarson A. Long-term beta-blockade in dilated cardiomyopathy. Effects of short- and long-term metoprolol treatment followed by withdrawal and readministration of metoprolol. *Circulation* 1989; **80**: 551–563.