Recovered Left Ventricular Ejection Fraction and Its Prognostic Impacts in Hospitalized Heart Failure Patients with Reduced Ejection Fraction

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Summary
It has been recently recognized that recovery of left ventricular ejection fraction (EF), termed “recovered EF”, occurs in a proportion of heart failure patients with reduced EF (HFrEF), and is associated with better prognosis. However, the clinical characteristics of “recovered EF” have not been fully examined.

Consecutive 567 patients hospitalized due to HFrEF (EF < 40% at 1st assessment at hospital discharge) were enrolled, and EF was re-assessed within half a year in an outpatient setting (2nd assessment). Among these HFrEF patients, 235 remained EF < 40% (reduced, rEF group), 82 changed to EF 40-49% (midrange, mrEF group), and 250 recovered to EF > 50% (preserved, pEF group “recovered EF”) at the 2nd examination. Age was lower and body mass index and systolic blood pressure were higher in pEF than in rEF. The prevalence of atrial fibrillation (AF) and usage of an implantable cardiac defibrillator and cardiac resynchronization therapy were highest in pEF. Left ventricular end diastolic dimension (LVDd) was the smallest in the pEF group. Multivariable logistic regression analysis revealed that younger age, presence of AF, and lower levels of LVDd were predictors of “recovered EF”. Kaplan-Meier analysis found that pEF presented the lowest cardiac event rate ($P = 0.003$) and all-cause mortality ($P = 0.001$). In multivariable Cox proportional hazard analyses, pEF (versus rEF) was an independent predictor of both cardiac event rate (HR = 0.668, 95%CI 0.450-0.994, $P = 0.046$) and all-cause mortality (HR = 0.655, 95%CI 0.459-0.934, $P = 0.019$).

Hospitalized HFrEF patients with recovered EF are associated with younger age, higher presence of AF, and better prognosis.

Key words: Co-morbidity, Recover, Prognosis

Heart failure (HF) is a major cause of death among the elderly in many countries.1-4 The ‘left ventricular ejection fraction’ is among the most ingrained and commonly used to manage HF in clinical practice. Ejection fraction (EF) is used in the diagnosis, characterization, prognosis, patient triage, and treatment selection of HF.5-9 HF with reduced EF (HFrEF; EF < 40%) is well characterized and established with respect to evidence-based therapy [e.g. renin-angiotensin-aldosterone system inhibitors, beta blockers, and cardiac resynchronization therapy (CRT)].5-9 whereas HF with preserved EF (HFrEF; EF ≥ 50%) is a common and complex syndrome without evidence-based therapy.10,11 On the other hand, changes in EF and its prognostic impact on stable HFrEF patients have recently been reported,12 and it has been suggested that the recovery of EF, known as “recovered EF”, occurs in a proportion of stable HFrEF patients, and is associated with better prognosis.13-18 However, changes in EF in patients with decompensated and hospitalized HFrEF, their clinical characteristics, and prognosis are still not fully understood.

Therefore, the aim of the present study was to clarify changes in EF in patients with decompensated and hospitalized HFrEF, their clinical characteristics, and their prognosis.

Methods
This was a prospective observational study of 629 decompensated and hospitalized HFrEF patients who were discharged from Fukushima Medical University Hospital between 2010 and 2016, and who had an EF < 40% at...
the time of hospital discharge (1st EF assessment). The diagnosis of decompensated HF was made by several cardiologists based on the HF guidelines. Patients who had been admitted due to acute coronary syndrome and had previously undergone hemodialysis were excluded. EF was premeditatedly re-assessed in 567 patients in the outpatient setting within half a year (mean 4 months) post discharge (2nd EF assessment). Of the 629 patients, 53 failed to undergo a 2nd EF assessment for a reason attributable to the patient or the physician, and all-cause death or hospitalization due to decompensated HF occurred in 9 patients before the 2nd EF assessment. Thus, we divided the remaining 567 HFrEF patients, who had an EF < 40% at the 1st EF assessment, into 3 groups based on the 2nd EF assessment: "HFrEF at 1st EF assessment and persistently remained as reduced EF at 2nd EF assessment: rEF (EF < 40%, n = 235)", "HFrEF at 1st EF assessment and subsequently became midrange EF at 2nd EF assessment: mEF (EF 40-49%, n = 82)" and "HFrEF at 1st EF assessment and then recovery to preserved EF at 2nd EF assessment: pEF: recovered EF (EF ≥ 50%, n = 250)".

We compared the clinical features, laboratory data, and echocardiography and electrocardiogram parameters. The patients were followed up until 2018 for cardiac events and all-cause death. Cardiac events were defined as worsened HF and cardiac death. Cardiac death was classified by independent experienced cardiologists as death from worsened HF, ventricular fibrillation documented by electrocardiogram or implantable devices, or acute coronary syndrome. Worsened HF was defined as hospitalization due to decompensated HF. Status and dates of death were obtained from the patient medical records. If these data were unavailable, the status was ascertained by a telephone call to the physician at the referring hospital. We were able to follow-up on all patients. Those administering the survey were blind to the analyses, and written informed consent was obtained from all study subjects. The study protocol was approved by the ethical committee of Fukushima Medical University, the investigation conformed to the principles outlined in the Declaration of Helsinki, and reporting of the study conforms to STROBE along with references to STROBE and the broader EQUATOR guidelines.

We evaluated several comorbidities that often coexist and are associated with adverse prognost in HF patients. Coronary artery disease (CAD) was confirmed by either myocardial scintigraphy or coronary computed tomography angiography and/or coronary angiography. Atrial fibrillation (AF) was identified by electrocardiography performed during hospitalization and/or from medical records. AF included 1) paroxysmal or persistent AF or 2) chronic AF. Hypertension was defined as the recent use of antihypertensive drugs, systolic blood pressure ≥ 140 mmHg, and/or diastolic blood pressure ≥ 90 mmHg. Diabetes mellitus was defined as the recent use of antidiabetic drugs, a fasting glucose value of ≥ 126 mg/dL, a casual glucose value of ≥ 200 mg/dL, and/or HbA1c ≥ 6.5% (National Glycohemoglobin Standardization Program). Dyslipidemia was defined as the recent use of cholesterol-lowering drugs, a triglyceride value of ≥ 150 mg/dL, a low-density lipoprotein cholesterol value of ≥ 140 mg/dL, and/or a high-density lipoprotein cholesterol value of < 40 mg/dL. Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate of < 60 mL/minute/1.73 m² according to the Modification of Diet in Renal Disease formula. Anemia was defined as hemoglobin levels of < 12.0 g/dL in females and < 13.0 g/dL in males. Hyperuricemia was defined as the regular usage of antihyperuricemic agents or serum uric acid levels of over 7 mg/dL. Chronic obstructive pulmonary disease was defined as forced expiratory volume in one second/forced vital capacity < 70% by spirometry according to the Global Initiative for Chronic Obstructive Lung Disease, the American Thoracic Society/European Respiratory Society guidelines and/or from medical records.

**Measurement of parameters of laboratory data, electrocardiograms, and echocardiography:** Blood samples were obtained from all patients at Fukushima Medical University Hospital at hospital discharge. B-type natriuretic peptide (BNP) levels were measured using a specific immunoradiometric assay (Shionoria BNP kit, Shionogi, Osaka, Japan). High-sensitivity troponin I levels were measured using EDTA anticoagulated plasma using a refined assay (Abbott-Architect, Abbott Laboratories, Abbott Park, IL, USA).

The standard resting ECG was recorded in the supine position using a CardioStar FCP-7541 ECG (Fukuda Den-shi, Co., Ltd., Tokyo) and stored digitally at hospital discharge. This system allows automatic measuring of QT and QTc intervals. The QT interval was measured from the beginning of the QRS complex until the T wave returns to the isoelectric line. The median QT interval was then calculated and corrected for the heart rate.

Echocardiography was performed blindly by experienced echocardiographers using standard techniques at hospital discharge (1st EF assessment). The echocardiographic parameters investigated included left ventricular diastolic dimension (LVDd), left ventricular systolic dimension (LVDs), LVEF, the ratio of early transmirtal flow velocity to mitral annular velocity (mitral valve E/e’), inferior vena cava diameter (IVC), tricuspid regurgitation pressure gradient (TR-PG), and right ventricular fractional area change (RV-FAC). LVEF was calculated using Simpson’s method in a 4-chamber view. The RV-FAC, defined as (end diastolic area - end systolic area)/end diastolic area × 100, was used as a measure of right ventricular systolic function. All measurements were performed using ultrasound systems (ACUSON Sequoia, Siemens Medical Solutions USA, Inc., Mountain View, CA, USA).

**Statistical analysis:** Categorical variables are expressed as numbers and percentages. The chi-square test was used for comparisons of categorical variables and followed by Fisher’s exact test when appropriate. Normality was confirmed using the Shapiro-Wilk test in each group. Parametric variables are presented as the mean ± SD, and non-parametric variables (e.g. BNP, troponin I and C-reactive protein) are presented as the median and interquartile range. Parametric variables were compared using analysis of variance (ANOVA), and equality was tested by the Levene test. If data were equal, ANOVA was followed by Tukey’s honest significant difference. If data were not equal, the Games-Howell post hoc test was used.
parametric variables were compared using the Kruskal-Wallis test. We performed logistic regression analysis allowing for interaction between the onset of “recovered EF” and each possible confounding factor. Kaplan-Meier analysis was used for presenting the cardiac event rate and all-cause mortality, and the log-rank test was used for initial comparisons. Kaplan-Meier estimates of the survival curves were plotted against time to follow-up period. These curves helped in identifying non-proportionality patterns in hazard function such as convergence (difference in risk between the groups decreases with time), divergence, or crossing of the curves. In addition, a Schoenfeld test for the violation of proportional hazards, which can be used to assess the correlation between scaled residuals and time, was also conducted. The prognostic value was evaluated by Cox proportional hazard analysis, and was tested by univariate and multivariate Cox regression analysis. Univariable and multivariable Cox proportional hazard analyses were used to evaluate changes of EF as a predictor of cardiac event rate and all-cause mortality. Univariable parameters with $P$ values of $< 0.05$ were included in the multivariable analysis. The propor-

### Table 1. Clinical Features Based on EF Classification at 2nd EF Assessment ($n = 567$)

| Etiology | rEF ($n = 235$) | mrEF ($n = 82$) | pEF ($n = 250$) | $P$-value |
|----------|----------------|----------------|---------------|-----------|
| **Age (years)** | 67.2 ± 14.0 | 65.8 ± 13.9 | 62.4 ± 15.0* | 0.001 |
| **Male gender (n, %)** | 167 (71.1) | 62 (75.6) | 179 (71.6) | 0.722 |
| **Body mass index (kg/m²)** | 22.6 ± 4.2 | 23.6 ± 3.9 | 23.9 ± 4.3* | 0.004 |
| **Systolic blood pressure (mmHg)** | 122.0 ± 32.0 | 132.9 ± 32.6* | 130.0 ± 35.5* | 0.008 |
| **Diastolic blood pressure (mmHg)** | 72.6 ± 21.5 | 79.2 ± 21.8* | 77.7 ± 24.8* | 0.019 |
| **Heart rate (bpm)** | 83.6 ± 23.3 | 93.2 ± 29.3* | 88.0 ± 28.8 | 0.014 |
| **NYHA functional class III/IV** | 13 (5.5) | 5 (6.1) | 5 (2.0) | 0.086 |
| **Diagnosis** | | | | |
| **Cardiomyopathy** | 109 (46.4) | 33 (40.2) | 92 (36.8) | 0.099 |
| **Ischemic etiology** | 88 (37.4) | 31 (37.8) | 72 (28.8) | 0.092 |
| **Valvular heart disease** | 19 (8.1) | 9 (11.0) | 48 (19.2) | 0.001 |
| **Arrhythmic cause** | 5 (2.1) | 3 (3.7) | 14 (5.6) | 0.140 |
| **Others** | 14 (6.0) | 6 (7.3) | 24 (9.6) | 0.321 |
| **Co-morbidity** | | | | |
| **Coronary artery disease (n, %)** | 93 (39.6) | 35 (42.7) | 85 (34.0) | 0.262 |
| **AF (n, %)** | 67 (28.5) | 32 (39.0) | 105 (42.0) | 0.007 |
| **Paroxysmal or persistent AF (n, %)** | 39 (16.6) | 18 (22.0) | 57 (22.8) | 0.212 |
| **Chronic AF (n, %)** | 28 (11.9) | 14 (17.1) | 48 (19.2) | 0.086 |
| **Hypertension (n, %)** | 164 (69.8) | 52 (63.4) | 185 (74.0) | 0.173 |
| **Diabetes (n, %)** | 110 (46.8) | 47 (57.3) | 117 (46.8) | 0.212 |
| **Dyslipidemia (n, %)** | 174 (74.0) | 65 (79.3) | 191 (76.4) | 0.612 |
| **Chronic kidney disease (n, %)** | 143 (60.9) | 56 (68.3) | 141 (56.4) | 0.152 |
| **Anemia (n, %)** | 120 (51.1) | 41 (50.0) | 114 (45.6) | 0.464 |
| **Hyperuricemia (n, %)** | 168 (71.5) | 61 (74.4) | 177 (70.8) | 0.821 |
| **COPD (n, %)** | 49 (20.9) | 25 (30.5) | 64 (25.6) | 0.178 |
| **Smoking (n, %)** | 127 (54.5) | 41 (51.9) | 127 (51.6) | 0.805 |
| **Alcohol (n, %)** | 19 (8.2) | 9 (11.4) | 25 (10.2) | 0.623 |
| **Treatment** | | | | |
| **RAS inhibitor (n, %)** | 187 (79.6) | 67 (81.7) | 216 (86.4) | 0.130 |
| **Mineral receptor antagonist (n, %)** | 119 (50.6) | 42 (51.2) | 130 (52.0) | 0.956 |
| **Calcium channel blocker (n, %)** | 53 (22.6) | 23 (28.0) | 80 (32.0) | 0.066 |
| **Beta blocker (n, %)** | 211 (89.8) | 75 (91.5) | 230 (92.0) | 0.688 |
| **Diuretic (n, %)** | 182 (77.4) | 75 (91.5) | 183 (73.2) | 0.003 |
| **Inotropic (n, %)** | 51 (21.7) | 21 (25.6) | 41 (16.4) | 0.131 |
| **Statin (n, %)** | 84 (35.7) | 36 (43.9) | 103 (41.2) | 0.309 |
| **Digitals (n, %)** | 30 (12.8) | 19 (23.2) | 33 (13.2) | 0.052 |
| **Amiodarone (n, %)** | 78 (33.2) | 29 (35.4) | 48 (19.2) | 0.001 |
| **Antiplatelet agent (n, %)** | 102 (43.4) | 36 (43.9) | 117 (46.8) | 0.738 |
| **Anticoagulant (n, %)** | 148 (63.0) | 50 (61.0) | 153 (61.2) | 0.906 |
| **PCI (n, %)** | 65 (27.7) | 25 (30.5) | 67 (26.8) | 0.811 |
| **Catheter ablation (n, %)** | 19 (8.1) | 12 (14.6) | 23 (9.2) | 0.214 |
| **ICD (n, %)** | 17 (7.3) | 14 (17.7) | 46 (18.7) | 0.001 |
| **CRT (n, %)** | 17 (7.2) | 11 (13.4) | 37 (14.8) | 0.027 |

*EF indicates ejection fraction; HFrEF, heart failure with reduced EF; rEF, HFrEF at 1st EF assessment and persistently remained reduced EF at 2nd assessment; mrEF, HFrEF at 1st EF assessment and changed to midrange EF at 2nd assessment; pEF, HFrEF at 1st EF assessment and recovered to preserved EF at 2nd assessment; NYHA, New York Heart Association; AF, atrial fibrillation; COPD, chronic obstructive pulmonary disease; RAS, renin-angiotensin-aldosterone system; PCI, percutaneous coronary intervention; ICD, implantable cardiac defibrillator; and CRT, cardiac resynchronization therapy. *$P < 0.05$ and **$P < 0.01$ versus rEF.*
Table II. Laboratory and Echocardiographic Data Based on EF Classification at 2nd EF Assessment (n = 567)

| Laboratory data | rEF (n = 235) | mrEF (n = 82) | pEF (n = 250) | P-value |
|-----------------|---------------|---------------|---------------|---------|
| White blood cells (*10^3/μL) | 6.9 ± 2.7 | 8.4 ± 3.7* | 7.6 ± 3.3† | 0.002 |
| Hemoglobin (g/dL) | 12.9 ± 2.2 | 13.0 ± 2.5 | 13.0 ± 2.3 | 0.862 |
| BNP (pg/mL) § | 452.1 (155.7-954.9) | 511.1 (155.9-786.3) | 409.5 (180.9-812.3) | 0.607 |
| Troponin I (ng/mL) § | 0.050 (0.027-0.196) | 0.051 (0.029-0.661) | 0.060 (0.040-0.228) | 0.121 |
| eGFR (mL/min/1.73 cm²) | 51.8 ± 22.0 | 54.1 ± 19.7 | 57.5 ± 25.1 | 0.063 |
| C-reactive protein (mg/dL) § | 0.23 (0.08-0.88) | 0.21 (0.07-0.86) | 0.20 (0.07-0.84) | 0.101 |
| Total protein (g/dL) | 7.0 ± 0.7 | 6.9 ± 0.8 | 6.9 ± 0.8 | 0.402 |
| Albumin (g/dL) | 3.7 ± 0.6 | 3.6 ± 0.8 | 3.6 ± 0.6 | 0.335 |
| Total bilirubin (mg/dL) | 1.0 ± 0.6 | 0.9 ± 0.5 | 1.0 ± 0.6 | 0.597 |
| Direct bilirubin (mg/dL) | 0.1 ± 0.1 | 0.2 ± 0.2 | 0.1 ± 0.3 | 0.677 |
| Sodium (mEq/L) | 138.5 ± 3.7 | 139.3 ± 3.9 | 139.0 ± 4.0 | 0.270 |
| Echocardiographic data | | | | |
| LV EF (%) | 28.5 ± 7.3 | 32.1 ± 7.8 | 33.2 ± 7.3† | 0.021 |
| LVDD (mm) | 58.4 ± 10.5 | 57.7 ± 9.8 | 54.5 ± 9.6** | < 0.001 |
| LVDs (mm) | 50.2 ± 10.9 | 47.9 ± 10.6 | 43.2 ± 11.8**†† | < 0.001 |
| Mitral valve E/E’ | 16.1 ± 8.5 | 15.3 ± 9.8 | 14.4 ± 6.8 | 0.128 |
| IVC (mm) | 15.2 ± 5.1 | 15.8 ± 5.0 | 15.3 ± 5.3 | 0.677 |
| TR-PG (mmHg) | 26.4 ± 12.3 | 31.4 ± 15.5 | 27.3 ± 12.6 | 0.062 |
| RV-FAC (%) | 37.1 ± 13.5 | 37.7 ± 19.6 | 39.2 ± 12.3 | 0.546 |
| ECG | | | | |
| Rhythm sinusal/atrial fibrillation/ pacing | 155 (66.0)/28 (11.9) / 54 (65.9)/14 (17.1) / 163 (65.2)/52 (20.8) / | 0.035 |
| CRBBB | 17 (7.2) | 7 (8.5) | 21 (8.4) | 0.873 |
| CLBBB | 52 (22.1) | 14 (17.1) | 35 (14.0) | |
| HR (excluding pacing, n = 465) | 75.1 ± 16.1 | 75.1 ± 15.4 | 73.3 ± 16.3 | 0.425 |
| PQ (msec) | 175.8 ± 30.4 | 184.4 ± 35.3 | 175.4 ± 29.4 | 0.167 |
| QRS (msec) | 117.8 ± 23.3 | 115.2 ± 25.9 | 114.0 ± 26.2 | 0.320 |
| QT (msec) | 411.3 ± 48.7 | 408.2 ± 48.1 | 410.2 ± 47.9 | 0.321 |
| QTc (msec) | 456.6 ± 35.7 | 451.2 ± 34.8 | 448.8 ± 43.7 | 0.148 |

EF indicates ejection fraction; HFrEF, heart failure with reduced EF; rEF, HFrEF at 1st EF assessment and persistently remained reduced EF at 2nd assessment; mrEF, HFrEF at 1st EF assessment and changed to midrange EF at 2nd assessment; pEF, HFrEF at 1st EF assessment and recovered to preserved EF at 2nd assessment; BNP, B-type natriuretic peptide; GFR, glomerular filtration rate; LVDD, left ventricular end diastolic dimension; LVDs, left ventricular end systolic dimension; IVC, inferior vena cava diameter; TR-PG, tricuspid regurgitation pressure gradient; RV-FAC, right ventricular fractional area change; CRBBB, complete right bundle branch block; CLBBB, complete left bundle branch block.

*P < 0.05 and **P < 0.01 versus rEF; †P < 0.05 and ††P < 0.01 versus mrEF. § Data are presented as median (interquartile range).

Results

The clinical characteristics and treatments of patients at hospital discharge are presented in Table I. Age was lower and body mass index and blood pressure were higher in the pEF group than in the rEF group. In addition, the prevalence of AF and taking diuretics or amiodarone were the lowest, and usages of implantable cardiac defibrillator and CRT therapy were the highest in pEF among the groups. In contrast, the prevalence of other comorbidities and treatment did not significantly differ among the 3 groups. Laboratory data and electrocardiography and echocardiography findings are presented in Table II. The white blood cell level was the highest in the mrEF group, while LV EF was the highest and LVDd and LVDs were the smallest in the pEF group among the groups. In contrast, other parameters, including hemoglobin, BNP, troponin I, C-reactive protein, total protein, sodium, mitral valve E/E’, IVC, TR-PG, RV-FAC, PQ, QRS, QT, and QTc did not significantly differ among the groups. In the multivariable logistic regression analysis (Table III), younger age, presence of AF, lower levels of LVDD, and higher levels of LVEF at 1st EF assessment were predictors of “recovered EF”.

During the follow-up period after the 2nd EF assessment (mean 1,201 ± 808 days, range 20-2,954 days), 197 cardiac events, including 160 hospitalizations due to HF and 37 cardiac deaths, occurred, as well as 179 all-cause mortalities (106 cardiac deaths and 73 non-cardiac deaths). In the Kaplan-Meier analysis (Figure), the pEF group presented the lowest cardiac event rate (P = 0.003) and all-cause mortality (P = 0.001). In the multivariable Cox proportional hazard analyses (Table IV), pEF (versus rEF) was an independent predictor of both cardiac event rate (hazard ratio [HR] 0.668, 95% confidence interval [CI] 0.450-0.994, P = 0.046) and all-cause mortality (HR = 0.655, 95%CI 0.459-0.934, P = 0.019).
In the present study, we demonstrated that patients with “recovered EF”, which was 44.1% in the present study, was associated with younger age, higher presence of AF, and lower levels of LVDd, and better prognosis of cardiac event rate, as well as all-cause mortality in HFrEF patients.

In stable HFrEF patients, EF recovery was observed in 9.1 - 24.2%. 13-17,25) The relatively higher prevalence of “recovered EF” (44.1%) than those in previous studies 12-17,25) may be due to the greater number of patients with acute phase of decompensated HFrEF in the present study compared to the outpatient setting of other studies.

Several reported factors of EF recovery in stable HFrEF patients were as follows: younger age, lower NYHA class, lower prevalence of male gender, CAD, diabetes, CKD, chronic obstructive pulmonary disease and CLBBB, higher prevalence of AF and hypertension, higher levels of baseline EF, body mass index, blood pressure and sodium, and lower levels of LVDd and circulating levels of uric acid, troponin T, BNP and NT-pro BNP.12-15,17) Concordant with the previous studies based on stable HFrEF patients, 12-17,25) younger age, higher presence of AF, lower levels of LVDd, and higher levels of baseline EF were associated with “recovered EF” in the present study from decompensated and hospitalized HFrEF patients. In addition, although the etiology of HFrEF could be associated with “recovered EF”, associations between EF recovery and the etiology of cardiomyopathy or valvular heart disease have not been reported. On the contrary, ischemic etiology is reportedly less likely to present EF recovery in stable HFrEF patients 12-15,17) and the etiology of HF (e.g. higher prevalence of ischemic etiology in the

### Table III. Logistic Regression Analysis: Associations between the Clinical Profiles and “Recovered EF”

| Variable                                      | Univariable       | Multivariable     |
|-----------------------------------------------|-------------------|-------------------|
|                                              | OR     | 95%CI | P-value | OR     | 95%CI | P-value |
| Age                                           | 0.979  | 0.968-0.991 | < 0.001 | 0.963  | 0.947-0.979 | < 0.001 |
| Male gender                                   | 0.969  | 0.670-1.401 | 0.866   |        |        |        |
| Body mass index                               | 1.058  | 1.016-1.101 | 0.006   | 1.042  | 0.986-1.103 | 0.146   |
| Systolic blood pressure                       | 1.004  | 1.000-1.009 | 0.073   |        |        |        |
| Heart rate                                    | 1.003  | 0.996-1.009 | 0.407   |        |        |        |
| NYHA class III or IV                          | 0.339  | 0.124-0.926 | 0.035   | 0.266  | 0.066-1.074 | 0.063   |
| Coronary artery disease                       | 0.761  | 0.539-1.074 | 0.120   |        |        |        |
| Atrial fibrillation                           | 1.595  | 1.129-2.253 | 0.008   | 2.026  | 1.290-3.182 | 0.002   |
| Hypertension                                  | 1.331  | 0.921-1.924 | 0.128   |        |        |        |
| Diabetes                                      | 1.897  | 0.643-1.249 | 0.519   |        |        |        |
| Dyslipidemia                                  | 1.057  | 0.717-1.557 | 0.781   |        |        |        |
| Chronic kidney disease                        | 0.767  | 0.547-1.076 | 0.124   |        |        |        |
| Anemia                                        | 0.812  | 0.583-1.132 | 0.220   |        |        |        |
| Hyperuricemia                                 | 0.932  | 0.645-1.345 | 0.706   |        |        |        |
| Chronic obstructive pulmonary disease         | 1.130  | 0.769-1.661 | 0.534   |        |        |        |
| Peripheral artery disease                     | 0.869  | 0.545-1.388 | 0.869   |        |        |        |
| Smoking                                       | 0.915  | 0.655-1.278 | 0.602   |        |        |        |
| Alcohol                                       | 1.147  | 0.610-2.023 | 0.635   |        |        |        |
| Log BNP                                       | 0.830  | 0.599-1.151 | 0.265   |        |        |        |
| Log troponin I                                | 1.148  | 0.942-1.398 | 0.172   |        |        |        |
| Left ventricular end diastolic dimension      | 0.963  | 0.945-0.981 | < 0.001 | 0.962  | 0.940-0.986 | 0.002   |
| LV EF                                         | 1.087  | 1.065-1.110 | < 0.001 | 1.082  | 1.057-1.108 | < 0.001 |
| Complete left bundle branch block             | 0.791  | 0.376-1.662 | 0.536   |        |        |        |
| QRS                                           | 0.995  | 0.988-1.002 | 0.189   |        |        |        |
| QT                                            | 1.000  | 0.996-1.004 | 0.949   |        |        |        |
| QTc                                           | 0.996  | 0.991-1.000 | 0.090   |        |        |        |
| RAS inhibitors                                | 1.576  | 1.000-2.483 | 0.050   |        |        |        |
| Mineral receptor antagonist                   | 1.050  | 0.753-1.463 | 0.774   |        |        |        |
| Calcium channel blocker                       | 1.492  | 1.030-2.161 | 0.034   | 1.472  | 0.884-2.452 | 0.137   |
| Beta blocker                                  | 1.247  | 0.692-2.245 | 0.463   |        |        |        |
| Diuretic                                      | 0.638  | 0.429-0.948 | 0.026   | 0.922  | 0.535-1.588 | 0.769   |
| Inotropic                                     | 0.608  | 0.340-1.022 | 0.063   | 1.126  | 0.644-1.968 | 0.677   |
| Statin                                        | 1.150  | 0.820-1.615 | 0.418   |        |        |        |
| Digitalis                                     | 0.832  | 0.517-1.339 | 0.448   |        |        |        |
| Amiodarone                                    | 1.181  | 0.973-1.271 | 0.125   |        |        |        |
| PCI                                           | 0.999  | 0.696-1.433 | 0.995   |        |        |        |
| Catheter ablation                             | 0.997  | 0.578-1.721 | 0.992   |        |        |        |
| Implantable cardiac defibrillator             | 2.085  | 1.277-3.403 | 0.003   | 2.019  | 0.849-4.558 | 0.091   |
| Cardiac resynchronization therapy             | 2.193  | 1.064-3.021 | 0.028   | 1.402  | 0.555-3.541 | 0.475   |

EF indicates ejection fraction; OR, odds ratio; CI, confidence interval; NYHA, New York Heart Association; BNP, B-type natriuretic peptide; RAS, renin-angiotensin-aldosterone system; and PCI, percutaneous coronary intervention.

Discussion

In the present study, we demonstrated that patients with “recovered EF”, which was 44.1% in the present study, was associated with younger age, higher presence of AF, and lower levels of LVDd, and better prognosis of cardiac event rate, as well as all-cause mortality in HFrEF patients.

In stable HFrEF patients, EF recovery was observed in 9.1 - 24.2%. 13-17,25) The relatively higher prevalence of “recovered EF” (44.1%) than those in previous studies 12-17,25) may be due to the greater number of patients with acute phase of decompensated HFrEF in the present study compared to the outpatient setting of other studies.

Several reported factors of EF recovery in stable HFrEF patients were as follows: younger age, lower NYHA class, lower prevalence of male gender, CAD, diabetes, CKD, chronic obstructive pulmonary disease and CLBBB, higher prevalence of AF and hypertension, higher levels of baseline EF, body mass index, blood pressure and sodium, and lower levels of LVDd and circulating levels of uric acid, troponin T, BNP and NT-pro BNP.12-15,17) Concordant with the previous studies based on stable HFrEF patients, 12-15,25) younger age, higher presence of AF, lower levels of LVDd, and higher levels of baseline EF were associated with “recovered EF” in the present study from decompensated and hospitalized HFrEF patients. In addition, although the etiology of HFrEF could be associated with “recovered EF”, associations between EF recovery and the etiology of cardiomyopathy or valvular heart disease have not been reported. On the contrary, ischemic etiology is reportedly less likely to present EF recovery in stable HFrEF patients 12-15,17) and the etiology of HF (e.g. higher prevalence of ischemic etiology in the
Rates of cardiac events and all-cause mortality with changes in left ventricular ejection fraction (EF) in heart failure with reduced EF (HFrEF). Kaplan-Meier analysis, during the follow-up period after 2nd assessment of EF, for cardiac event rate and all-cause mortality based on changes in EF at 2nd assessment. rEF, HFrEF at 1st EF assessment and persistently remained reduced EF at 2nd assessment; mrEF, HFrEF at 1st EF assessment and transferred to midrange EF at 2nd assessment; pEF, HFrEF at 1st EF assessment and recovered to preserved EF at 2nd assessment.

Table IV. Cox Proportional Hazard Model of Cardiac Events and All-Cause Mortality

|                     | HR  | 95% CI     | P-value |
|---------------------|-----|------------|---------|
| Cardiac event (197 events/567 patients) |     |            |         |
| rEF                 | Ref |            |         |
| mrEF                | 0.897 | 0.597-1.349 | 0.602   |
| pEF “recovered EF” | 0.595 | 0.438-0.809 | 0.001   |
| pEF “recovered EF” adjusted* | 0.668 | 0.450-0.994 | 0.046   |
| All-cause mortality (179 events/567 patients) |     |            |         |
| rEF                 | Ref |            |         |
| mrEF                | 0.773 | 0.503-1.188 | 0.241   |
| pEF “recovered EF” | 0.541 | 0.392-0.747 | < 0.001 |
| pEF “recovered EF” adjusted* | 0.655 | 0.459-0.934 | 0.019   |

HFrEF indicates heart failure with reduced EF; rEF, HFrEF at 1st EF assessment and persistently remained reduced EF at 2nd assessment; mrEF, HFrEF at 1st EF assessment and changed to midrange EF at 2nd assessment; pEF “recovered EF”, HFrEF at 1st EF assessment and recovered to preserved EF at 2nd assessment. *Adjusted: adjusted for age, gender, body mass index, systolic blood pressure, heart rate, New York Heart Association class III or IV, presence of coronary artery disease, atrial fibrillation, hypertension, diabetes, dyslipidemia, chronic kidney disease, anemia, hyperuricemia, chronic obstructive pulmonary disease, smoking, alcohol, usage of renin-angiotensin-aldosterone system inhibitors, mineral receptor antagonist, calcium channel blocker, beta blockers, diuretics, inotropic agent, statin, digitalis, implantable cardiac defibrillator, cardiac resynchronization therapy, B-type natriuretic peptide and left ventricular ejection fraction at 1st assessment.

Thus, EF changes seem to be important for deciding treatment and predicting prognosis, as is the management of the associated factors with EF changes in HFrEF patients.

**Study limitations:** The present study has several limitations. First, as a prospective cohort study of a single center with a relatively small number of patients, the results may not be representative of the general population. Second, we could not fully examine EF at the 2nd assessment (90.1%) because of lost follow-up and/or occurrence of an event before the 2nd EF assessment, and selection bias
could not be fully denied. Although EF was re-assessed in the outpatient setting within half a year, the duration of the 1st and 2nd assessment of each patient differs. Third, the present study included only variables during hospitalization for decompensated HF, and we did not take into consideration changes in treatment or medical parameters other than EF. Fourth, since this was a prospective observational study, the causal relationships and mechanisms of “recovered EF” (e.g. clinical background, neurohumoral changes, impact of medications or catheter ablation, etc.) on better prognosis could not be fully explained. Therefore, the present results should be viewed as preliminary, and further studies with larger populations are needed.

Conclusions
EF changes are important for deciding treatment and predicting prognosis in decompensated and hospitalized HFrEF patients, as well as in stable HFrEF patients. In addition, several confounding factors are associated with EF changes in HFrEF patients.

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Disclosure
Conflicts of interest: Akioi Yoshihisa and Tomofumi Misaka belong to the Department of Advanced Cardiac Therapeutics, which is supported by Fukuda-Denshi Co, Ltd. Tetsuro Yokokawa belongs to the Department of Pulmonary Hypertension which is supported by Acterion Pharmaceuticals Japan Co, Ltd. These companies are also not associated with the contents of this study.

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