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Temporal changes in left ventricular ejection fraction and their prognostic impacts in patients with Stage B heart failure

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ABSTRACT

Background: We have recently demonstrated that left ventricular ejection fraction (LVEF) dynamically changes over time with prognostic impacts in Stage C/D patients, namely, those who have a current or past history of heart failure (HF). However, it is unknown whether this is also the case in asymptomatic Stage B patients, namely, those who have a risk of HF, but do not have a history of HF.
Methods: In our CHART-2 Study ($N = 10,219$), we enrolled 4005 Stage B patients and divided them into 3 groups by LVEF; preserved EF (pEF, LVEF ≥50%, $N = 3526$), mid-range EF (mrEF, LVEF 41–49%, $N = 302$), and reduced EF (rEF, LVEF ≤40%, $N = 177$). We examined the prognostic impacts of LVEF transitions among the 3 groups in comparison with 4477 patients with Stage C/D HF.
Results: Stage B were characterized by less severe clinical status and better prognosis compared with Stage C/D. Stage B in mrEF and rEF at baseline dynamically transitioned to other groups at 1-year, whereas those in pEF unchanged; at 1-year, mrEF transitioned to pEF/rEF by 50/16%, and rEF transitioned to pEF/mrEF by 25/31%, respectively, whereas pEF transitioned to mrEF/rEF by only 3.6/0.7%, respectively, which were consistent with findings in findings with Stage C/D. Although LVEF decrease was directly associated with all-cause mortality in both the Stage B and Stage C/D with pEF, factors related to LVEF changes were different between the 2 groups.
Conclusions: In Stage B, LVEF dynamically changes with prognostic impacts as in Stage C/D, whereas different determination factors may be involved in the 2 stages.
Clinical trial registration: Chronic Heart Failure Analysis and Registry in the Tohoku District (CHART)-2 (NCT00418041).

1. Introduction

Heart failure (HF) is a leading cause of mortality and morbidity worldwide [1]. For example, in the United States, the estimated number of HF patients aged ≥20 years has increased from 5.7 million in 2009–2012 to 6.2 million in 2013–2016 [2]. In 2005 and 2013, the American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) proposed and updated a concept of HF stages in order to highlight the progressive nature of HF, beginning with risk factors (Stage A), progressing through a period of asymptomatic cardiac dysfunction (Stage B), development of symptomatic HF (Stage C) and finally refractory HF (Stage D) [3,4]. The concept of HF stage underlines the importance of prevention and treatment in the early stages, especially in Stage B [3–5].

In Stage B patients, reduced LVEF is the risk factor for onset of symptomatic HF (Stage C), as well as left ventricular (LV) hypertrophy, post-myocardial infarction (MI) wall motion abnormalities, and significant valvular disease [6–9]. However, the previous observational studies only focused on the prognostic relevance of baseline LVEF at enrollment [6–8], but not on temporal changes in LVEF in Stage B patients.

In our Chronic Heart Failure Analysis and Registry in the Tohoku District-2 (CHART-2) Study ($N = 10,219$) [9–12], we have recently demonstrated that LVEF dynamically changes over time with significant prognostic impacts in Stage C/D patients [10]. However, it remains to be examined whether this is also the case in Stage B patients. In the present study, we thus examined the temporal changes in LVEF and their

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prognostic impacts in Stage B patients in our CHART-2 Study in comparison with Stage C/D patients.

2. Methods

2.1. The CHART-2 Study and the study design and follow-up and study outcome

The CHART-2 Study is a multicenter, prospective, and observational study in Japan, where we enrolled a total of 10,219 stable patients aged ≥20 years with either coronary artery disease (Stage A, $N = 928$), asymptomatic structural heart disease (Stage B, $N = 4405$), or a current and/or past history of HF (Stage C/D, $N = 4876$) at cardiology outpatient clinics or just before discharge at the Tohoku University Hospital and 23 affiliated hospitals in the Tohoku district, Japan. Detailed criteria of Stage B patients are shown in Supplemental definitions [11].

The diagnosis of HF in this study was made by attending cardiologists based on the criteria of the Framingham study [13]. Follow-up data, including medical history, laboratory and echocardiogram by data, and clinical outcomes, were collected at the time of baseline and recorded annually thereafter by clinical research coordinators. Follow-up by reviewing medical records, mail surveys, and telephone interviews were conducted by clinical research coordinators at least once a year. The study outcome was all-cause death and HF admission. The study protocol was approved by the local ethics committee of each participating hospital and informed consent was obtained from all patients (NCT00418041). In this study, we redefined Stage B patients as those with ischemic heart disease (IHD), valvular heart disease (VHD), hypertensive heart disease (HHD), and cardiomyopathy (CM) without symptoms or history of HF. For comparison with patients with Stage B, we only enrolled Stage C/D patients who have IHD, VHD, HHD or CM as a main etiology of HF. Definitions of IHD, VHD, HHD are shown in Supplemental files. We divided 4005 Stage B patients and 4477 Stage C/D patients into 3 groups by baseline LVEF as follows; preserved LVEF (pEF, LVEF ≥50%), mid-range LVEF (mrEF, LVEF 41–49%), and reduced LVEF (rEF, LVEF ≤40%) [4]. To measure LVEF, we employed the Teichholz formula or Simpson method. We examined the baseline characteristics, clinical outcomes, and factors related to temporal LVEF changes in each LVEF category and compared the differeneces between Stage B and Stage C/D patients and between Stage B patients with and those without development of de-novo HF during the follow-up period.

2.2. Statistical analysis

Continuous variables were expressed as mean ± standard deviation or median with interquartile range as appropriate and were compared by Welch's *t*-test. Categorical variables were expressed as numeral with percentage and were compared by the Fisher's exact test. For the patient background, 3 groups (pEF, mrEF, rEF) with Stage B or Stage C/D were compared by one-way ANOVA for normally distributed variables, and Kruskal-Walls test for non-normally distributed variables. To adjust the multiplicity of pairwise comparisons, Tukey's honestly significant difference (HSD) with ANOVA, and Dwass-Steel Critchlow, Fligner method for multiple comparison with Kruskall-Wallis test [14]. The multiplicity of pairwise comparisons of the categorical variables was adjusted by the Holm's method. Incidence rate per 1000 person-years among the groups with Stage B and Stage C/D were compared with the exact binominal test for all-cause death, cardiovascular (CV) deaths including HF death, sudden death, acute myocardial infarction (AMI) death, and stroke death, and non-CV death. We assessed the determinants of all-cause death using multivariable Cox proportional hazards model. All of the potential confounders were shown in the Supplemental files and included in the Cox proportional hazard model analysis with stepwise variable selection with significance level of P value < 0.2. Model selection was done with Bayesian information criterion (BIC) criteria [15]. We performed Student's *t*-test to examine the differences in temporal LVEF changes from baseline to 1-year between Stage B and Stage C/D patients and between Stage B patients with and those without de-novo HF after 1-year. Furtheremore, we asssesed the trajectory in the 3 groups from baseline to 1 year at follow-up and all-cause death by a simple Cox model. A two-sided P value of <0.05 was considered to be statistically significant. All statistical analyses were performed using R software (version 3.5.3) (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Baseline patient characteristics

Supplemental Fig. 1 shows the flow charts of the present study. We classified the Stage B patients based on their baseline LVEF as follows; pEF (LVEF ≥50%, $N = 3526$), mrEF (LVEF 41–49%, $N = 302$), and rEF (LVEF ≤40%, $N = 177$) (Supplemental Fig. 1A). We also classified the Stage C/D patients by baseline LVEF as follows; pEF ($N = 3032$), mrEF ($N = 685$), and rEF ($N = 760$) (Supplemental Fig. 1B). Tables 1A, 1B, 1C, 1D, 1E show the baseline characteristics of patients with Stage B and those of Stage C/D. When compared with Stage C/D patients, those in Stage B were younger and had lower prevalences of diabetes mellitus (DM), atrial fibrillation (AF), and etiology of cardiomyopathy (CM) and lower LV mass index (LVMI) and BNP levels. The Stage B patients had lower prescription rates of beta-blocker, ACE-I/ARB, and diuretic, higher prevalence of ischemic heart disease (IHD), and higher frequency of calcium channel blocker (CCB) use. In Stage B group, pEF patients were older and had higher prevalence of women, and BNP levels and left ventricular end-diastolic diameter (LVDd) were increased in the order of pEF, mrEF to rEF, as in Stage C/D patients.

3.2. Mortality rates and causes of deaths in Stage B and C/D

When compared with Stage C/D patients, Stage B patients were characterized by lower incidence of deaths, except for non-cardiovascular (CV) death in mrEF subgroup (Fig. 1). While incidence rates of all-cause death and CV death, but not of non-CV death, were significantly increased from pEF, mrEF to rEF in Stage C/D patients, a significant increase of mortality incidence was noted from pEF to mrEF for all-cause death and from pEF to mrEF and rEF for CV death in Stage B patients (Fig. 1). As compared with Stage C/D patients, Stage B patients had lower incidence for HF death in all of pEF, mrEF and rEF, for sudden death in pEF and rEF, and for AMI death in pEF (Supplemental Fig. 2).

3.3. Temporal changes in LVEF in Stage B and C/D

Fig. 2 shows the transitions of LVEF during the 5 years of follow-up in Stage B (upper panel) and Stage C/D (lower panel) patients. Stage B patients with mrEF and rEF at baseline dynamically transitioned to other groups at 1-year, whereas those with pEF unchanged; mrEF transitioned to pEF and rEF by 50.0/15.7%, and rEF transitioned to pEF and mrEF by 24.5/31.0%, respectively, whereas pEF transitioned to mrEF and rEF only by 3.6/0.7%, respectively. Similar trends were noted in Stage C/D patients, while improvement of LVEF was less evident compared with Stage B. When stratified by ischemic etiology (Supplemental Table 4A, B, and Fig. 4B to E), rEF patients with ischemic heart disease (IHD) had less improvement of LVEF in both Stage B and Stage C/D. Supplemental Table 1 shows the factors related to LVEF changes from baseline to 1-year in Stage B and Stage C/D patients. Left ventricular end-diastolic diameter (LVDd) was inversely correlated with LVEF change in mrEF and rEF subgroups in both Stage B and C/D. IHD was inversely correlated with LVEF changes in all categories of Stage C/D, but not in Stage B (Supplemental Table 1).

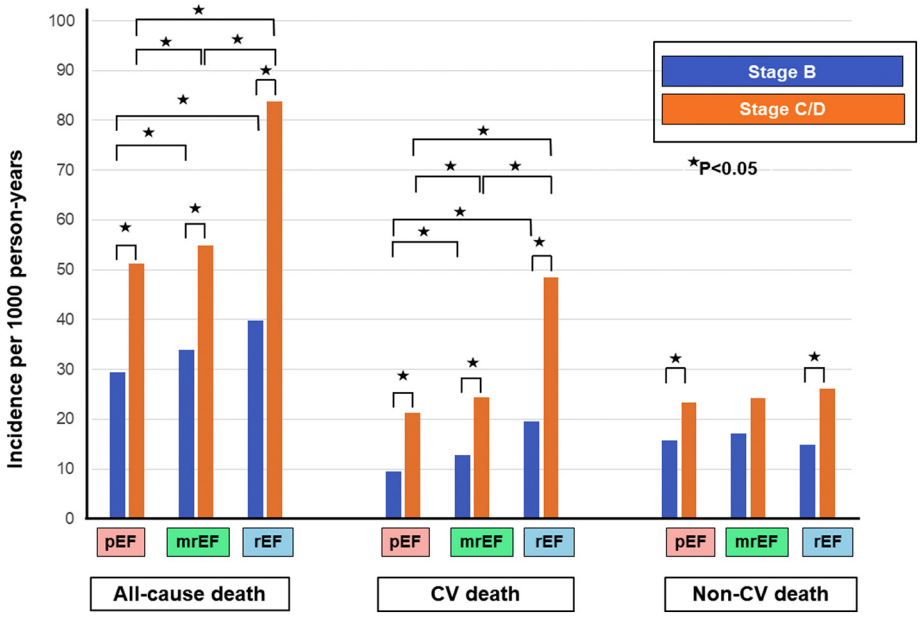

Fig. 1. Incidence rates of death stratified by LVEF in Stage B and Stage C/D. LVEF, left ventricular ejection fraction; mrEF, mid-range left ventricular ejection fraction; pEF, preserved left ventricular ejection fraction; rEF, reduced left ventricular ejection fraction.

3.4. Temporal change in LVEF and development of de-novo HF in Stage B

During the follow-up period, 415 patients in Stage B developed de-novo HF defined as HF requiring hospitaliztion after the first year during the observation period. Stage B patients who developed de-novo HF had increased incidence of death in all of pEF, mrEF and rEF as well as higher frequency of trasitions from pEF to mrEF and rEF, from mrEF to rEF, and lower frequency of transitions from mrEF to pEF and from rEF to pEF and rEF (Supplemental Figs. 3, 4F).

3.5. Association between temporal changes in LVEF and all-cause death and HF admission

In Stage B, LVEF transitions from pEF at baseline to mrEF or rEF at 1-year were significantly associated with increased 5-year mortality (to mrEF, hazard ratio (HR) (95%CI) 1.71 (1.19–2.44), $P = 0.003$; to rEF, HR 2.31 (1.15–4.64), $P = 0.019$). In Stage C/D, the transitions from any LVEF category at baseline to rEF at 1-year were associated with increased 5-year risk for all-cause death (from pEF, HR 1.32 (1.02–1.70), $P < 0.001$; from mrEF HR 1.89 (1.43–2.49), $P < 0.001$; from rEF: HR 2.07 (1.76–2.44), $P < 0.001$). LVEF transition from rEF to pEF was also associated with increased 5-year risk for all-cause death (HR 1.52 (1.14–2.04), $P = 0.004$) (Fig. 3A). Prognostic factors were comparable between Stage B and C/D patients in the pEF, mrEF and rEF subgroups (Supplemental Table 2). In Stage B pEF, LVEF transition from pEF at baseline to rEF at 1-year was significantly associated with increased 5-year risk for HF admission (HR 3.46 (1.42–8.38), $P = 0.006$) in simple Cox proportional hazard model (Fig. 3B). After adjusted for age, sex, and BNP, the transition from any LVEF category at baseline to rEF at 1-year were associated with increased 5-year risk for HF admission

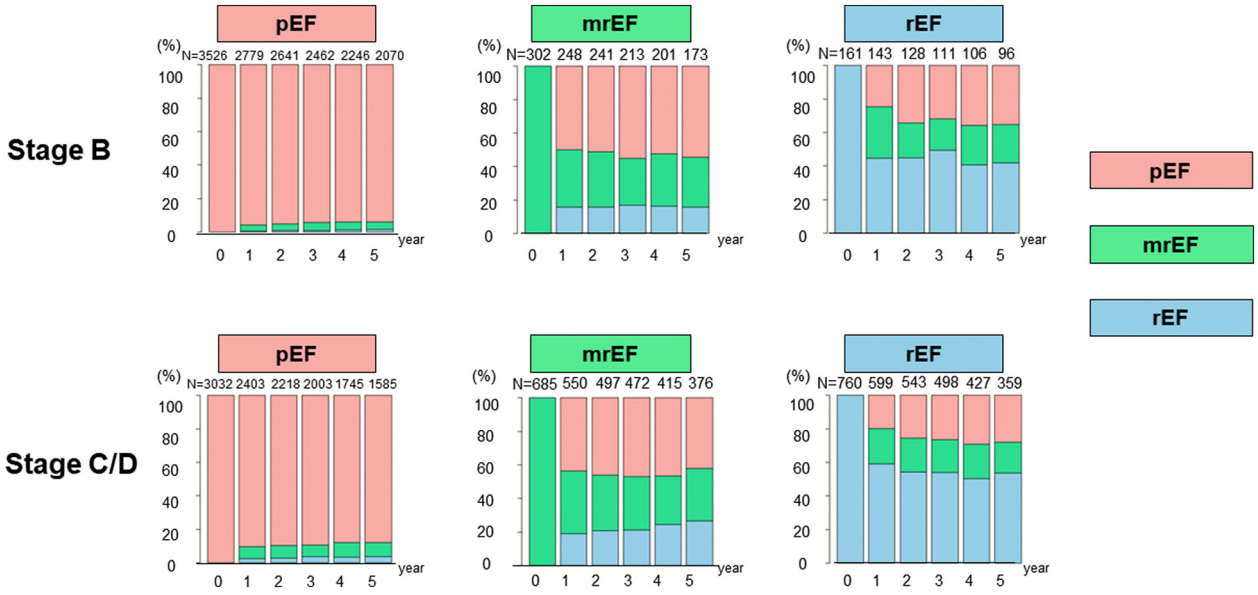

Fig. 2. Transitions of LVEF in HF patients by LVEF categories. In Stage B vs. Stage C/D. LVEF, left ventricular ejection fraction; mrEF, mid-range left ventricular ejection fraction; pEF, preserved left ventricular ejection fraction; rEF, reduced left ventricular ejection fraction.

[from pEF, HR 4.77 (1.38–11.61), $P = 0.001$; from mrEF HR 2.62 (1.16–5.90), $P = 0.020$; from rEF: HR 4.34 (2.65–7.13), $P < 0.001$].

4. Discussion

In our study, reflecting the definition of asymptomatic Stage B versus symptomatic C/D patients, Stage B patients were characterized by less severe clinical status and better prognosis than Stage C/D patients. The major findings of the present study are as follows: 1) despite the differences in clinical characteristics, both Stage B and Stage C/D patients with rEF (LVEF ≤40%) and mrEF (LVEF 41–49%) dynamically transitioned to other categories, especially within 1 year, whereas those with pEF (LVEF ≥50%) remained unchanged, and 2) LVEF decrease was directly associated with all-cause mortality in both the Stage B and Stage C/D patients in pEF, and those in Stage B, as compared with Stage C/D, while LVDd was more inversely associated with LVEF changes in rEF. These results indicate the importance of longitudinal assessment of LVEF in those patients for risk stratification. To the best of our knowledge, this is the first study that addresses the temporal changes in LVEF for 5 years in Stage B patients in comparison with Stage C/D patients.

4.1. Comparison of baseline charactreristics between Stage B and Stage C/D patients

In the present study, we compared the baseline charactristics and mortalities between Stage B and Stage C/D patients, in the same cohort, the CHART-2 Study. Compared with Stage C/D patients, those in Stage B in pEF and rEF were characterized by lower prevalence of DM and lower BNP levels (Tables 1C, 1D, 1E). In addition, the present study revealed that Stage B patients had lower incidence of CV death, especially HF death, compared with Stage C/D patients. These differences could be explained by the differences in severity of clinical status between Stages B and C/D patients and support the concept of ACCF/AHA HF staging,

Table 1A
Baseline patient characteristics.

	Stage B ($N = 4005$)				Stage C/D ($N = 4477$)			
	pEF ($N = 3526$)	mrEF ($N = 302$)	rEF ($N = 177$)	*P*-value	pEF ($N = 3032$)	mrEF ($N = 685$)	rEF ($N = 760$)	*P*-value
Age,mean (SD), y	68.5 ± 11.4	66.7 ± 11.2	66.0 ± 13.0	0.001	70.0 ± 11.7	68.6 ± 11.6	67.1 ± 12.7	<0.001
Female sex, N. (%)	1022 (29.0)	56 (18.5)	34 (19.2)	<0.001	1037 (34.2)	179 (26.1)	174 (22.9)	<0.001
BMI, mean (SD), kg/m^2	24.4 ± 3.5	24.3 ± 3.7	23.7 ± 3.4	0.036	24.1 ± 3.9	23.8 ± 3.9	23.2 ± 4.0	<0.001
Smoking, N. (%)	1621 (48.6)	148 (53.4)	92 (56.1)	0.013	1292 (45)	301 (46.7)	376 (52.6)	0.001
Previous history, N. (%)								
Hypertension	3309 (93.8)	275 (91.1)	161 (91.0)	0.060	2854 (94.1)	633 (92.4)	664 (87.4)	<0.001
Diabetes mellitus	1244 (35.3)	114 (37.7)	59 (33.3)	0.588	1212 (40.0)	281 (41.0)	328 (43.2)	0.273
Dyslipidemia	2935 (83.2)	250 (82.8)	153 (86.4)	0.536	2491 (82.2)	564 (82.3)	633 (83.3)	0.774
Stroke	684 (19.4)	58 (19.2)	31 (17.5)	0.860	632 (20.8)	150 (21.9)	143 (18.8)	0.318
AF	965 (27.4)	77 (25.5)	44 (24.9)	0.632	1284 (42.3)	274 (40.0)	285 (37.5)	0.042
Cancer	500 (14.2)	45 (14.9)	18 (10.2)	0.297	450 (14.8)	84 (12.3)	92 (12.1)	0.058
Etiology, N. (%)								
IHD	1881 (53.3)	215 (71.2)	114 (64.4)	<0.001	1565 (51.6)	380 (55.5)	390 (51.3)	0.165
HHD	928 (26.3)	40 (13.2)	19 (10.7)	<0.001	707 (23.3)	93 (13.6)	76 (10.0)	<0.001
VHD	376 (10.7)	6 (2)	12 (6.8)	<0.001	373 (12.3)	43 (6.3)	32 (4.2)	<0.001
CM	341 (9.7)	41 (13.6)	32 (18.1)	<0.001	387 (12.8)	169 (24.7)	263 (34.6)	<0.001
DCM	55 (1.6)	34 (11.3)	28 (15.8)	<0.001	233 (7.7)	148 (21.6)	244 (32.1)	<0.001
HCM	183 (5.2)	2 (0.7)	0 (0%)	<0.001	99 (3.3)	8 (1.2)	9 (1.2)	<0.001
Hemodynamics and echocardiographic findings								
Systolic BP, mmHg	131.2 ± 17.6	127.2 ± 17.2	128.2 ± 19.2	<0.001	128.9 ± 18.5	125.8 ± 18.8	118.7 ± 19.5	<0.001
Diastolic BP, mmHg	75.0 ± 11.5	74.4 ± 12.3	75.0 ± 12.0	0.712	73.0 ± 12.0	72.3 ± 12.0	70.1 ± 12.1	<0.001
Heart rate, bpm	69.6 ± 13.1	72.3 ± 15.5	72.5 ± 15.5	<0.001	71.6 ± 14.6	73.2 ± 14.7	74.0 ± 15.7	<0.001
LVEF, %	67.2 ± 8.5	45.5 ± 2.6	33.8 ± 5.7	–	65.2 ± 8.9	45.4 ± 2.7	31.8 ± 6.2	–
LVDd, mm	48.2 ± 6.4	54.6 ± 6.9	57.0 ± 9.3	<0.001	49.1 ± 7.3	55.6 ± 7.7	62.0 ± 9.2	<0.001
LAD, mm	40.1 ± 7.6	40.2 ± 7.5	41.2 ± 8.6	0.173	42.4 ± 9.1	42.6 ± 8.4	44.1 ± 8.9	<0.001
LVMI, g/m^2	126.1 ± 37.5	131.2 ± 38.0	138.7 ± 42.4	<0.001	130.7 ± 43.4	146.9 ± 46.7	162.8 ± 50.8	<0.001
Laboratory findings								
Hemoglobin, g/dL	13.6 ± 1.7	13.5 ± 1.8	13.9 ± 1.8	0.070	13.1 ± 2.0	13.2 ± 2.1	13.3 ± 2.0	0.020
BUN, mg/dL	16.9 ± 6.9	17.2 ± 7.5	17.3 ± 6.8	0.664	19.6 ± 9.6	20.4 ± 10.1	21.9 ± 12.0	<0.001
Creatinine, mg/dL	0.9 ± 0.7	1.0 ± 0.9	1.0 ± 1.0	0.039	1.0 ± 0.7	1.1 ± 0.7	1.2 ± 1.0	<0.001
Ccr, mL/min	74.1 ± 30.1	74.2 ± 29.8	72.6 ± 33.0	0.804	65.8 ± 30.1	66.0 ± 33.9	64.1 ± 33.8	0.405
Albumin, g/dL	4.2 ± 0.4	4.1 ± 0.4	4.1 ± 0.5	0.021	4.1 ± 0.5	4.0 ± 0.5	4.0 ± 0.5	0.029
Sodium, mEq/L	141.3 ± 2.5	140.9 ± 2.4	141.3 ± 2.3	0.005	141.0 ± 2.8	140.9 ± 2.8	140.4 ± 2.9	<0.001
BNP, pg/mL	52.1 (22.6, 121.1)	60.0 (24.9, 159.4)	88.6 (49.0, 169.1)	<0.001	85.4 (33.4, 190.3)	125.2(47.8, 275.5)	209.0(90.3, 453.0)	<0.001
CRP, mg/dL	0.1 (0.1, 0.3)	0.1 (0.1, 0.3)	0.1 (0.1, 0.4)	0.044	0.1 (0.1, 0.3)	0.2 (0.1, 0.4)	0.2 (0.1, 0.5)	<0.001
Medications, N. (%)								
Beta-blocker	1190 (33.7)	134 (44.4)	88 (49.7)	<0.001	1294 (42.7)	432 (63.1)	526 (69.2)	<0.001
ACE-I/ARB	2172 (61.6)	226 (74.8)	126 (71.2)	<0.001	2182 (72.0)	548 (80.0)	625 (82.2)	<0.001
Diuretic	601 (17.0)	74 (24.5)	58 (32.8)	<0.001	1521 (50.2)	451 (65.8)	615 (80.9)	<0.001
Aldosterone antagonist	143 (4.1)	23 (7.6)	17 (9.6)	<0.001	568 (18.7%)	197 (28.8)	324 (42.6)	<0.001
CCB	1857 (52.7)	114 (37.7)	60 (33.9)	<0.001	1405 (46.3%)	203 (29.6)	140 (18.4)	<0.001
Statin	1507 (42.7)	149 (49.3)	75 (42.4)	0.085	1175 (38.8%)	279 (40.7)	299 (39.3)	0.622

Results are expressed as mean ± SD or frequency (%). BNP (brain natriuretic peptide) and CRP (C reactive protein) are shown in median with interquartile range (IQR). ACE-I, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; BMI, body mass index; BP, blood pressure; BUN, blood urea nitrogen; CCB, calcium channel blocker; CM, cardiomyopathy; Ccr, creatinine clearance; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; HHD, hypertensive heart disease; IHD, ischemic heart disease; LAD, left atrial diameter; LVDd, left ventricular end-diastolic diameter; LVDs, left ventricular end-systolic diameter; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; mrEF, mid-range left ventricular ejection fraction; pEF, preserved left ventricular ejection fraction; rEF, reduced left ventricular ejection fraction; VHD, valvular heart disease.

Table 1B
Baseline patient characteristics (adjust).

	Stage B ($N = 4005$)						
	pEF ($N = 3526$)	mrEF ($N = 302$)	rEF ($N = 177$)	*P*-value	mrEFv.s.rEF adjust.*P*-value	pEFv.s.rEF. adjust.*P*-value	pEFv.s.mrEF. adjust.*P*-value
Age,mean (SD), y	68.5 ± 11.4	66.7 ± 11.2	66.0 ± 13.0	0.001	0.771	0.012	0.028
Female sex, N. (%)	1022 (29.0)	56 (18.5)	34 (19.2)	<0.001	0.904	0.009	<0.001
BMI, mean (SD), kg/m^2	24.4 ± 3.5	24.3 ± 3.7	23.7 ± 3.4	0.036	0.144	0.027	0.939
Smoking, N. (%)	1621 (48.6)	148 (53.4)	92 (56.1)	0.062	0.621	0.197	0.267
Previous history, N. (%)							
Hypertension	3309 (93.8)	275 (91.1)	161 (91.0)	0.060	>0.999	0.300	0.195
Diabetes mellitus	1244 (35.3)	114 (37.7)	59 (33.3)	0.588	>0.999	>0.999	>0.999
Dyslipidemia	2935 (83.2)	250 (82.8)	153 (86.4)	0.536	0.903	0.903	0.903
Stroke	684 (19.4)	58 (19.2)	31 (17.5)	0.860	>0.999	>0.999	>0.999
AF	965 (27.4)	77 (25.5)	44 (24.9)	0.632	>0.999	>0.999	>0.999
Cancer	500 (14.2)	45 (14.9)	18 (10.2)	0.297	0.447	0.447	0.731
Etiology, N. (%)							
IHD	1881 (53.3)	215 (71.2)	114 (64.4)	<0.001	0.127	0.008	<0.001
HHD	928 (26.3)	40 (13.2)	19 (10.7)	<0.001	0.473	<0.001	<0.001
VHD	376 (10.7)	6 (2.0)	12 (6.8)	<0.001	0.023	0.103	<0.001
CM	341 (9.7)	41 (13.6)	32 (18.1)	<0.001	0.190	0.002	0.071
DCM	55 (1.6)	34 (11.3)	28 (15.8)	<0.001	0.160	<0.001	<0.001
HCM	183 (5.2)	2 (0.7)	0 (0)	<0.001	0.533	<0.001	<0.001
Hemodynamics and echocardiographic findings							
Systolic BP, mmHg	131.2 ± 17.6	127.2 ± 17.2	128.2 ± 19.2	<0.001	0.832	0.062	<0.001
Diastolic BP, mmHg	75.0 ± 11.5	74.4 ± 12.3	75.0 ± 12.0	0.712	0.847	0.999	0.690
Heart rate, bpm	69.6 ± 13.1	72.3 ± 15.5	72.5 ± 15.5	<0.001	0.992	0.017	0.002
LVEF, %	67.2 ± 8.5	45.5 ± 2.6	33.8 ± 5.7	–	–	–	–
LVDd, mm	48.2 ± 6.4	54.6 ± 6.9	57.0 ± 9.3	<0.001	0.001	<0.001	<0.001
LAD, mm	40.1 ± 7.6	40.2 ± 7.5	41.2 ± 8.6	0.173	0.346	0.147	0.976
LVMI, g/m^2	126.1 ± 37.5	131.2 ± 38.0	138.7 ± 42.4	<0.001	0.105	<0.001	0.074
Laboratory findings							
Hemoglobin, g/dL	13.6 ± 1.7	13.5 ± 1.8	13.9 ± 1.8	0.070	0.084	0.070	0.857
BUN, mg/dL	16.9 ± 6.9	17.2 ± 7.5	17.3 ± 6.8	0.664	0.966	0.736	0.842
Creatinine, mg/dL	0.93 ± 0.7	1.0 ± 0.9	1.0 ± 1.0	0.039	0.955	0.160	0.142
Ccr, mL/min	74.1 ± 30.1	74.2 ± 29.8	72.6 ± 33.0	0.804	0.832	0.792	0.997
Albumin, g/dL	4.2 ± 0.4	4.1 ± 0.4	4.1 ± 0.5	0.021	0.453	0.781	0.017
Sodium, mEq/L	141.3 ± 2.5	140.9 ± 2.4	141.3 ± 2.3	0.005	0.092	0.999	0.004
BNP, pg/mL	52.1 (22.6, 121.1)	60.0 (24.9, 159.4)	88.6 (49.0, 169.1)	<0.001	0.007	<0.001	0.099
CRP, mg/dL	0.1 (0.1, 0.3)	0.1 (0.1, 0.3)	0.1 (0.1, 0.4)	0.044	0.988	0.212	0.125
Medications, N. (%)							
Beta-blocker	1190 (33.7)	134 (44.4)	88 (49.7)	<0.001	0.296	<0.001	<0.001
ACE-I/ARB	2172 (61.6)	226 (74.8)	126 (71.2)	<0.001	0.393	0.022	<0.001
Diuretic	601 (17.0)	74 (24.5)	58 (32.8)	<0.001	0.057	<0.001	0.003
Aldosterone antagonist	143 (4.1)	23 (7.6)	17 (9.6)	<0.001	0.495	0.005	0.014
CCB	1857 (52.7)	114 (37.7)	60 (33.9)	<0.001	0.432	<0.001	<0.001
Statin	1507 (42.7)	149 (49.3)	75 (42.4)	0.085	0.310	0.938	0.088
	Stage C/D ($N = 4477$)						
	pEF ($N = 3032$)	mrEF ($N = 685$)	rEF ($N = 760$)	*P*-value	mrEFv.s.rEF. adjust.*P*-value	pEFv.s.rEF. adjust.*P*-value	pEFv.s.mrEF. adjust.*P*-value
Age,mean (SD), y	70.0 ± 11.7	68.6 ± 11.6	67.1 ± 12.7	<0.001	0.059	<0.001	0.012
Female sex, N. (%)	1037 (34.2)	179 (26.1)	174 (22.9)	<0.001	0.159	<0.001	<0.001
BMI, mean (SD), kg/m^2	24.1 ± 3.9	23.8 ± 3.9	23.2 ± 4.0	<0.001	0.005	<0.001	0.274
Smoking, N. (%)	1292 (45.0)	301 (46.7)	376 (52.6)	0.001	0.060	0.001	0.457
Previous history, N. (%)							
Hypertension	2854 (94.1)	633 (92.4)	664 (87.4)	<0.001	0.003	<0.001	0.095
Diabetes mellitus	1212 (40.0)	281 (41.0)	328 (43.2)	0.273	0.848	0.350	0.848
Dyslipidemia	2491 (82.2)	564 (82.3)	633 (83.3)	0.774	>0.999	>0.999	>0.999
Stroke	632 (20.8)	150 (21.9)	143 (18.8)	0.318	0.450	0.455	0.534
AF	1284 (42.3)	274 (40.0)	285 (37.5)	0.042	0.531	0.045	0.531
Cancer	450 (14.8)	84 (12.3)	92 (12.1)	0.058	0.936	0.167	0.182
Etiology, N. (%)							
IHD	1565 (51.6)	380 (55.5)	390 (51.3)	0.165	0.251	0.903	0.206
HHD	707 (23.3)	93 (13.6)	76 (10.0)	<0.001	0.040	<0.001	<0.001
VHD	373 (12.3)	43 (6.3)	32 (4.2)	<0.001	0.096	<0.001	<0.001
CM	387 (12.8)	169 (24.7)	263 (34.6)	<0.001	<0.001	<0.001	<0.001
DCM	233 (7.7)	148 (21.6)	244 (32.1)	<0.001	<0.001	<0.001	<0.001
HCM	99 (3.3)	8 (1.2)	9 (1.2)	<0.001	>0.999	0.004	0.004

(continued on next page)

Table 1B (*continued*)

	Stage C/D ($N = 4477$)						
	pEF ($N = 3032$)	mrEF ($N = 685$)	rEF ($N = 760$)	*P*-value	mrEFv.s.rEF. adjust.*P*-value	pEFv.s.rEF. adjust.*P*-value	pEFv.s.mrEF. adjust.*P*-value
Hemodynamics and echocardiographic findings							
Systolic BP, mmHg	128.9 ± 18.5	125.8 ± 18.8	118.7 ± 19.5	<0.001	<0.001	<0.001	<0.001
Diastolic BP, mmHg	73.0 ± 12.0	72.3 ± 12.0	70.1 ± 12.1	<0.001	0.002	<0.001	0.360
Heart rate, bpm	71.6 ± 14.6	73.2 ± 14.7	74.0 ± 15.7	<0.001	0.515	<0.001	0.039
LVEF, %	65.2 ± 8.9	45.4 ± 2.7	31.8 ± 6.2	–	–	–	–
LVDd, mm	49.1 ± 7.3	55.6 ± 7.7	62.0 ± 9.2	<0.001	<0.001	<0.001	<0.001
LAD, mm	42.4 ± 9.1	42.6 ± 8.4	44.1 ± 8.9	<0.001	0.005	<0.001	0.732
LVMI, g/m^2	130.7 ± 43.4	146.9 ± 46.7	162.8 ± 50.8	<0.001	<0.001	<0.001	<0.001
Laboratory findings							
Hemoglobin, g/dL	13.1 ± 2.0	13.2 ± 2.1	13.3 ± 2.0	0.020	0.461	0.017	0.489
BUN, mg/dL	19.6 ± 9.6	20.4 ± 10.1	21.9 ± 12.0	<0.001	0.014	<0.001	0.159
Creatinine, mg/dL	1.0 ± 0.7	1.1 ± 0.7	1.2 ± 1.0	<0.001	0.050	<0.001	0.260
Ccr, mL/min	65.8 ± 30.1	66.0 ± 33.9	64.1 ± 33.8	0.405	0.490	0.415	0.977
Albumin, g/dL	4.1 ± 0.5	4.0 ± 0.5	4.0 ± 0.5	0.029	0.758	0.035	0.322
Sodium, mEq/L	141.0 ± 2.8	140.9 ± 2.8	140.4 ± 2.9	<0.001	0.004	<0.001	0.265
BNP, pg/mL	85.4(33.4, 190.3)	125.2(47.8, 275.5)	209.0 (90.3, 453.0)	<0.001	<0.001	<0.001	<0.001
CRP, mg/dL	0.1 (0.1, 0.3)	0.2 (0.1, 0.4)	0.2 (0.1, 0.5)	<0.001	0.341	0.001	0.212
Medications, N. (%)							
Beta-blocker	1294 (42.7)	432 (63.1)	526 (69.2)	<0.001	0.014	<0.001	<0.001
ACE-I/ARB	2182 (72.0)	548 (80.0)	625 (82.2)	<0.001	0.299	<0.001	<0.001
Diuretic	1521 (50.2)	451 (65.8)	615 (80.9)	<0.001	<0.001	<0.001	<0.001
Aldosterone antagonist	568 (18.7)	197 (28.8)	324 (42.6)	<0.001	<0.001	<0.001	<0.001
CCB	1405 (46.3)	203 (29.6)	140 (18.4)	<0.001	<0.001	<0.001	<0.001
Statin	1175 (38.8)	279 (40.7)	299 (39.3)	0.622	>0.999	>0.999	>0.999

Results are expressed as mean ± SD or frequency (%). BNP (brain natriuretic peptide) and CRP (C reactive protein) are shown in median with interquartile range (IQR).
ACE-I, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; BMI, body mass index; BP, blood pressure; BUN, blood urea nitrogen; CCB, calcium channel blocker; CM, cardiomyopathy; Ccr, creatinine clearance; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; HHD, hypertensive heart disease; IHD, ischemic heart disease; LAD, left atrial diameter; LVDd, left ventricular end-diastolic diameter; LVDs, left ventricular end-systolic diameter; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; mrEF, mid-range left ventricular ejection fraction; pEF, preserved left ventricular ejection fraction; rEF, reduced left ventricular ejection fraction; VHD, valvular heart disease.

highllighing the importance of prevention and treatment at early stages [16].

BNP is an established marker that may reflect the severity of CVD [17,18]. We previously reported that BNP levels have comparable prognostic impacts among HFpEF, borderline HFpEF, and HFrEF patients [17]. Furthermore, Kotecha et al. reported that BNP levels can independently identify patients with subtle impairment of cardiac function [18]. In the present study, Stage B patients in each LVEF category had lower BNP levels than those in Stage C/D, which could be another explanation for the difference in the long-term prognosis between the 2 stages. The Stage B patients were also characterized by younger age and higher albumin levels compared with Stage C/D patients, suggesintg the importance of assessment of general status in HF [19,20]. Indeed, severel studies showed the usufulness of assessment of nutrition by Geriatric Nutritional Risk Index (GNRI) in Stage B patients [19,21].

DM also increases the risk of development of HF in Stage B patients [9,22], and is a strong prognostic factor in Stage C patients [23]. A privous report from the CHARM programme showed that DM was associated with a higher risk of CV death and non-CV death, particularly in patients with pEF [23]. Indeed, among the pEF population in the present study, baseline prevalence of diabetes and atrial fibrillation was lower in Stage B than in Stage C/D (Table 1C). Furthermore, baseline BNP levels were lower in Stage B than in Stage C/D. In this study, the lack of significant interaction for BNP in the mrEF and rEF groups may have been due to the limited sample size rather than due to similarities in the magnitude of the association between BNP and the outcome. The patients in Stage B had lower prevalence of diabetes and atrial fibrillation as well as lower incidence of CV death including HF death, compared to those in Stage C/D. These results may indicate the importance of prevention and early treatment for diabetes and atrial fibrillation among Stage B patients.

4.2. Mortality rates and causes of deaths by LVEF in Stage B patients

In the present study, we further examined the mode of death in Stage B patients stratified by LVEF at baseline compared with those in Stage C/D. Stage B patients had lower event rates across all mode of deaths compared with Stage C/D patients. In addition, the present study revealed that Stage B patients had lower incidence of CV death, especially HF death, than Stage C/D patients. However, it should be notecd that, even in Stage B, mortality was still high, particularly in the rEF subpopulation. Hobbs et al. reported that patients with borderline LV systolic function (LVEF 40–50%) on echocardiography had a poor prognosis in the community-based study [24]. Echouffo-Tcheugui et al. also reported that asymptomatic LV systolic or diastolic dysfunction increased the risk of progression to overt HF [25]. These lines of evidence indicate that LVEF at baseline is a strong predictor for death in patients with high risk for HF [24,25], suggesting the importance of initial assessment of LVEF in Stage B patients.

4.3. Temporal changes in LVEF in Stage B and C/D

We further examined the temporal changes in LVEF for 5 years in Stage B and C/D patients in our CHART-2 Study, in the wide range of baseline LVEF. The present findings indicate that Stage B patients with rEF or mrEF dynamically transition to other categories, especially within 1 year, whereas those with pEF remain unchanged. Although there were some differences in LVEF changes between Stage B and Stage C/D patients in pEF subpoplulation, we consider that this trend in temporal LVEF changes in Stage B was almost comparable to that in Stage C/D patients in the present study. Since it also has been reported that patients with incident or new-onset HF experience dynamic LVEF changes during follow-up [26,27], it can be concluded that LVEF dramatically changes over time not only in Stage C/D [9] but also in Stage B.

Table 1C
Baseline patient characteristics (pEF: Stage B v.s. Stage C/D).

pEF	Stage B	Stage C/D	*P*-value
	pEF ($N = 3526$)	pEF ($N = 3032$)	
Age,mean (SD), y	68.5 ± 11.4	70.0 ± 11.7	<0.001
Female sex, N. (%)	1022 (29.0)	1037 (34.2)	<0.001
BMI, mean (SD), kg/m^2	24.4 ± 3.5	24.1 ± 3.9	<0.001
Smoking, N. (%)	1621 (48.6)	1292 (45.0)	0.005
Previous history, N. (%)			
Hypertension	3309 (93.8)	2854 (94.1)	0.640
Diabetes mellitus	1244 (35.3)	1212 (40.0)	<0.001
Dyslipidemia	2935 (83.2)	2491 (82.2)	0.252
Stroke	684 (19.4)	632 (20.8)	0.146
AF	965 (27.4)	1284 (42.3)	<0.001
Cancer	500 (14.2)	450 (14.8)	0.460
Etiology, N. (%)			
IHD	1881 (53.3)	1565 (51.6)	0.165
HHD	928 (26.3)	707 (23.3)	0.005
VHD	376 (10.7)	373 (12.3)	0.039
CM	341 (9.7)	387 (12.8)	<0.001
DCM	55 (1.6)	233 (7.7)	<0.001
HCM	183 (5.2)	99 (3.3)	<0.001
Hemodynamics and echocardiographic findings			
Systolic BP, mmHg	131.2 ± 17.6	128.9 ± 18.5	<0.001
Diastolic BP, mmHg	75.0 ± 11.5	73.0 ± 12.0	<0.001
Heart rate, bpm	69.6 ± 13.1	71.6 ± 14.6	<0.001
LVEF, %	67.2 ± 8.5	65.2 ± 8.9	<0.001
LVDd, mm	48.2 ± 6.4	49.1 ± 7.3	<0.001
LAD, mm	40.1 ± 7.6	42.4 ± 9.1	<0.001
LVMI, g/m^2	126.1 ± 37.5	130.7 ± 43.4	<0.001
Laboratory findings			
Hemoglobin, g/dL	13.6 ± 1.7	13.1 ± 2.0	<0.001
BUN, mg/dL	16.9 ± 6.9	19.6 ± 9.6	<0.001
Creatinine, mg/dL	0.9 ± 0.7	1.0 ± 0.7	<0.001
Ccr, mL/min	74.1 ± 30.1	65.8 ± 30.1	<0.001
Albumin, g/dL	4.2 ± 0.4	4.1 ± 0.5	<0.001
Sodium, mEq/L	141.3 ± 2.5	141.0 ± 2.8	<0.001
BNP, pg/mL	52.1 (22.6, 121.1)	85.4 (33.4, 190.3)	<0.001
CRP, mg/dL	0.1 (0.1, 0.3)	0.1 (0.1, 0.3)	<0.001
Medications, N. (%)			
Beta-blocker	1190 (33.7)	1294 (42.7)	<0.001
ACE-I/ARB	2172 (61.6)	2182 (72.0)	<0.001
Diuretic	601 (17.0)	1521 (50.2)	<0.001
Aldosterone antagonist	143 (4.1)	568 (18.7)	<0.001
CCB	1857 (52.7)	1405 (46.3)	<0.001
Statin	1507 (42.7)	1175 (38.8)	0.001

Table 1D
Baseline patient characteristics (mrEF: Stage B v.s. Stage C/D).

mrEF	Stage B	Stage C/D	*P*-value
	mrEF ($N = 302$)	mrEF ($N = 685$)	
Age,mean (SD), y	66.7 ± 11.2	68.6 ± 11.6	0.018
Female sex, N. (%)	56 (18.5)	179 (26.1)	0.010
BMI, mean (SD), kg/m^2	24.3 ± 3.7	23.8 ± 3.9	0.051
Smoking, N. (%)	148 (53.4)	301 (46.7)	0.062
Previous history, N. (%)			
Hypertension	275 (91.1)	633 (92.4)	0.525
Diabetes mellitus	114 (37.7)	281 (41.0)	0.360
Dyslipidemia	250 (82.8)	564 (82.3)	0.928
Stroke	58 (19.2)	150 (21.9)	0.353
AF	77 (25.5)	274 (40.0)	<0.001
Cancer	45 (14.9)	84 (12.3)	0.261
Etiology, N. (%)			
IHD	215 (71.2)	380 (55.5)	<0.001
HHD	40 (13.2)	93 (13.6)	0.920
VHD	6 (2.0)	43 (6.3)	0.004
CM	41 (13.6)	169 (24.7)	<0.001
DCM	34 (11.3)	148 (21.6)	<0.001
HCM	2 (0.7)	8 (1.2)	0.732
Hemodynamics and echocardiographic findings			
Systolic BP, mmHg	127.2 ± 17.2	125.8 ± 18.8	0.247
Diastolic BP, mmHg	74.4 ± 12.3	72.3 ± 12.0	0.011
Heart rate, bpm	72.3 ± 15.5	73.2 ± 14.7	0.434
LVEF, %	45.5 ± 2.6	45.4 ± 2.7	0.667
LVDd, mm	54.6 ± 6.9	55.6 ± 7.7	0.051
LAD, mm	40.2 ± 7.5	42.6 ± 8.4	<0.001
LVMI, g/m^2	131.2 ± 38.0	146.9 ± 46.7	<0.001
Laboratory findings			
Hemoglobin, g/dL	13.5 ± 1.8	13.2 ± 2.1	0.010
BUN, mg/dL	17.2 ± 7.5	20.4 ± 10.1	<0.001
Creatinine, mg/dL	1.0 ± 0.9	1.1 ± 0.7	0.244
Ccr mL/min	74.23 ± 29.76	66.0 ± 33.9	<0.001
Albumin, g/dL	4.1 ± 0.4	4.0 ± 0.5	0.325
Sodium, mEq/L	140.9 ± 2.4	140.9 ± 2.8	0.995
BNP, pg/mL	60.0 (24.9, 159.4)	125.2 (47.8, 275.5)	<0.001
CRP, mg/dL	0.1 (0.1, 0.3)	0.2 (0.1, 0.4)	0.523
Medications, N. (%)			
Beta-blocker	134 (44.4)	432 (63.1)	<0.001
ACE-I/ARB	226 (74.8)	548 (80.0)	0.078
Diuretic	74 (24.5)	451 (65.8)	<0.001
Aldosterone antagonist	23 (7.6)	197 (28.8)	<0.001
CCB	114 (37.7)	203 (29.6)	0.015
Statin	149 (49.3)	279 (40.7)	0.012

During the follow-up period, 10.4% of Stage B patients developed de-novo HF, defined as HF requiring hospitalization. As compared with Stage B patients without de-novo HF, those with de-novo HF were older and had higher baseline BNP levels. Furthermore, among the Stage B patients in rEF, those with de-novo HF after 1-year showed less LVEF increase from baseline to 1-year. Thus, among the Stage B patients, the extent of temporal LVEF changes could affect subsequent development of de-novo HF, underlying the importance of LVEF management in Stage B patients to prevent de-novo HF, particularly for those in rEF.

4.4. Association between temporal changes in LVEF and all-cause death and HF admission in the Stage B and Stage C/D

We and others have shown that reduction in LVEF in HF patients was strongly associated with higher mortality [10,28,29]. In Stage B patients, decreased LVEF indicates heightened risk of HF admission suggesting that the change of LVEF is a significant maker to predict the development for HF. We further examined the prognostic impacts of temporal changes in LVEF in patients at risk for HF in Stage B. The present study demonstrated that, as in Stage C/D HF, decrease in LVEF at 1-year was associated with higher events of CV deaths including HF death and sudden deaths in Stage B patients, a similary finding with a previous study for Stage C/D [30]. This finding underlines the importance of longitudinal assessment by echocardiography even in Stage B patients with preserved LVEF at baseline. Brian et al. reported that, among the patients with dilated cardiomyopathy whose HF symptoms and cardiac dysfunction had recovered, HF symptoms and cardiac dysfunction were significantly worsened in the treatment withdrawal group, indicating that early and continuous intervention with cardioprotective medications may prevent the onset of HF among Stage B patients [31].

4.5. Factors related to LVEF changes in each LVEF category in Stage B and Stage C/D

We further examined the factors related to LVEF changes in each LVEF category. We found that, IHD was significantly associated with temporal LVEF changes in Stage C/D patients. This finding with Stage B patients is in contrast to the previous reports with Stage C/D HF that demonstrated that IHD was inversely associated with LVEF changes in HF patients, particularly those with HFrEF [10,26,32]. Thus, it remains to be examined whether IHD are associated with LVEF changes in future studies. Contrary to and IHD, LVDd was significantly associated with

Table 1E
Baseline patient characteristics (rEF: Stage B v.s. Stage C/D).

rEF	Stage B	Stage C/D	*P*-value
	rEF ($N = 177$)	rEF ($N = 760$)	
Age,mean (SD), y	66.0 ± 13.0	67.1 ± 12.7	0.282
Female sex, N. (%)	34 (19.2)	174 (22.9)	0.316
BMI, mean (SD), kg/m^2	23.7 ± 3.4	23.2 ± 4.0	0.071
Smoking, N. (%)	92 (56.1)	376 (52.6)	0.436
Previous history, N. (%)			
Hypertension	161 (91.0)	664 (87.4)	0.200
Diabetes mellitus	59 (33.3)	328 (43.2)	0.018
Dyslipidemia	153 (86.4)	633 (83.3)	0.364
Stroke	31 (17.5)	143 (18.8)	0.748
AF	44 (24.9)	285 (37.5)	0.002
Cancer	18 (10.2)	92 (12.1)	0.519
Etiology, N. (%)			
IHD	114 (64.4)	390 (51.3)	0.002
HHD	19 (10.7)	76 (10.0)	0.782
VHD	12 (6.8)	32 (4.2)	0.166
CM	32 (18.1)	263 (34.6)	<0.001
DCM	28 (15.8)	244 (32.1)	<0.001
HCM	0 (0)	9 (1.2)	0.221
Hemodynamics and echocardiographic findings			
Systolic BP, mmHg	128.2 ± 19.2	118.7 ± 19.5	<0.001
Diastolic BP, mmHg	75.0 ± 12.0	70.1 ± 12.1	<0.001
Heart rate, bpm	72.5 ± 15.5	74.0 ± 15.7	0.243
LVEF, %	33.8 ± 5.7	31.8 ± 6.2	<0.001
LVDd, mm	57.0 ± 9.3	62.0 ± 9.2	<0.001
LAD, mm	41.2 ± 8.6	44.1 ± 8.9	<0.001
LVMI, g/m^2	138.7 ± 42.4	162.8 ± 50.8	<0.001
Laboratory findings			
Hemoglobin, g/dL	13.9 ± 1.8	13.3 ± 2.0	<0.001
BUN, mg/dL	17.3 ± 6.8	21.9 ± 12.0	<0.001
Creatinine, mg/dL	1.0 ± 1.0	1.2 ± 1.0	0.067
Ccr, mL/min	72.6 ± 33.0	64.1 ± 33.8	0.003
Albumin, g/dL	4.1 ± 0.5	4.0 ± 0.5	0.012
Sodium, mEq/L	141.3 ± 2.3	140.4 ± 2.9	<0.001
BNP, pg/mL	88.6 (49.0, 169.1)	209.0 (90.3, 453.0)	<0.001
CRP, mg/dL	0.1 (0.1, 0.4)	0.2 (0.1, 0.5)	0.203
Medications, N. (%)			
Beta-blocker	88 (49.7)	526 (69.2)	<0.001
ACE-I/ARB	126 (71.2)	625 (82.2)	0.002
Diuretic	58 (32.8)	615 (80.9)	<0.001
Aldosterone antagonist	17 (9.6)	324 (42.6)	<0.001
CCB	60 (33.9)	140 (18.4)	<0.001
Statin	75 (42.4)	299 (39.3)	0.496

Results are expressed as mean ± SD or frequency (%). BNP (brain natriuretic peptide) and CRP (C reactive protein) are shown in median with interquartile range (IQR). ACE-I, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; BMI, body mass index; BP, blood pressure; BUN, blood urea nitrogen; CCB, calcium channel blocker; CM, cardiomyopathy; Ccr, creatinine clearance; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; HHD, hypertensive heart disease; IHD, ischemic heart disease; LAD, left atrial diameter; LVDd, left ventricular end-diastolic diameter; LVDs, left ventricular end-systolic diameter; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; mrEF, mid-range left ventricular ejection fraction; pEF, preserved left ventricular ejection fraction; rEF, reduced left ventricular ejection fraction; VHD, valvular heart disease.

LVEF changes in Stage B patients with mrEF and rEF. This finding was consistent wth the report by Yeboach et al., in which both pEF and rEF patients with dilated LV had worse prognosis compared with pEF patients with normal-size LV [33]. Thus, longitudinal assessment of LV size may also be important for better management of Stage B patients.

4.6. Study limitations

Several limitations should be mentioned for the present study. First, LVEF was measured at each participating hospital that may have caused under- or over-estimation of LVEF. Second, since our CHART-2 Study is an observational study in Japan, caution is needed when generalizing the data to other patient populations. Third, since the diagnosis and etiologies of HF were determined by attending physicians, there might have been some inter-physician/facility biases. In addition, although we employed strict inclusion and exclusion criteria for Stage B and Stage C patients, some asymptomatic patients with preserved LVEF could have been overlooked. Fourth, relatively small sample sizes in Stage B mrEF and rEF might have limited the statistical power to evaluate prognostic significance of clinical confounders for LVEF. Fifth, since the CHART-2 Study enrolled only Japanese patients, further studies are warranted to comfirm our findings in the western populations. However, since data on etiologies were collected prospectively at enrollment without knowledge of outcomes of patients, assignment bias may be minimal. Furthermore, in this study we have enrolled Stage B patients only with IHD, VHD, HHD, or CM, limiting the influence of heterogeneity of Stage B patients.

5. Conclusions

In the present study, we were able to demonstrate that in Stage B patients, as in Stage C/D patients, LVEF dynamically changes over time. Decrease or stable low LVEF were associated with heighten risk of all-cause death or HF hospitalization in Stage B and Stage C/D while LVDd was more inversely associated with LVEF changes in rEF, warranting importance of longitudinal assessment of LVEF for better management of Stage B patients.

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CRediT authorship contribution statement

Hajime Aoyanagi: Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation, Writing - original draft, Visualization. **Kotaro Nochioka:**Methodology, Software, Validation, Formal analysis, Writing - review & editing, Visualization. **Yasuhiko Sakata:** Methodology, Writing - review & editing, Project administration. **Masanobu Miura:**Writing - review & editing. **Takashi Shiroto:**Writing - review & editing. **Ruri Abe:**Investigation, Resources, Data curation. **Shintaro Kasahara:**Investigation, Resources, Data curation. **Masayuki Sato:**Investigation, Resources, Data curation. **Takahide Fujihashi:**Investigation, Resources, Data curation. **Shinsuke Yamanaka:**Investigation, Resources, Data curation. **Hideka Hayashi:**Investigation, Resources, Data curation. **Koichiro Sugimura:**Writing - review & editing. **Jun Takahashi:**Writing - review & editing. **Satoshi Miyata:**Software, Validation, Formal analysis. **Hiroaki Shimokawa:**Conceptualization, Supervision, Funding acquisition.

Declaration of competing interest

All authors declare no competing interests for the present study. Conflict of interests is shown in Supplemental files.

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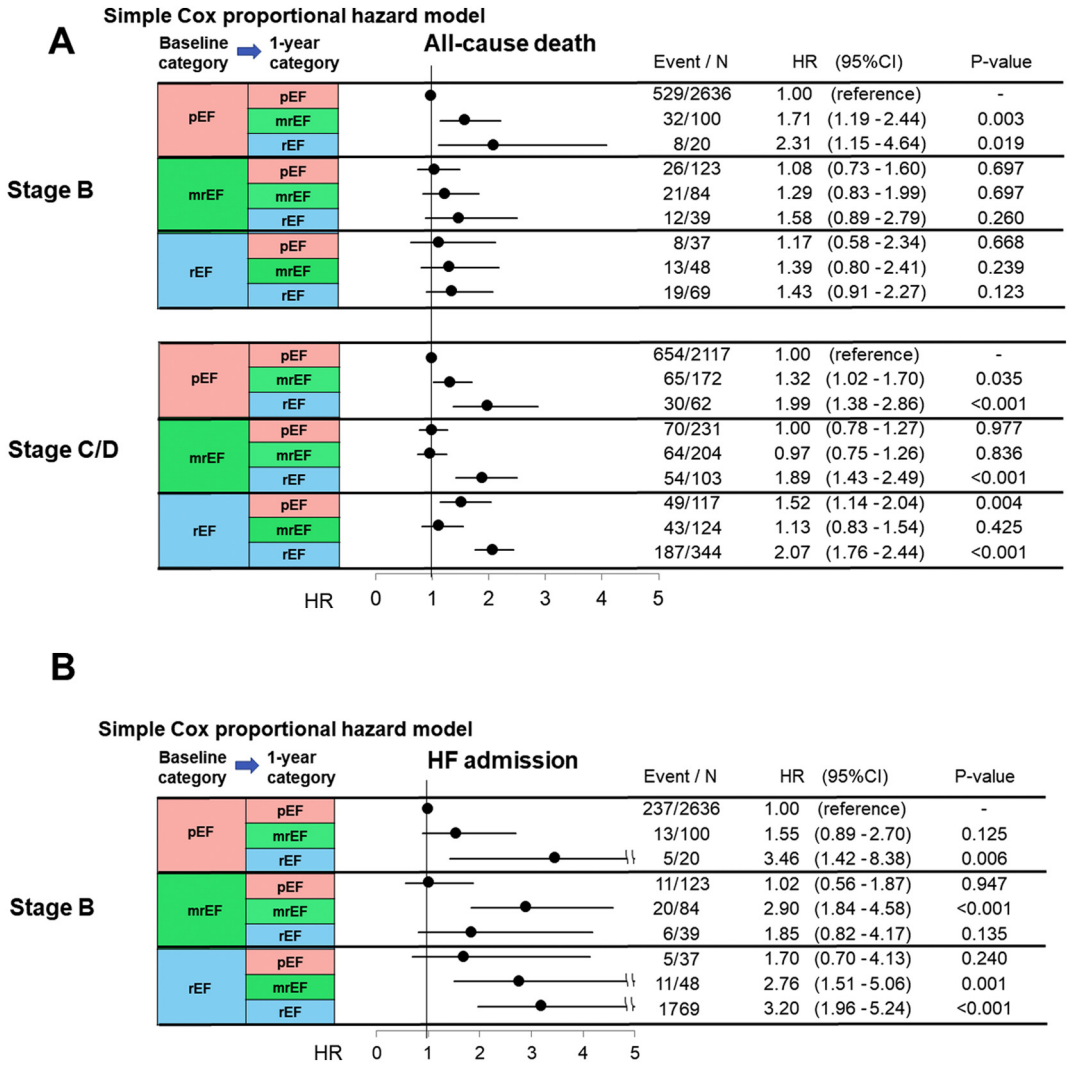

Fig. 3. Prognostic impacts of transitions of LVEF categories from baseline to 1-year. (A) All-cause death, (B) HF admission. CI, confidence interval; HF, heart failure; HR, hazard ratio; LVEF, left ventricular ejection fraction; mrEF, mid-range left ventricular ejection fraction; pEF, preserved left ventricular ejection fraction; rEF, reduced left ventricular ejection fraction.

Contributors

Contributors is shown in Supplemental files.

References

[1] A.P. Ambrosy, G.C. Fonarow, J. Butler, O. Chioncel, S.J. Greene, M. Vaduganathan, et al., The global health and economic burden of hospitalizations for heart failure: lessons learned from hospitalized heart failure registries, J. Am. Coll. Cardiol. 63 (2014) 1123–1133.

[2] E.J. Benjamin, P. Muntner, A. Alonso, M.S. Bittencourt, C.W. Callaway, A.P. Carson, et al., Heart disease and stroke statistics-2019 update: a report from the American Heart Association, Circulation 139 (2019) e56–528.

[3] S.A. Hunt, W.T. Abraham, M.H. Chin, A.M. Feldman, G.S. Francis, T.G. Ganiats, et al., ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure): developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the Heart Rhythm Society, Circulation 112 (2005) e154–e235.

[4] C.W. Yancy, M. Jessup, B. Bozkurt, J. Butler, D.E. Casey Jr., et al., ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines, Circulation 128 (2013) (2013) e240–e327.

[5] L.R. Goldberg, M. Jessup, Stage B heart failure, Circulation 113 (2006) 2851–2860.

[6] T.J. Wang, J.C. Evans, E.J. Benjamin, D. Levy, E.C. LeRoy, R.S. Vasan, Natural history of asymptomatic left ventricular systolic dysfunction in the community, Circulation 108 (2003) 977–982.

[7] Desta L, Jernberg T, Spaak J, Hofman-Bang C, Persson H. Heart failure with normal ejection fraction is uncommon in acute myocardial infarction settings but associated with poor outcomes: a study of 91,360 patients admitted with index myocardial infarction between 1998 and 2010. Eur J Heart Fail. 18 (2016) 46–53.

[8] J. Yeboah, C.J. Rodriguez, B. Stacey, J.A. Lima, S. Liu, J.J. Carr, et al., Prognosis of individuals with asymptomatic left ventricular systolic dysfunction in the multi-ethnic study of atherosclerosis (MESA), Circulation 126 (2012) 2713–2719.

[9] Takada T, Sakata Y, Nochioka K, Miura M, Aoyanagi H, Shimokawa H, et al. Risk of de-novo heart failure and competing risk in asymptomatic patients with structural heart diseases. Int. J. Cardiol. (2020) (in press).

[10] K. Tsuji, Y. Sakata, K. Nochioka, M. Miura, T. Yamauchi, H. Shimokawa, et al., Characterization of heart failure patients with mid-range left ventricular ejection fraction-a report from the CHART-2 Study, Eur. J. Heart Fail. 19 (2017) 1258–1269.

[11] N. Shiba, K. Nochioka, M. Miura, H. Kohno, H. Shimokawa, Trend of westernization of etiology and clinical characteristics of heart failure patients in Japan, Circ. J. 75 (2011) 823–833.

[12] K. Nochioka, Y. Sakata, J. Takahashi, S. Miyata, M. Miura, H. Shimokawa, et al., Prognostic impact of nutritional status in asymptomatic patients with cardiac diseases, Circ. J. 77 (2013) 2318–2326.

[13] M. Donald, Lloyd-Jones. The risk of congestive heart failure: sobering lessons from the Framingham heart study, Curr. Cardiol. Rep. 3 (2001) 184–190.

[14] Myles Hollander, Douglas A Wolfe, Eric Chicken. Nonparametric Statistical Methods, 3rd ed. 848.

[15] S.I. Vrieze, Model selection and psychological theory: a discussion of the differences between the Akaike information criterion (AIC) and the Bayesian information criterion (BIC), Psychol. Methods 17 (2012) 228–243.

[16] K.A. Ammar, S.J. Jacobsen, D.W. Mahoney, J.A. Kors, M.M. Redfield, J.C. Burnett Jr., et al., Prevalence and prognostic significance of heart failure stages: application of the American College of Cardiology/American Heart Association heart failure staging criteria in the community, Circulation 115 (2007) 1563–1570.

[17] S. Kasahara, Y. Sakata, K. Nochioka, T. Yamauchi, T. Onose, K. Tsuji, et al., Comparable prognostic impact of BNP levels among HFpEF, Borderline HFpEF and HFrEF: a report from the CHART-2 Study, Heart Vessel. 33 (2018) 997–1007.
[18] D. Kotecha, M.D. Flather, D. Atar, P. Collins, J. Pepper, E. Jenkins, et al., B-type natriuretic peptide trumps other prognostic markers in patients assessed for coronary disease, BMC Med. 17 (2019) 72.
[19] M. Minamisawa, T. Miura, H. Motoki, Y. Ueki, H. Nishimura, K. Shimizu, et al., Geriatric nutritional risk index predicts cardiovascular events in patients at risk for heart failure, Circ. J. 82 (2018) 1614–1622.
[20] X. Song, A. Mitnitski, K. Rockwood, Prevalence and 10-year outcomes of frailty in older adults in relation to deficit accumulation, J. Am. Geriatr. Soc. 58 (2010) 681–687.
[21] S.H. Yoo, H.Y. Kook, Y.J. Hong, J.H. Kim, Y. Ahn, M.H. Jeong, Influence of undernutrition at admission on clinical outcomes in patients with acute myocardial infarction, J. Cardiol. 69 (2017) 555–560.
[22] J.P. van Melle, M. Bot, P. de Jonge, R.A. de Boer, D.J. van Veldhuisen, M.A. Whooley, Diabetes, glycemic control, and new-onset heart failure in patients with stable coronary artery disease: data from the heart and soul study, Diabetes Care 33 (2010) 2084–2089.
[23] M.R. MacDonald, M.C. Petrie, F. Varyani, J. Ostergren, E.L. Michelson, J.B. Young, et al., Impact of diabetes on outcomes in patients with low and preserved ejection fraction heart failure: an analysis of the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) programme, Eur. Heart J. 29 (2008) 1377–1385.
[24] F.D. Hobbs, A.K. Roalfe, R.C. Davis, M.K. Davies, R. Hare, Midlands Research Practices C. Prognosis of all-cause heart failure and borderline left ventricular systolic dysfunction: 5 year mortality follow-up of the Echocardiographic Heart of England Screening Study (ECHOES), Eur. Heart J. 28 (2007) 1128–1134.
[25] J.B. Echouffo-Tcheugui, S. Erqou, J. Butler, C.W. Yancy, G.C. Fonarow, Assessing the risk of progression from asymptomatic left ventricular dysfunction to overt heart failure: a systematic overview and meta-analysis, JACC Heart Fail. 4 (2016) 237–248.
[26] Vedin O, Lam CSP, Koh AS, Benson L, Teng THK, Tay WT, et al. Significance of ischemic heart disease in patients with heart failure and preserved, midrange, and reduced ejection fraction: a nationwide cohort study. Circ Heart Fail. 10 (2017) e003875.
[27] C.L. Clarke, G.K. Grunwald, L.A. Allen, A.E. Baron, P.N. Peterson, D.W. Brand, et al., Natural history of left ventricular ejection fraction in patients with heart failure, Circ. Cardiovasc. Qual. Outcomes 6 (2013) 680–686.
[28] J. Lupon, G. Gavidia-Bovadilla, E. Ferrer, M. de Antonio, A. Perera-Lluna, J. Lopez-Ayerbe, et al., Dynamic trajectories of left ventricular ejection fraction in heart failure, J. Am. Coll. Cardiol. 72 (2018) 591–601.
[29] S.D. Solomon, N. Anavekar, H. Skali, J.J. McMurray, K. Swedberg, S. Yusuf, et al., Influence of ejection fraction on cardiovascular outcomes in a broad spectrum of heart failure patients, Circulation 112 (2005) 3738–3744.
[30] T.S. Hall, T.G. von Lueder, F. Zannad, P. Rossignol, K. Duarte, T. Chouihed, et al., Relationship between left ventricular ejection fraction and mortality after myocardial infarction complicated by heart failure or left ventricular dysfunction, Int. J. Cardiol. 272 (2018) 260–266.
[31] B.P. Halliday, R. Wassall, A.S. Lota, Z. Khalique, J. Gregson, S. Newsome, et al., Withdrawal of pharmacological treatment for heart failure in patients with recovered dilated cardiomyopathy (TRED-HF): an open-label, pilot, randomised trial, Lancet 393 (2019) 61–73.
[32] G. Savarese, O. Vedin, D. D'Amario, A. Uijl, U. Dahlstrom, G. Rosano, et al., Prevalence and prognostic implications of longitudinal ejection fraction change in heart failure, JACC Heart Fail. 7 (2019) 306–317.
[33] J. Yeboah, D.A. Bluemke, W.G. Hundley, C.J. Rodriguez, J.A. Lima, D.M. Herrington, Left ventricular dilation and incident congestive heart failure in asymptomatic adults without cardiovascular disease: multi-ethnic study of atherosclerosis (MESA), J. Card. Fail. 20 (2014) 905–911.