European Journal of Heart Failure (2017)
doi:10.1002/ejhf.807

Characterization of heart failure patients with mid-range left ventricular ejection fraction—a report from the CHART-2 Study

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Received 25 October 2016; revised 23 January 2017; accepted 8 February 2017

Background The new category of heart failure (HF), HF with mid-range left ventricular ejection fraction (LVEF) (HFmrEF), has recently been proposed. However, the clinical features of HFmrEF, with reference to HF with preserved LVEF (HFpEF) and HF with reduced LVEF (HFrEF) in the same HF cohort, remain to be fully examined.

Methods and results In the Chronic Heart Failure Analysis and Registry in the Tohoku District-2 Study, we examined 3480 consecutive HF patients with echocardiography data consisting of 2154 HFpEF (LVEF ≥50%), 596 HFmrEF (LVEF 40–49%) and 730 HFrEF (LVEF <40%). While clinical characteristics and prognostic factors of HFmrEF were intermediate between HFpEF and HFrEF, prognosis of HFmrEF resembled HFpEF and the prognostic impact of cardiovascular medications in HFmrEF resembled that of HFrEF. Analysis of LVEF transition among the three groups revealed that HFmrEF and HFrEF dynamically transitioned to other categories, especially within 1 year, whereas HFpEF did not; HFmrEF at registration transitioned to HFpEF and HFrEF by 44% and 16% at 1 year, and 45% and 21% at 3 years, respectively. Landmark analysis demonstrated that, regardless of HF stages at registration, HFmrEF patients at 1 year had mortality comparable to that of HFpEF patients, which was better than HFrEF patients, but HFmrEF patients at registration had increased mortality when transitioned to HFrEF at 1 year.

Conclusions These results indicate that clinical characteristics of HFmrEF are intermediate between HFpEF and HFrEF and that HFmrEF dynamically transitions to HFpEF or HFrEF, especially within 1 year, suggesting that HFmrEF represents a transitional status or an overlap zone between HFpEF and HFrEF, rather than an independent entity of HF.

Keywords Heart failure • Left ventricular ejection fraction • Prognosis

Introduction

In management of heart failure (HF), cut-off by left ventricular ejection fraction (LVEF) is important because most clinical trials for HF use it when selecting patients.[1,2] Indeed, previous major HF trials mainly enrolled patients with an LVEF ≤35–40%, and effective therapies have been demonstrated only in this category of HF patients to date.[3–6] Thus, it is reasonable that the clinical guidelines set the cut-off for HF with reduced LVEF (HFrEF) around 35–40% in order to advocate managements for such patients. In contrast, there have been arguments over setting a specific LVEF cut-off for HF with preserved LVEF (HFpEF) because there have been no robust pathophysiological or prognostic data advocating an appropriate LVEF cut-off for HFpEF.[7] Recently, however, LVEF 50% seems to have been embraced as a cut-off for HFpEF in order to clearly distinguish it from HFrEF in the clinical guidelines of the European Society of Cardiology (ESC)[1] and the American College of Cardiology Foundation (ACCF)/American Heart Association

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(AHA),[2] leaving a gap of LVEF of 40–49% as a middle range. To address this gap between HFpEF and HFrEF, the 2016 ESC guidelines have recently proposed a new category, termed as 'HF with mid-range LVEF' (HFmrEF), for HF patients with LVEF of 40–49%.[1]

In line with this proposal, several studies have recently examined the characteristics of HFmrEF patients hospitalized for acute HF in the Get With The Guidelines registry,[8,9] reporting that HFmrEF may resemble HFpEF with an exceptional aetiology of ischaemia, in which it more closely resembles HFrEF.[9] However, no reports to date have comprehensively examined the clinical features of HFmrEF, with reference to HFpEF and HFrEF, in the same registry of patients with stable chronic HF (CHF). In the present study, we compared the clinical characteristics, outcomes and prognostic factors among patients with HFpEF, HFmrEF, and HFrEF registered in our Chronic Heart Failure Analysis and Registry in the Tohoku District-2 (CHART-2) Study,[10–14] in order to elucidate the complete picture of HFmrEF in a clinical setting. Furthermore, we also examined the changes in LVEF after registration and how changes in LVEF affect the prognosis thereafter.

Methods

The CHART-2 Study

Details of the CHART-2 Study have been previously described.[10–14] Briefly, the CHART-2 Study is a multicentre, prospective observational study in Japan, where 10 219 stable patients aged ≥20 years with either coronary artery disease ($n = 868$), asymptomatic structural heart disease ($n = 4475$), or a current or past history of symptomatic HF ($n = 4876$) at cardiology outpatient clinics or just before discharge were enrolled at the Tohoku University Hospital and 23 affiliated hospitals in the Tohoku District, Japan.[10–14] The diagnosis of HF was made by attending cardiologists based on the criteria of the Framingham study[15] and the main aetiology of HF was determined in each patient: ischaemic heart disease (IHD) was defined by the presence of a history of previous myocardial infarction or coronary artery disease; valvular heart disease (VHD) as moderate to severe aortic and/or mitral valve disease without a previous history of valvular surgery; and hypertensive heart disease (HHD) by the presence of a history of hypertension but without a diagnosis of hypertrophic cardiomyopathy (HCM).[14] All of the patient information, including demographic, medical history, laboratory and echocardiography data, was recorded at the time of enrolment in the CHART-2 Study, and thereafter annually obtained by trained clinical research coordinators. The study protocol was approved by the local ethics committee of each participating hospital and informed consent was obtained from all patients (NCT 00418041).

Study design

Among the 10 219 patients registered in the CHART-2 Study, 4876 had a current or previous history of symptomatic HF. Of these patients, we initially selected 4683 (96.0%) consecutive patients who had echocardiography LVEF data available at the time of registration. We then redefined HF according to the ESC guidelines.[1] In particular, patients with LVEF ≥50% and those with LVEF 40–49% were defined as HFpEF and HFmrEF, respectively, if they had (i) HF symptoms and signs, (ii) elevated B-type natriuretic peptide (BNP) (>35 pg/mL) or *N*-terminal pro-brain natriuretic peptide (NT-proBNP) (>125 pg/mL), and (iii) relevant structural heart disease (LV mass index ≥115 g in men and ≥95 g in women or left atrial dilatation ≥40 mm) and/or diastolic abnormality (E/A ratio <0.75 or ≥1.5 or deceleration time of E-wave <140 ms).[1] Finally, we enrolled 3480 consecutive HF patients, divided into three groups: HFpEF (LVEF ≥50%, $n = 2154$), HFmrEF (LVEF 40–49%, $n = 596$), and HFrEF (LVEF < 40%, $n = 730$), and compared their baseline characteristics, clinical outcomes, and prognostic factors.

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. Incidences of all-cause death, cardiovascular (CV) death, non-CV death, admission for worsening HF, non-fatal acute myocardial infarction (AMI), and non-fatal stroke were estimated using Kaplan–Meier curves and were compared by the log-rank tests. Incidence rate per 1000 person-years was compared with the exact binominal test. Determinants of all-cause death were examined using multivariable Cox proportional hazard model. All of the potential confounding factors were included in the simple Cox proportional hazard model analysis, and factors were then selected using stepwise variable selection procedure. The covariates that may have potentially influenced outcomes included in the present study were; age, sex, blood pressure, heart rate, history of admission for HF, diabetes mellitus, hypertension, cerebrovascular disease, atrial fibrillation (AF), malignant tumour, body mass index (BMI), blood chemistry data [serum levels of haemoglobin, albumin, creatinine, blood urea nitrogen (BUN), and BNP], LVEF, left atrial diameter, LV end-diastolic dimension, and use of drugs at baseline [beta-blockers, renin–angiotensin system inhibitors (RASI), calcium channel blockers, statins, aldosterone antagonists (AA) and diuretics], and HF aetiologies [IHD, dilated cardiomyopathy (DCM), HHD, VHD, and HCM]. The classification and regression trees (CART) analysis is an empirical, statistical technique based on recursive binary partitioning of the data space to predict the response.[16] The CART analysis was utilized to detect the effective prognostic factors in the HFpEF, HFmrEF, and HFrEF groups. Interactions among subgroups were estimated using Cox proportional hazard model including interaction terms and the same variables mentioned above. The changes in LVEF from registration to 1 year at follow-up were estimated by mean with standard error of the mean, and were compared among the subgroups divided according to age, sex, IHD aetiology and use of beta-blocker, RASI, and AA, with the Welch's two sample *t*-test and one-way analysis of variance (ANOVA), as appropriate. To examine the relationship between 1-year transition of LVEF and prognosis thereafter among the three groups, we performed the landmark analysis by the linear mixed effect model,[16] using lme4 and lmerTest packages of R software (R Foundation for Statistical Computing, Vienna, Austria). To explore determinants of LVEF at 1-year follow-up, we used the simple and the multivariable linear regression models using the same covariates for the above Cox models. To select an optimal subset of the covariates, we adopted a stepwise variable selection procedure. The initial candidates for variable selection were the set of the covariates with *P*-values less than 0.1 in the simple linear regression analysis. A *P*-value of <0.05 and a *P*-value for interaction of <0.10 were considered as statistically significant in the present study. All statistical analyses were performed using R software (version 3.0.3) (R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline patient characteristics

Baseline characteristics of the study patients and rates of missing data are shown in *Table 1* and the Supplementary material online, *Table S1*. Among the 3480 patients, 2298 (66.0%) were male and 1182 (34.0%) were female. The prevalence of HFpEF, HFmrEF, and HFrEF was 61.9% ($n = 2154$), 17.1% ($n = 596$), and 21.0% ($n = 730$), respectively. The follow-up rates at 1, 2, and 3 years were 86.9% ($n = 1871$), 84.0% ($n = 1808$), and 79.7% ($n = 1717$) for HFpEF, 86.7% ($n = 517$), 82.7% ($n = 493$), and 81.4% ($n = 484$) for HFmrEF, and 87.7% ($n = 640$), 86.6% ($n = 632$), and 84.9% ($n = 620$) for HFrEF, respectively. As shown in *Table 1*, HFmrEF patients had largely intermediate characteristics between HFpEF and HFrEF; from HFpEF, HFmrEF, to HFrEF, the prevalences of female, BMI, hypertension, and atrial fibrillation, systolic and diastolic blood pressures, and serum levels of albumin, estimated glomerular filtration rate, and high-density lipoprotein cholesterol were decreased significantly, while age and the prevalence of history of admission for HF, heart rate, LV diastolic and systolic dimensions, haemoglobin level, and serum levels of BUN, creatinine, and BNP were increased. With regard to HF aetiology, HFmrEF patients had intermediate prevalence between HFpEF and HFrEF; the prevalence of HHD, DCM, VHD, and HCM in HFmrEF were all intermediate between those in HFpEF and HFrEF, whereas that of IHD, the most frequently observed aetiology of HF, was comparable among the three groups (*Table 1*).

Long-term prognosis and prognostic factors for patients with heart failure with mid-range ejection fraction

Figure 1 shows the Kaplan–Meier curve estimates for deaths and CV events in HFpEF, HFmrEF, and HFrEF patients. It is evident that HFmrEF patients had intermediate incidences of all-cause death, CV death, and admission because of HF between HFpEF and HFrEF patients (all *P*-values for trend <0.001), while those of non-CV death, AMI, or stroke did not differ significantly among the three groups. The prognostic factors in the three groups are shown in *Table 2*. In addition to the common prognostic factors among the three groups (age, stroke, cancer, serum BNP levels, and diuretics), the stepwise multivariable Cox regression analysis selected 11 other factors that were predictive of all-cause death for at least one of the three groups. Interestingly, the factors identified for HFmrEF were all involved in either HFpEF (heart rate and haemoglobin) or HFrEF (beta-blockers).

Medications and long-term prognosis for patients with heart failure with mid-range ejection fraction

We compared the relationship between prognosis and medications, including beta-blockers, RASI, AA, statins, calcium channel blockers, and diuretics among the three groups. As shown in *Figure 2*, the prognostic impacts of these medications in HFmrEF were different from those in HFpEF, but were almost comparable to those in HFrEF; use of beta-blockers was positively associated with, and that of diuretics was negatively associated with improved mortality in HFmrEF and HFrEF, but not in HFpEF patients, whereas statin use was associated with reduced mortality in HFpEF, but not in HFmrEF or HFrEF (*Figure 2*).

Left ventricular ejection fraction transitions among the three groups

Figure 3 shows the temporal trends in LVEF for 3 years after registration among the 3 groups. The results demonstrate that HFmrEF and HFrEF dynamically transitioned to other categories, whereas most of HFpEF did not. The Supplementary material online, *Figure S1* and *Figure S2* show the changes in LVEF and transition rates among the survivors of the three groups for 1 and 3 years, respectively. It was found that HFmrEF at registration transitioned to HFpEF and HFrEF by 44% and 16% at 1 year, and 45% and 21% at 3 years, respectively. HFrEF at registration transitioned to HFpEF and HFmrEF by 18% and 22% at 1 year, and 26% and 21% at 3 years, respectively. In contrast, HFpEF transitioned to HFmrEF and HFrEF by only 8% and 2% at 1 year, and by only 8% and 4% at 3 years, respectively.

Predictive factors for changes in left ventricular ejection fraction

Table 3 shows the relationships between clinical backgrounds at baseline and LVEF changes in the simple linear regression analysis. The IHD aetiology was negatively and female sex was positively associated with an increase in LVEF at 1 year in all three groups. The multivariable linear regression analysis showed that HFpEF, HFmrEF, and HFrEF groups had different sets of factors related to LVEF changes from baseline 1-year (*Table 4*). Among the factors selected, female sex, and heart rate were significantly associated with increased LVEF, while history of IHD and stroke were significantly associated with a decrease in LVEF in HFpEF. In contrast, IHD histology and LV dilatation were significantly associated with LVEF decrease in HFmrEF, and hyperuricaemia, BNP levels, IHD histology, and LV dilatation were significantly associated with decreased LVEF in HFrEF. No medications at baseline were associated with LVEF changes in all groups, although beta-blockers and diuretics were insignificantly associated with decreased LVEF in HFrEF.

Prognostic impacts of the transition of left ventricular ejection fraction among the three groups

Finally, we examined the relationship between the transition of LVEF among the three groups and the prognosis in 1-year survivors. As shown in *Figure 4* and the Supplementary material online, *Table S2*, regardless of HF stages at registration, HFpEF at 1 year was associated with comparable mortality to that of HFpEF at 1 year, but was associated with decreased mortality compared with HFrEF

Table 1 Baseline clinical characteristics of heart failure patients by left ventricular ejection fraction

	All patients ($n = 3480$)			
	HFpEF ($n = 2154$)	HFmrEF ($n = 596$)	HFrEF ($n = 730$)	*P*-value
Age, years	71.7 ± 10.9	69.0 ± 11.6	66.9 ± 12.7	<0.001
Female sex, *n* (%)	844 (39.2)	168 (28.2)	170 (23.3)	<0.001
Body mass index, kg/m^2	23.2 ± 4.7	22.8 ± 5.3	22.7 ± 4.8	0.018
HF aetiology, *n* (%)				
IHD	950 (44.1)	315 (52.9)	366 (50.1)	<0.001
HHD	527 (24.5)	85 (14.3)	68 (9.3)	<0.001
VHD	311 (14.4)	35 (5.9)	32 (4.4)	<0.001
DCM	137 (6.4)	121 (20.3)	235 (32.2)	<0.001
HCM	75 (3.5)	8 (1.3)	9 (1.2)	<0.001
Clinical history, *n* (%)				
Hypertension	1963 (91.2)	535 (89.8)	618 (84.7)	<0.001
Diabetes mellitus	727 (33.8)	215 (36.1)	278 (38.1)	0.090
Dyslipidaemia	1697 (78.8)	478 (80.2)	600 (82.2)	0.134
Atrial fibrillation	1116 (51.8)	259 (43.5)	278 (38.1)	<0.001
Stroke	472 (21.9)	132 (22.1)	138 (18.9)	0.198
AMI	580 (26.9)	245 (41.1)	287 (39.3)	<0.001
Hospitalization for HF	1133 (52.6)	378 (63.4)	563 (77.1)	<0.001
Cancer	341 (15.8)	79 (13.3)	84 (11.5)	0.011
NYHA class, *n* (%)				<0.001
I	453 (21.1)	110 (18.5)	104 (14.3)	
II	1462 (68.2)	413 (69.6)	487 (67.0)	
III	220 (10.3)	66 (11.1)	124 (17.1)	
IV	9 (0.4)	4 (0.7)	12 (1.7)	
Previous treatments, *n* (%)				
PCI	561 (26.0)	205 (34.5)	213 (29.2)	<0.001
CABG	207 (9.6)	51 (8.6)	74 (10.1)	0.618
PMI	208 (9.7)	58 (9.7)	49 (6.7)	0.046
ICD	30 (1.4)	23 (3.9)	51 (7.0)	<0.001
CRT	11 (0.5)	11 (1.8)	41 (5.6)	<0.001
Haemodynamics				
Systolic BP, mmHg	127.9 ± 19.2	124.7 ± 19.3	117.9 ± 19.5	<0.001
Diastolic BP, mmHg	71.9 ± 12.1	71.8 ± 12.3	69.8 ± 12.1	<0.001
Heart rate, b.p.m.	71.7 ± 14.9	73.4 ± 14.7	74.0 ± 5.7	<0.001
LVDd, mm	49.3 ± 7.5	55.8 ± 7.9	62.1 ± 9.1	<0.001
LVDs, mm	31.4 ± 6.8	42.9 ± 6.9	52.6 ± 9.2	<0.001
LVEF, %	64.8 ± 8.99	44.9 ± 2.8	31.1 ± 6.1	<0.001
Laboratory data				
Haemoglobin, g/dL	12.8 ± 1.9	13.0 ± 2.0	13.35 ± 2.02	<0.001
BUN, mg/dL	20.5 ± 10.5	21.1 ± 11.1	21.85 ± 11.76	0.020
Creatinine, mg/dL	1.0 ± 0.7	1.1 ± 0.8	1.17 ± 0.95	0.004
Albumin, g/dL	4.0 ± 0.4	3.9 ± 0.4	4.0 ± 0.4	0.273
eGFR, mL/min/1.73 m^2	58.7 ± 20.9	58.6 ± 22.1	58.2 ± 21.7	0.854
Triglyceride, mg/dL	121.4 ± 75.1	125.6 ± 83.7	132.98 ± 113.2	0.009
HDL-C, mg/dL	52.5 ± 16.0	51.3 ± 15.6	48.4 ± 14.5	<0.001
LDL-C, mg/dL	103.9 ± 29.5	103.1 ± 31.6	107.5 ± 32.8	0.038
BNP, pg/mL	126.9 (71.4, 239.0)	164.5 (83.4, 310.7)	216.0 (97.4, 468.0)	<0.001
Medication, *n* (%)				
Beta-blockers	1000 (46.4)	380 (63.8)	508 (69.6)	<0.001
ACEI	910 (42.2)	304 (51.0)	421 (57.7)	<0.001
ARB	734 (34.1)	173 (29.0)	195 (26.7)	0.001
AA	418 (19.4)	175 (29.3)	319 (43.7)	<0.001
Statins	719 (33.4)	236 (39.6)	283 (38.8)	0.003
CCB	952 (44.2)	161 (27.0)	132 (18.1)	<0.001
Diuretics	1125 (52.2)	377 (63.3)	556 (76.2)	<0.001

Continuous variables are expressed as mean ± standard deviation, except BNP levels, which are expressed as median with interquartile range.
AA, aldosterone antagonists; ACEI, angiotensin converting enzyme inhibitors; AMI, acute myocardial infarction; ARB, angiotensin II receptor blockers; BNP, B-type natriuretic peptide; BP, blood pressure; BUN, blood urea nitrogen; CABG, coronary artery bypass graft; CCB, calcium channel blockers; CRT, cardiac resynchronization therapy; DCM, dilated cardiomyopathy; eGFR, estimated glomerular filtration rate; HCM, hypertrophic cardiomyopathy; HDL-C, high-density lipoprotein cholesterol; HF, heart failure; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HHD, hypertensive heart disease; ICD, implantable cardioverter defibrillator; IHD, ischaemic heart disease; LDL-C, low-density lipoprotein cholesterol; LVDd, left ventricular diastolic dimension; LVDs, left ventricular systolic dimension; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; PMI, pacemaker implantation; VHD, valvular heart disease.

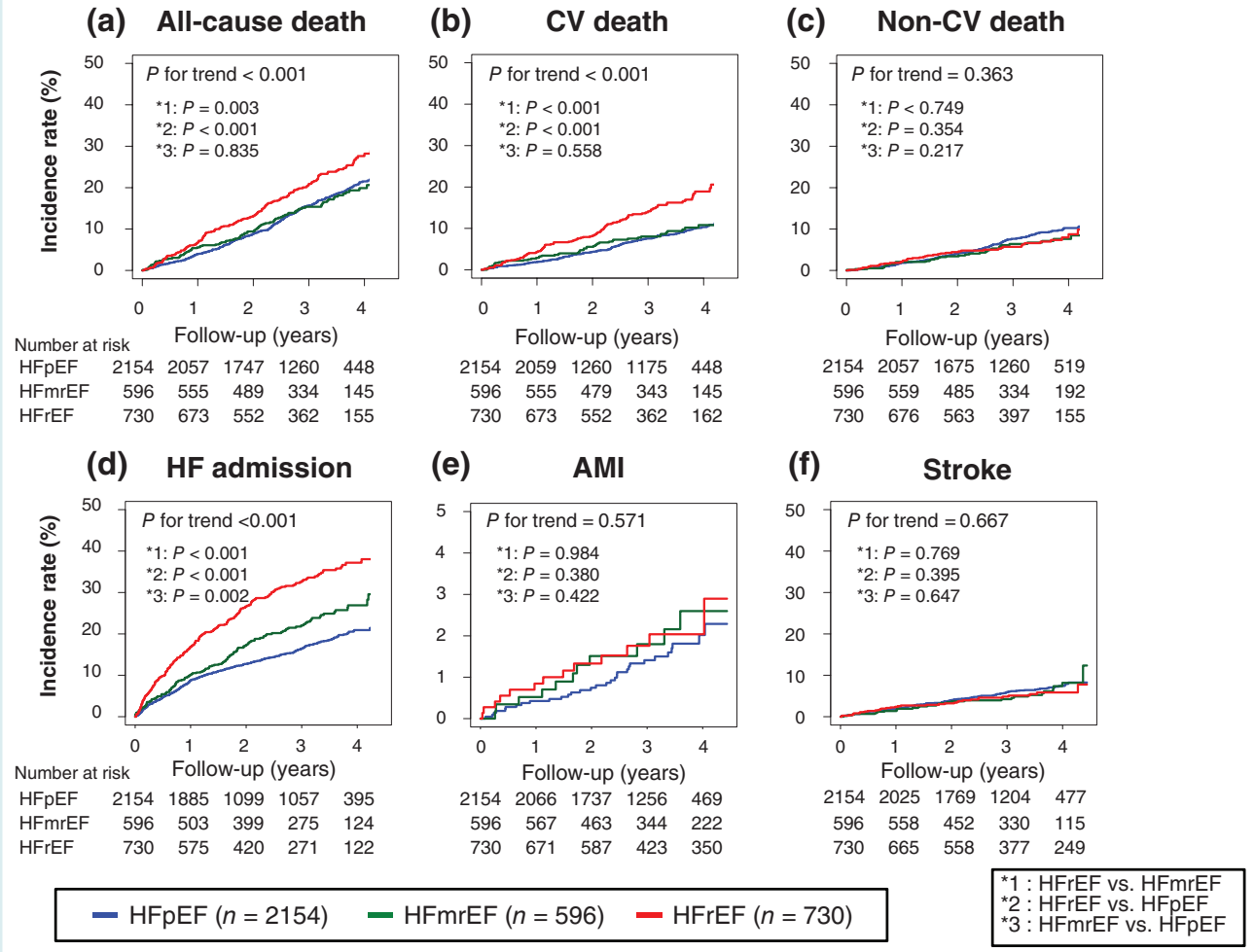

Figure 1 Long-term survival of patients with heart failure (HF) by left ventricular ejection fraction. Kaplan–Meier curves for (a) all-cause death, (b) cardiovascular (CV) death, (c) non-CV death, (d) HF admission, (e) non-fatal acute myocardial infarction (AMI), and (f) non-fatal stroke in patients with HF with preserved (HFpEF), mid-range (HFmrEF), or reduced ejection fraction (HFrEF).

at 1 year. HFmrEF at registration had increased mortality after 1 year when transitioned to HFrEF at 1 year, but not when transitioned to HFpEF or remaining in HFmrEF at 1 year (*Figure 4* and the Supplementary material online, *Table S2*). Prognostic impacts were comparable among HFmrEF patients at 1 year who were HFpEF at baseline, those who were HFmrEF at baseline, and those who were HFrEF at baseline (see the Supplementary material online, *Table S2*). With regard to HF admission, regardless of HF stages at registration, patients with HFmrEF at 1 year had incidences of HF admission before and after 1-year follow-up, which were comparable to incidence of HF in patients with HFpEF at enrolment and remained in HFpEF at 1-year (see the Supplementary material online, *Figure S3*). In contrast, regardless of HF stage at registration, patients with HFrEF at 1 year had increased incidences of admission because of HF before and after 1-year follow-up, compared with patients with HFpEF at enrolment and remained in HFpEF at 1 year (see the Supplementary material online, *Figure S3*).

Discussion

In the present study, we examined the characteristics and outcomes of HFmrEF patients registered in our CHART-2 Study, which is the largest prospective observational study for stable CHF in Japan.[10–14] The present study clearly demonstrates that: (i) clinical characteristics and prognostic factors of HFmrEF were intermediate between HFpEF and HFrEF; (ii) there were important LVEF transitions in HFmrEF and HFrEF, especially within 1 year after registration, whereas HFpEF largely remained in HFpEF; (iii) prognosis of HFmrEF resembled that of HFpEF, while the prognostic impact of CV medications in HFmrEF resembled that in HFrEF; and (iv) HFmrEF was associated with worse prognosis only when transitioned to HFrEF. To the best of our knowledge, this is the first large-scale prospective observational study examining the clinical features of HFmrEF, with reference to HFpEF and HFrEF, in the same HF cohort.

Table 2 Prognostic factors for heart failure patients by left ventricular ejection fraction

	HFpEF			HFmrEF			HFrEF		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Age >75 years	2.59	1.98–3.37	<0.001	1.94	1.75–2.34	0.013	2.01	1.35–2.99	<0.001
BNP, /100 pg/mL	1.09	1.05–1.14	<0.001	1.08	1.02–1.15	0.008	1.08	1.04–1.12	<0.001
Cancer	1.29	0.98–1.69	0.060	3.13	1.93–5.07	<0.001	1.36	0.96–1.82	0.092
Diuretics	1.24	0.96–1.60	0.085	2.30	1.33–3.96	0.002	1.98	1.19–3.30	0.008
Stroke	1.30	1.01–1.68	0.039	1.53	1.06–2.21	0.024	1.58	1.05–2.39	0.028
Albumin	0.47	0.36–0.60	<0.001						
BMI	0.96	0.93–0.99	0.019						
BUN, /10 mg/dL	1.01	1.03–1.19	0.003						
Female sex	0.88	0.62–1.00	0.042						
Statins	0.83	0.64–0.96	0.025						
Heart rate, /10 b.p.m.	1.10	1.03–1.19	0.003	1.11	0.96–1.29	0.123			
Haemoglobin	0.93	0.87–1.00	0.076	0.89	0.78–1.01	0.076			
Beta-blockers				0.76	0.52–1.07	0.075	0.62	0.42–0.91	0.032
Creatinine							1.15	0.98–1.34	0.080
Hypertension							0.60	0.38–0.96	0.032
Systolic BP, /10 mmHg							0.92	0.84–1.01	0.120

BMI, body mass index; BNP, B-type natriuretic peptide; BP, blood pressure; BUN, blood urea nitrogen; CI, confidence interval; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio.

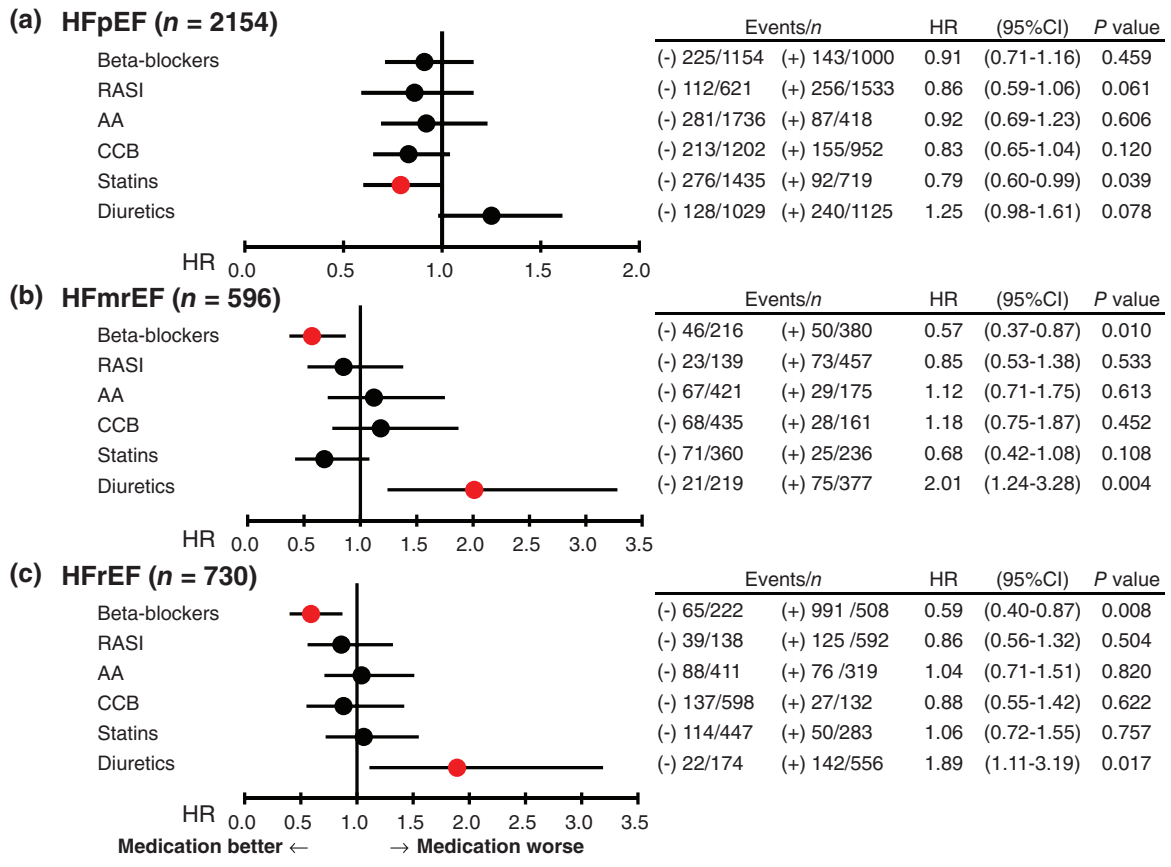

Figure 2 Prognostic impact of medications in heart failure patients by left ventricular ejection fraction. (a) Heart failure with preserved ejection fraction (HFpEF), (b) heart failure with mid-range ejection fraction (HFmrEF), and (c) heart failure with reduced ejection fraction (HFrEF). AA, aldosterone antagonists; CCB, calcium channel blockers; CI confidence interval; HR, hazard ratio; RASI, renin–angiotensin system inhibitors.

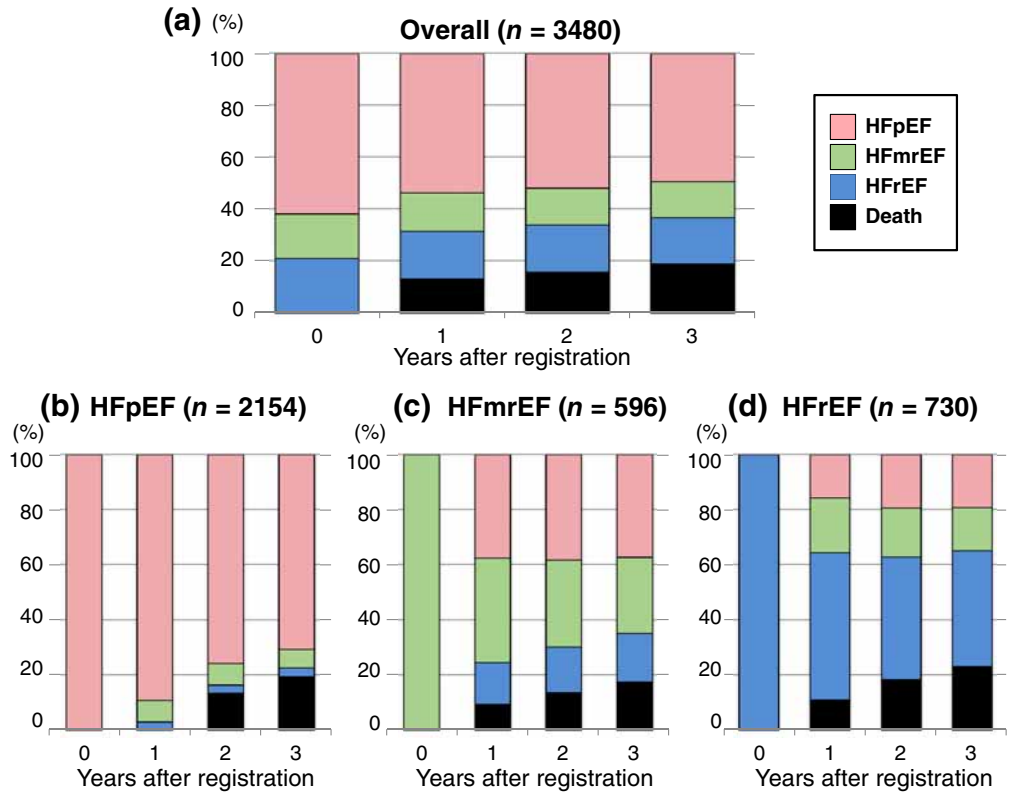

Figure 3 Transitions of heart failure among heart failure patients by left ventricular ejection fraction. (a) Overall population, (b) heart failure with preserved ejection fraction (HFpEF), (c) heart failure with mid-range ejection fraction (HFmrEF), and (d) heart failure with reduced ejection fraction (HFrEF) patients.

Prevalence of heart failure with preserved, mid-range, and reduced ejection fraction in the CHART-2 Study

In the present study, the prevalence of HFmrEF was 17.1%, while that of HFpEF and HFrEF was 61.9% and 21.0%, respectively. This prevalence of HFmrEF was comparable with the previous reports in Western countries, although that of HFpEF was higher and that of HFrEF was lower in the present study.[8,9,17,18] The high prevalence of HFpEF may represent the characteristics of the CHART-2 Study that mainly enrolled outpatients with stable CHF in the contemporary clinical setting in Japan. Indeed, we have entered into a super-aged society (≥21% the elderly population aged ≥65 years) in 2007 in Japan, and enrolled consecutive HF patients at participating hospitals between October 2006 and March 2010. Importantly, the prevalence of HFpEF, HFmrEF, and HFrEF in the present study was similar to that in the Cardiovascular Health Study (CHS), where 5888 elderly (≥65 years) persons were recruited from the community in the USA.[17] In the CHS, among 269 (4.9%) participants with congestive HF, the prevalence of LVEF ≥55%, 45–54% and ≤45% was 63%, 15%, and 22%, respectively.[17] Thus, the present results may provide clinically important information, particularly for the aging society worldwide.

Clinical characteristics of patients with heart failure with mid-range ejection fraction

In the present study, HFmrEF was characterized by intermediate characteristics between HFpEF and HFrEF. Similarly, the prevalence of each HF aetiology in HFmrEF was generally intermediate between HFrEF and HFpEF except for IHD, the prevalence of which was comparable among the three groups. However, further considerations are needed, as it was reported that HFmrEF resembled HFpEF with the key exceptional characteristic of ischaemia, in which it resembled HFrEF in the Get With The Guidelines-Heart Failure (GWTG-HF) registry.[8,9] This discrepancy between the GWTG-HF and the present study could be explained by the difference in the inclusion criteria of the patients (hospitalized HF vs. stable CHF) rather than geographical difference (USA vs. Japan).[19] Indeed, the CHS, which examined the elderly population of the USA, reported a finding consistent with the present study that the clinical characteristics of HF patients with borderline LVEF were intermediate between HFpEF and HFrEF patients.[17] Thus, the clinical characteristics of HFmrEF should be interpreted differently when considering the study inclusion criteria.

Table 3 Associations between clinical backgrounds and left ventricular ejection fraction changes in the simple regression analysis

	HFpEF			HFmrEF			HFrEF		
Variable	***r***	**Coefficient**	***P*-value**	***r***	**Coefficient**	***P*-value**	***r***	**Coefficient**	***P*-value**
Age >75 years	−0.019	−0.365	0.469	0.092	1.967	0.080	−0.024	−0.636	0.620
Female sex	0.074	1.450	0.004	0.155	3.546	0.003	0.130	3.640	0.007
Body mass index, kg/m^2	0.044	0.114	0.094	−0.019	−0.056	0.718	−0.061	−0.177	0.209
Systolic BP, /10 mmHg	0.055	0.271	0.035	0.008	0.046	0.873	0.043	0.267	0.373
Heart rate, /10 b.p.m.	0.068	0.445	0.008	0.083	0.565	0.112	−0.007	−0.052	0.890
LVDd, /10 mm	−0.027	−0.318	0.300	−0.192	−2.477	0.000	−0.243	−3.082	0.000
Creatinine, mg/dL	−0.009	−0.164	0.725	0.015	0.177	0.775	−0.134	−2.341	0.005
BUN, mg/dL	0.001	0.001	0.980	0.019	0.018	0.723	−0.063	−0.064	0.194
Haemoglobin, mg/dL	−0.030	−0.150	0.245	−0.047	−0.243	0.370	−0.008	−0.052	0.864
Albumin	−0.024	−0.541	0.396	−0.095	−2.301	0.102	−0.083	−2.198	0.110
BNP, /100 pg/mL	−0.035	−0.181	0.173	−0.020	−0.083	0.705	−0.176	−0.647	0.000
Hypertension	−0.002	−0.067	0.940	0.017	0.606	0.750	−0.023	−0.794	0.632
Diabetes mellitus	−0.017	−0.336	0.519	−0.006	−0.122	0.912	0.046	1.124	0.336
Dyslipidaemia	0.021	0.498	0.417	0.030	0.760	0.568	−0.009	−0.320	0.844
Hyperuricaemia	0.001	0.025	0.960	−0.020	−0.425	0.700	−0.163	−4.314	0.001
Hospitalization for HF	0.012	0.239	0.630	0.096	2.042	0.067	−0.070	−1.926	0.145
Atrial fibrillation	0.039	0.747	0.134	0.080	1.668	0.127	0.104	2.558	0.031
Ischaemic heart disease	−0.058	−1.134	0.024	−0.198	−4.129	0.000	−0.100	−2.404	0.037
Stroke	−0.089	−2.118	0.001	−0.025	−0.636	0.638	−0.006	−0.203	0.898
Cancer	0.002	0.041	0.954	0.021	0.740	0.683	0.063	2.641	0.190
Beta-blockers	−0.013	−0.253	0.611	−0.005	−0.112	0.922	−0.106	−2.768	0.028
RASI	0.029	0.606	0.270	−0.005	−0.117	0.926	−0.015	−0.486	0.753
Statins	−0.026	−0.526	0.316	−0.069	−1.447	0.190	−0.032	−0.776	0.510
Diuretics	0.015	0.290	0.561	−0.029	−0.625	0.582	−0.124	−3.443	0.010
AA	0.027	0.651	0.293	−0.043	−0.985	0.408	−0.058	−1.395	0.236

AA, aldosterone antagonists; BNP, B-type natriuretic peptide; BP, blood pressure; BUN, blood urea nitrogen; HF, heart failure; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVDd, left ventricular diastolic dimension; RASI, renin–angiotensin system inhibitors.

Table 4 Associations between clinical backgrounds and left ventricular ejection fraction changes in the stepwise multivariable regression analysis

HFpEF			HFmrEF			HFrEF		
Variable	**Coefficient**	***P*-value**	**Variable**	**Coefficient**	***P*-value**	**Variable**	**Coefficient**	***P*-value**
Female sex	1.227	0.018	Age > 75 years	1.747	0.119	IHD	−3.081	0.010
BMI	0.118	0.091	Female sex	2.239	0.066	LVDd, /10 mm	−2.464	0.000
Systolic BP, /10 mmHg	0.297	0.024	IHD	−3.718	0.001	Hyperuricaemia	−2.916	0.027
HR, /10 b.p.m.	0.379	0.025	LVDd, /10 mm	−1.846	0.007	BNP, /100 pg/mL	−0.610	0.001
IHD	−1.003	0.053				Beta-blockers	−1.816	0.160
Stroke	−2.096	0.001				Diuretics	−2.456	0.077
						Atrial fibrillation	2.297	0.060

BMI, body mass index; BNP, B-type natriuretic peptide; BP, blood pressure; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, heart rate; IHD, ischaemic heart disease; LVDd, left ventricular diastolic dimension.

Long-term prognosis of heart failure patients by left ventricular ejection fraction

The present study demonstrates that HFmrEF had intermediate incidence of all-cause death, CV death, and HF admission between HFpEF and HFrEF, while incidences of non-CV death, AMI and stroke were comparable among the three groups. Importantly, however, it was noted that the incidence of all-cause and CV death in HFmrEF was closer to that in HFpEF than that in HFrEF. Thus, in terms of prognostic outcomes, stable chronic HFmrEF likely resembles HFpEF rather than HFrEF. These findings are partly

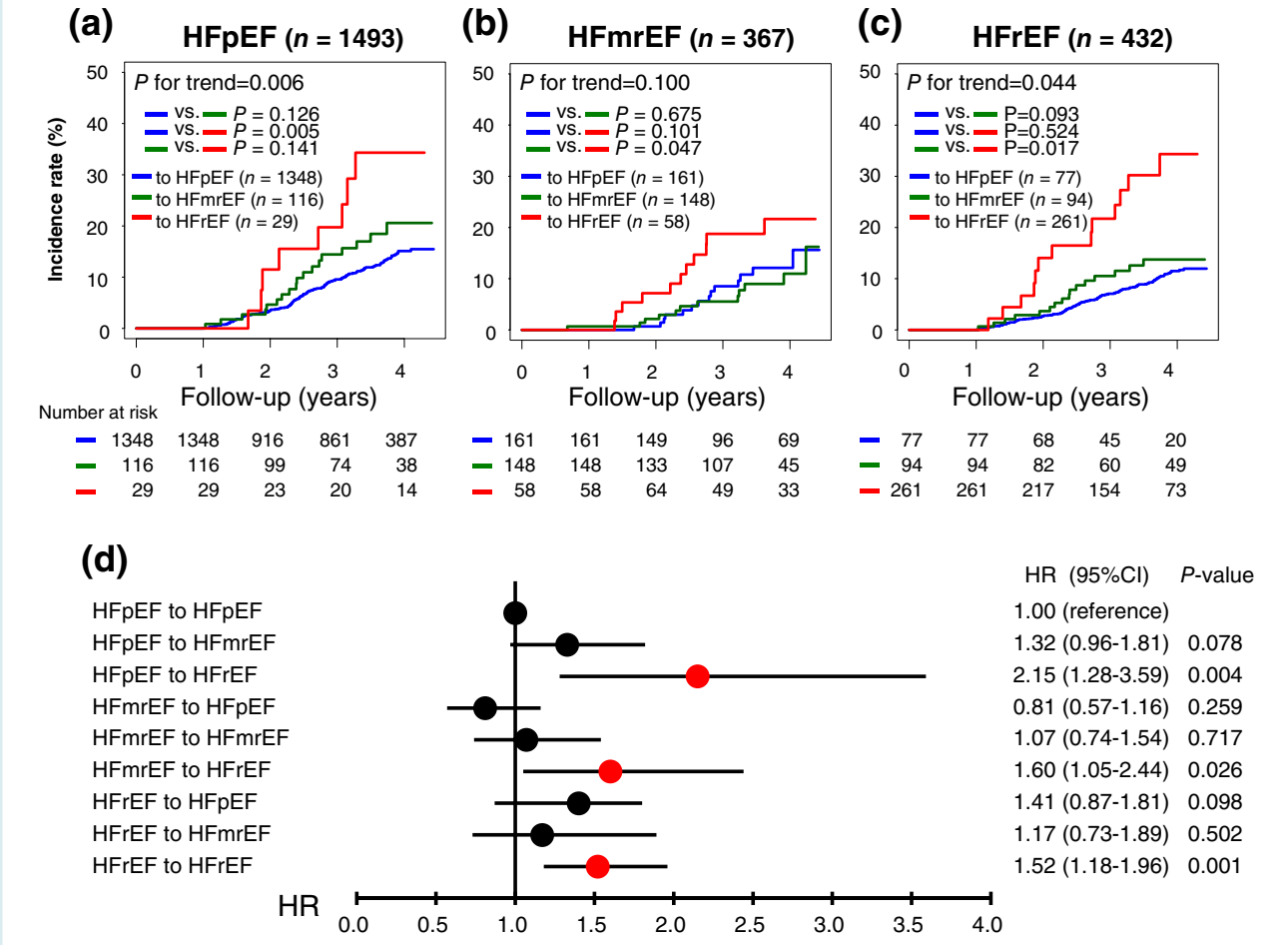

Figure 4 Long-term survival of heart failure patients after 1-year follow-up by left ventricular ejection fraction. Kaplan–Meier curves for patients with (a) heart failure with preserved ejection fraction (HFpEF), (b) heart failure with mid-range ejection fraction (HFmrEF), and (c) heart failure with reduced ejection fraction (HFrEF) at registration, and (d) adjusted risks for all-cause death according to the transitions after registration to 1 year among HFpEF, HFmrEF, and HFrEF. CI confidence interval; HR, hazard ratio;

consistent with a previous study reporting that all components of CV death declined with increasing LVEF up to 45%, after which the risk of these outcomes remained relatively stable with increasing LVEF.[18] However, we may need to consider the influence of LVEF on mortality between acute or hospitalized HF patients and stable CHF patients separately, as Cheng *et al.*[8] reported that, among patients hospitalized for HF, no differences were noted in mortality risk among the three groups after risk adjustment.

Differences in prognostic factors among the three groups by left ventricular ejection fraction

Although differences in clinical characteristics and prognosis among the three groups were examined in the previous studies, few studies have addressed the prognostic factors of HFmrEF in comparison with HFpEF or HFrEF. Interestingly, all of the prognostic factors identified for HFmrEF were also selected for HFpEF, HFrEF, or both in the present study, suggesting an intermediate phenotype of HFmrEF between HFpEF and HFrEF. Importantly, the present results demonstrate that the impacts of CV medications in HFmrEF were similar to those in HFrEF, but not to those in HFpEF; the use of beta-blockers was associated with reduced incidence of death in HFmrEF and HFrEF, but not in HFpEF, whereas statin use was associated with reduced incidence of all-cause death in HFpEF, but not in HFmrEF or HFrEF—a consistent finding with the previous reports.[8,9,20–23] This finding is of clinical importance because there has been no evidence for HFmrEF management and the ESC guidelines recommend therapies for HFmrEF patients based on the evidence for HFpEF rather than that for HFrEF.[1] In particular, it is underlined that the present study demonstrates beneficial prognostic impact of beta-blockers in HFmrEF patients as the first evidence in this field. However, we should interpret carefully the finding that use of RASI was not associated with better prognosis in HFmrEF or HFrEF, as more than 70% in both HFmrEF and HFrEF patients were treated with RASI in the CHART-2 Study, making it

difficult to appropriately adjust confounding bias for deciding use of RASI in the HF management even in the multivariable models.

Transitions of heart failure among the three groups by left ventricular ejection fraction

Although the clinical guidelines define HFmrEF as a gray zone between HFpEF and HFrEF, no studies have examined the transition among the three groups by LVEF. The present study clearly demonstrates the transitions among the three groups, particularly regarding the transitions to and from HFmrEF, in a prospective observational cohort. Thus, the present finding that HFmrEF patients dynamically transitioned to other categories supports a concept that HFmrEF is a transitional stage between HFpEF and HFrEF, and provides important information towards understanding the underlying pathophysiology of the condition. However, the present study also demonstrates that most of HFpEF and almost half of HFrEF patients remained in the HFpEF and HFrEF categories, respectively, during a 3-year follow-up, providing additional weight to the concept that HFpEF and HFrEF are distinct syndromes with fundamental pathophysiological differences.[11,24–27] Thus, we consider that HFmrEF represents a transitional status between HFpEF and HFrEF as well as an overlap zone of HFpEF with lower-end LVEF and HFrEF with higher-end LVEF, rather than an independent entity of HF.

Predictive factors for changes in left ventricular ejection fraction

The simple linear regression analysis showed that IHD aetiology was negatively associated with, and female sex was positively associated with increased LVEF at 1 year in all three groups, which is consistent with the findings of previous studies that LVEF is a dynamic factor related to sex and IHD aetiology in HF patients.[28,29] Importantly, the stepwise multivariable linear regression analysis showed that female sex was independently associated with LVEF increase only in HFpEF, while IHD aetiology was independently associated with a decrease in LVEF only in HFmrEF and HFrEF, providing a further insight into the pathophysiology of HFmrEF patients. In contrast to the previous study,[28] the stepwise multivariable linear regression analysis showed no association between the use of beta-blockers and improvement of LVEF in HFrEF. This discrepancy in the impact of beta-blockers on LVEF improvement should be carefully examined further, because the use of beta-blockers was consistently associated with better prognosis in the present and the previous studies.[28]

Prognostic impacts of the transition of heart failure among the three groups by left ventricular ejection fraction

The present study demonstrated that patients who had LVEF <40% (HFrEF) at registration but transitioned to HFpEF or HFmrEF at 1 year had better prognosis thereafter compared with those remaining in HFrEF at 1 year, which is consistent with the finding in the previous studies that recovery from reduced LVEF is associated with improved outcomes.[28,30–32] In the Department of Veterans Affairs Cooperative Vasodilator–Heart Failure Trials (V-HeFT), Cintron *et al.*[30] reported that improvement in LVEF (>5%) from baseline at 6 months (V-HeFT I) and 1 year (V-HeFT II) was the strongest predictor of mortality among the serial measurements and was significant after adjustment for therapy and baseline LVEF.[30] Dunlay *et al.*[28] reported that a decrease in LVEF over time was associated with reduced survival, whereas an increase in LVEF was associated with improved survival. Basuray *et al.*[31] also reported that patients with recovered LVEF, defined as those who had LVEF ≥50% but had a previous LVEF <50%, had better biomarker profile and event-free survival than HFrEF patients (defined as HF with LVEF <50%). Furthermore, a recent review of the medical records of 2507 adult outpatients by cardiologists in Emory Healthcare (Atlanta, Georgia, USA) revealed that HF patients with recovered LVEF had a different clinical course than those with HFpEF or HFrEF, with lower mortality, less frequent hospitalizations, and fewer composite endpoints.[32] These lines of evidence strongly suggest that recovery from reduced LVEF was associated with better prognosis in HF patients. Thus, we should underline the importance of management aiming at LVEF recovery in HF patients. In addition, the present results also indicate that transitions from HFpEF and HFmrEF at baseline to HFrEF at 1 year were associated with worse prognosis thereafter, suggesting the importance in preventing a decrease in LVEF for better prognosis of HF patients. Furthermore, compared with HFpEF and HFmrEF at 1 year, HFrEF patients at 1 year had more frequently experienced worsening HF requiring hospitalization after registration and by 1 year in the present study. Thus, although it remains to be examined whether HF worsening is precedent to a decrease in LVEF, we may need to prevent worsening of HF in order to improve LVEF and prognosis of HF patients.

Clinical significance of the present study

HFmrEF is a new category of HF that has been recently proposed in the clinical guidelines.[1,2] However, although several studies have been conducted to determine the clinical picture of HFmrEF among hospitalized patients,[8,9] there have been scarce evidence for stable HFmrEF patients. In this regard, the present study is of clinical importance, as it is the first study that comprehensively and directly examined the similarities and differences among stable patients with HFpEF, HFmrEF, and HFrEF, who were registered in the same prospective observational cohort study. The present study clearly demonstrated that clinical features of HFmrEF are intermediate between HFpEF and HFrEF, or close to either HFpEF or HFrEF and thus suggest that HFmrEF is a transitional stage from HFpEF to HFrEF, or from HFrEF to HFpEF, or an overlap zone of HFpEF with lower-end LVEF and HFrEF with higher-end LVEF, rather than a distinct entity from HF. These findings would help to address the knowledge gap in the understanding of HFmrEF in the current clinical guidelines.[1,2,33]

Study limitations

Several limitations should be mentioned for the present study. First, because the CHART-2 Study is an observational study in Japan, caution is needed when generalizing the data to other patient populations. Second, the diagnosis and aetiologies of HF were determined by the attending physicians, and we defined HFpEF, HFmrEF, and HFrEF based on LVEF data obtained at each institution without considering right ventricular function in the present study. In addition, precise ECG information including LBBB was not available in the present study. Thus, further studies are needed to confirm our observation under more strict definitions. Third, the prognostic impacts of changes in LVEF were examined only for 1-year changes after registration as the follow-up duration was 3.1 years. Thus, further studies with longer follow-up data are needed to elucidate the significance of longer-term changes in LVEF in HF patients. Fourth, the CHART-2 cohort, particularly the HFpEF subpopulation, has unique characteristics that are distinct from the Western cohorts. For example, in a Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) meta-analysis report, examining 30455 HF patients from 28 observational cohorts in which LVEF was not a study entry criterion, 15742 (52%) had LVEF <50% and 5945 (19%) had LVEF ≥50%, while 8768 (29%) had no LVEF data.[34] In this meta-analysis cohort, compared with HFpEF patients in the present study, those with LVEF ≥50% were 3 years older (72 years) and had 15 mmHg higher systolic blood pressure (143 ± 28 mmHg), 17% higher prevalence of females (52%), 12% lower prevalence of ischaemic aetiology (36%), and 14% lower prevalence of atrial fibrillation (29%).[34] Thus, further studies are needed before utilizing our findings in Western cohorts. Finally, in the ESC guidelines, HF is defined by BNP or NT-proBNP levels as well as HF symptoms and signs.[1] Although we strictly defined HF according to the ESC guidelines[1] at baseline, HF categories at follow-up were redefined based only on LVEF values without considering the changes in BNP levels or diastolic function during the follow-up period. Thus, caution is needed in interpreting and implementing our data in this regard.

Conclusions

The present study demonstrates that clinical characteristics of HFmrEF are intermediate between HFpEF and HFrEF, and that HFmrEF dynamically transitions to HFpEF or HFrEF, especially within 1 year, suggesting that HFmrEF represents a transitional status between HFpEF and HFrEF or an overlap zone of HFpEF with lower-end LVEF and HFrEF with higher-end LVEF, rather than an independent entity of HF.

Supplementary Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Changes in LVEF and transition rates among heart failure patients for 1 year by LVEF.

Figure S2. Changes in LVEF and transition rates among heart failure patients for 3 years by LVEF.

Figure S3. Heart failure admission and mortality of heart failure patients by left ventricular ejection fraction. Kaplan–Meier curves for heart failure (HF) within 1 year after registration in patients with (A) heart failure with preserved ejection fraction (HFpEF), (B) heart failure with mid-range ejection fraction (HFmrEF) and (C) heart failure with reduced ejection fraction (HFrEF) at registration, and (D) adjusted risks for HF admission within 1 year after registration according to the transitions after registration to 1 year among HFpEF, HFmrEF and HFrEF. Kaplan–Meier curves for mortality after 1-year follow-up in patients with (E) HFpEF, (F) HFmrEF and (G) HFrEF at registration, and (H) adjusted risks for mortality after 1-year follow-up according to the transitions after registration to 1 year among HFpEF, HFmrEF and HFrEF.

Table S1. Number of missing data in the CHART-2 study.

Table S2. Relative risks among subgroups.

Appendix S1. The CHART-2 study investigators.

Acknowledgements

The authors thank all members of the Tohoku Heart Failure Association and staff of the Department of Evidence-based Cardiovascular Medicine for their kind contributions (see the Supplementary material online, *Appendix S1*).

Funding

This study was supported in part by Grants-in Aid from the Ministry of Health, Labour, and Welfare, the Ministry of Education, Culture, Sports, Science, and Technology (H.S. and Y.S.), and the Agency for Medical Research and Development (H.S.).

Conflict of interest: The Department of Evidence-based Cardiovascular Medicine, Tohoku University Graduate School of Medicine, is supported in part by unrestricted research grants from Daiichi Sankyo Co., Ltd. (Tokyo, Japan), Bayer Yakuhin, Ltd (Osaka, Japan), Kyowa Hakko Kirin Co., Ltd (Tokyo, Japan), Kowa Pharmaceutical Co., Ltd (Tokyo, Japan), Novartis Pharma K.K. (Tokyo, Japan), Dainippon Sumitomo Pharma, Co., Ltd (Osaka, Japan), and Nippon Boehringer Ingelheim Co., Ltd (Tokyo, Japan). H.S. has received lecture fees from Bayer Yakuhin, Ltd, (Osaka, Japan), Daiichi Sankyo Co., Ltd. (Tokyo, Japan) and Novartis Pharma K.K. (Tokyo, Japan).

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