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Characteristics and Outcomes of Hospitalized Patients With Heart Failure and Reduced vs Preserved Ejection Fraction

— A Report From the Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD) —

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Background: Heart failure (HF) with preserved ejection fraction (EF) is common. We compared the characteristics, treatments, and outcomes in HF patients with reduced vs preserved EF by using the national registry database in Japan.

Methods and Results: The Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD) is a prospective observational study in a broad sample of patients hospitalized with worsening HF. The study enrolled 2,675 patients from 164 hospitals with an average of 2.4 years of follow-up. Patients with preserved EF (EF ≥50% by echocardiography; n=429) were more likely to be older, female, have hypertension and atrial fibrillation, and less likely to have ischemic etiology compared with those with reduced EF (EF <40%; n=985). Unadjusted risk of in-hospital mortality (6.5% vs 3.9%; P=0.03) and post-discharge mortality (22.7% vs 17.8%; P=0.058) was slightly higher in patients with preserved EF, which, however, were not different after multivariable adjustment. Patients with preserved EF had similar rehospitalization rates (36.2% vs 33.4%; P=0.515) compared with patients with reduced EF.

Conclusions: HF patients with preserved EF had a similar mortality risk and equally high rates of rehospitalization as those with reduced EF. Effective management strategies are critically needed to be established for this type of HF. (*Circ J* 2009; **73:** 1893 – 1900)

Key Words: Ejection fraction; Heart failure; Mortality; Outcome; Rehospitalization

A substantial portion of patients with symptomatic heart failure (HF) have been reported to have relatively normal or preserved left ventricular (LV) ejection fraction (EF).[1] 'HF with preserved EF' has been defined as the presence of typical HF symptoms and signs of an EF of more than 40 or 50%. Previous studies, including our own, showed that HF patients with preserved EF are older, more often female, and have hypertension compared to those with reduced EF.[1–4]

Recent large scale registry databases, such as EuroHeart Failure Survey, Acute Decompensated Heart Failure National Registry (ADHERE), and Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure (OPTIMIZE-HF) showed that patients with preserved and reduced EF had a similar prognosis.[5–7] However, in the EuroHeart Failure Survey, the detailed clinical information such as echocardiographic data was not provided and the outcomes were assessed by repeat interviews in 12 weeks of follow-up.[5] In the ADHERE study, the outcome information was limited during the hospital stay and long-term outcome data were not collected.[6] The OPTIMIZE-HF limited the post-discharge follow-up up to 60–90 days.[7] Therefore, even though these registries studied the outcomes in a large and broad sample of patients with HF, very little information is currently available based on the data with sufficient number of patients and the long-term follow-up over 1 year.

Furthermore, these studies have been conducted mainly

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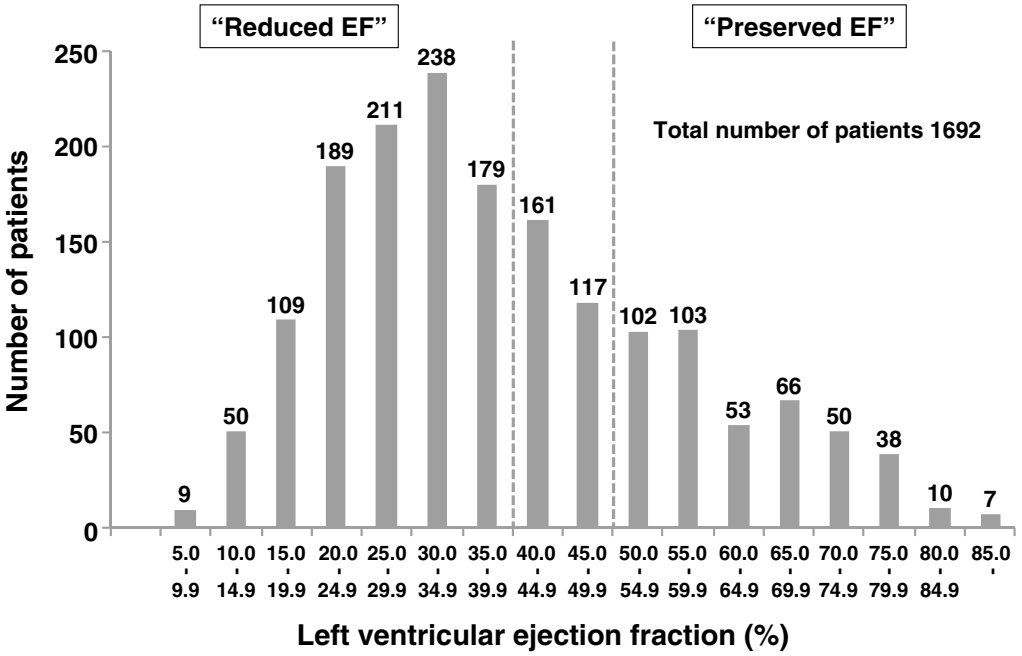

Figure 1. Histogram of left ventricular ejection fraction (EF) among patients hospitalized with heart failure (n=1,692).

in the USA and Europe and very limited information is available on the characteristics and outcomes of hospitalized HF patients in Japan.[3,8,9] Our previous studies in Fukuoka were the first detailed analysis of clinical characteristics, management, and outcomes including mortality and HF-related re-admission in HF patients encountered in routine clinical practice.[3,10,11] We showed that HF patients were elderly, contained a larger population of women especially elderly women, and had a higher incidence of overt HF despite a relatively preserved EF.[10] At 2.4 years of follow-up, cumulative survival rates were similar between patients with preserved systolic function and dysfunction.[3] Re-admission rates were also comparable between preserved and depressed systolic function. Even though our previous studies have provided a valuable insight into the characteristics of HF patients in Japan, the generalization of these results is questioned because it was conducted in a small number of patients (n=230). Therefore, it is of critical importance to analyze the data of HF patients on a national basis.

The Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD) is a national prospective registry database describing the clinical characteristics, treatments, and in-hospital as well as long-term outcomes of patients hospitalized due to the worsening of HF symptoms.[12] It included HF patients with both reduced and preserved EF and thus could enable us to compare these 2 groups of patients.

Methods

Baseline Patient Data

The details of the JCARE-CARD were described previously.[12] Briefly, eligible patients were those hospitalized due to worsening HF as the primary cause of admission. Baseline data were collected by using an electronic data capture system, which included demography, causes of HF, medical history, clinical status, plasma B-type natriuretic peptide, and medications at discharge.

Outcomes

The status of registered patients was surveyed during hospitalization and at least 1 year after discharge and the following information was obtained: death, causes of death, and rehospitalization as a result of the exacerbation of HF that required more than continuation of their usual therapy on previous admission.

Statistical Analysis

Patient characteristics and treatments were compared using Pearson χ^2 test for categorical variables and unpaired t-test for continuous variables. The relationship between EF and in-hospital outcomes was evaluated by logistic regression analysis. Cox proportional hazard modeling was applied to all-cause mortality, cardiac death, rehospitalization, and all-cause death or rehospitalization after discharge. Variables were included in the multivariate model, if they were $P<0.05$ by the univariate analysis. Gender and age were forced into all models. SPSS version 14.0 J was used for all statistical analyses, and $P<0.05$ was considered significant. Adjusted outcomes were presented as hazard ratio (HR) with 95% confidence interval (CI).

Results

Patient Characteristics

Out of the 2,675 patients registered for the JCARE-CARD, 332 patients did not have EF data and 651 patients had valvular heart diseases. Thus, the remaining 1,692 patients were included in the present study. Overall, patients registered in the JCARE-CARD displayed a wide distribution of EF values (**Figure 1**). In this analysis, 429 patients (26%) had EF ≥50% and were classified as having 'HF with preserved EF' and 985 patients (58%) had EF <40% (HF with reduced EF). The remaining 278 patients (16%) had EF between 40% and 50%.

Table 1. Baseline Characteristics of HF Patients With Reduced EF vs Preserved EF

Characteristic	Total cohort (n=1,692)	Reduced EF (n=985)	Preserved EF (n=429)	P-value
LVEF	38.8±16.8	27.0±7.4	62.4±9.4	<0.001
Demographics				
Age, year	71.0±13.3	66.6±13.8	73.6±12.6	<0.001
Older than 65 years, %	69.3	60.5	81.1	<0.001
Male, %	59.7	72.2	52.7	<0.001
Causes of HF, %				
Ischemic	32.0	39.8	25.4	<0.001
Hypertensive	24.6	21.6	44.3	<0.001
Cardiomyopathic, dilated	24.0	36.3	5.1	<0.001
Cardiomyopathic, hypertrophic	2.2	0.4	9.6	<0.001
Undetermined	15.7	13.7	26.8	<0.001
History				
Hypertension, %	52.6	50.4	68.3	<0.001
Diabetes mellitus, %	29.8	33.3	29.4	0.150
Hyperlipidemia, %	24.6	28.8	22.8	0.020
Chronic renal failure, %	11.7	10.4	14.9	0.015
Serum creatinine, mg/dl	1.38	1.36	1.40	0.712
Anemia, %	20.7	13.2	27.1	<0.001
Hemoglobin, g/dl	12.3	12.8	11.6	<0.001
Stroke, %	14.7	14.6	15.0	0.844
COPD, %	6.5	6.1	8.6	0.089
Atrial fibrillation, %	35.0	24.5	38.3	<0.001
Sustained VT/Vf, %	6.1	9.6	5.0	0.004
Previous PCI, %	17.4	20.8	15.2	0.014
Previous CABG, %	9.2	11.4	7.8	0.040
NYHA class at discharge, %				
I	34.9	35.7	37.3	0.428
II	54.5	55.7	53.6	
III	5.9	5.9	5.0	
IV	3.5	2.7	4.1	
Vital signs at discharge				
Body mass index, kg/m^2	22.7±4.2	22.7±4.2	22.8±4.4	0.658
Heart rate, beats/mim	70.5±12.0	70.9±12.4	69.4±12.5	0.041
Systolic blood pressure, mmHg	117.0±18.6	113.2±17.4	121.9±20.2	<0.001
Diastolic blood pressure, mmHg	66.1±11.6	66.0±11.8	66.8±11.9	0.243
Plasma BNP at discharge, pg/dl	390±508	396±551	366±386	0.415

HF, heart failure; EF, ejection fraction; LV, left ventricular; COPD, chronic obstructive pulmonary disease; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; NYHA, New York Heart Association; BNP, B-type natriuretic peptide.

Table 2. Discharge Medications of HF Patients With Reduced EF vs Preserved EF

	Total cohort (n=1,613)	Reduced EF (n=947)	Preserved EF (n=401)	P-value
ACE inhibitors	38.7	44.2	25.4	<0.001
ARB	46.4	45.9	48.9	0.322
ACE or ARB	79.1	83.5	70.1	<0.001
ACE and ARB	6.0	6.7	4.2	0.086
β-blocker	57.5	65.9	40.1	<0.001
Diuretic	87.0	88.1	84.8	0.101
Spironolactone	42.2	45.9	36.4	<0.001
Digitalis	27.2	28.7	24.2	0.088
Calcium channel blocker	25.4	17.1	42.9	<0.001
Nitrates	23.0	22.6	20.2	0.330
Anti-arrhythmic	18.5	20.9	17.2	0.119
Aspirin	48.4	49.2	43.9	0.074
Warfarin	39.8	42.9	37.7	0.075
Statin	21.0	23.1	15.0	<0.001

ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker. Other abbreviations see in Table 1.

Table 1 compares the baseline clinical characteristics among patients with reduced (n=985) and preserved EF (n=429). As expected, the mean EF was 27.0% in patients with reduced EF, whereas it was in the normal range for patients with preserved EF (62.4%). Compared with patients with reduced EF, the patients with preserved EF were significantly older and were more often women. The causes of HF were ischemic heart disease and dilated cardiomyopathy in a higher percentage of patients with reduced EF, whereas hypertensive heart disease and hypertrophic cardiomyopathy were more common in those with preserved EF. Patients with preserved EF were also more likely to have a history of hypertension, renal failure, anemia, and atrial fibrillation. In contrast, hyperlipidemia, sustained ventricular tachycardia or ventricular fibrillation, and previous coronary revascularization were more common in patients with reduced EF.

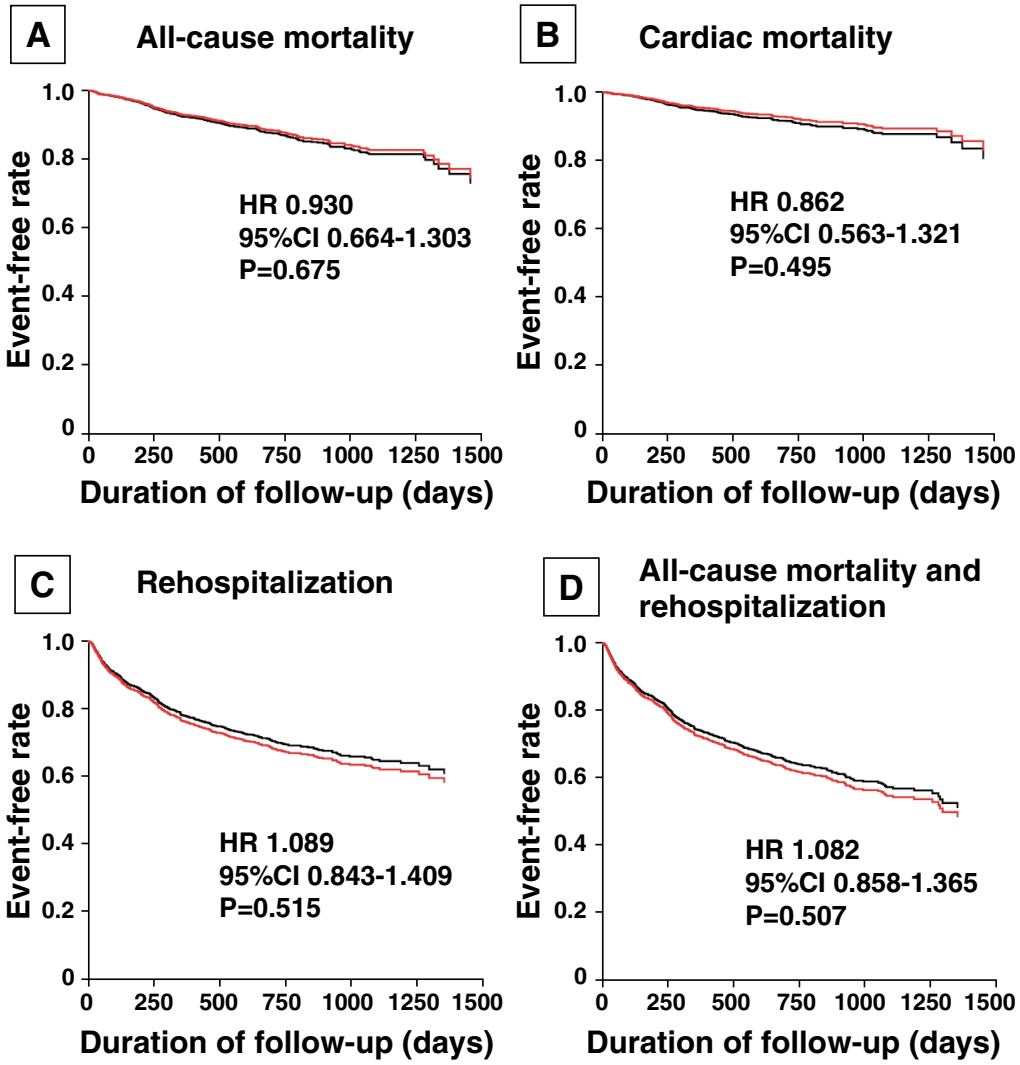

Figure 2. Adjusted event-free curves from (**A**) all-cause death, (**B**) cardiac death, (**C**) rehospitalization as a result of heart failure (HF), and (**D**) all-cause death or rehospitalization because of HF in patients with reduced ejection fraction (EF) (black lines; n=847) compared with preserved EF (red lines; n=370). The data were adjusted for differences in baseline variables, including age, gender, ischemic heart disease, dilated cardiomyopathy, hypertension, hyperlipidemia, renal failure, anemia, sustained ventricular tachycardia or fibrillation, atrial fibrillation or flutter, previous percutaneous coronary intervention, previous coronary artery bypass graft, heart rate, systolic blood pressure, discharge medications such as angiotensin converting enzyme inhibitor inhibitor, β-blocker, calcium channel blocker, and statin. HR, hazard ratio; CI, confidence interval.

Medication Use

Table 2 compares the medication use at the time of discharge. Angiotensin converting enzyme (ACE) inhibitors, β-blocker, spironolactone, and statin were more prescribed in patients with reduced EF. In contrast, more patients with preserved EF were prescribed calcium channel blockers.

In-Hospital Outcomes

Length of hospital stay was longer in patients with reduced EF than those with preserved EF (35.6 days vs 31.2 days; P=0.03). During the hospital stay, 66 patients died; 38 with reduced EF and 28 with preserved EF. Unadjusted in-hospital mortality rates were significantly higher in patients with preserved EF: 6.5% vs 3.9% for those with reduced EF (unadjusted odds ratio (OR) 1.74 and 95%CI 1.05–2.87; P=0.03). After multivariate adjustment, the adjusted OR for in-hospital mortality also tended to be higher in patients with preserved EF, which, however, did not reach statistical significance (adjusted OR 2.94 and 95%CI 0.89–9.72; P=0.08). The in-hospital mortality rate in patients with EF between 40% and 50% was 4.7%, which did not differ from those in patients with reduced or preserved EF.

Long-Term Outcomes After Hospital Discharge

The long-term follow-up data could be obtained in 1,217 (847 and 370 for reduced and preserved EF, respectively) out of 1,414 registered patients (90.3%). Mean post-discharge follow-up was 863±264 days (2.4±0.7 years); 869±259 for reduced EF and 852±273 days for preserved EF (P=0.32).

During the follow-up period of 2.4 years, 235 (19.3%) patients died; 150 (12.3%) from cardiac causes and 85 (7.0%) from non-cardiac causes. The rates of all-cause mortality within 1 year after discharge were 8.9% and 11.6% in

Table 3. Long-Term Outcomes for HF Patients With Reduced EF vs Preserved EF

Outcomes	Number (%)		Reduced EF (95%CI)	Rreserved EF (95%CI)
	Unadjusted HR (n=847)	Adjusted HR (n=370)		
All-cause mortality	151 (17.8%)	84 (22.7%)	1.296 (0.992–1.695) P=0.058	0.930 (0.664–1.303) P=0.675
Cardiac mortality	100 (11.8%)	50 (13.5%)	1.154 (0.820–1.624) P=0.412	0.862 (0.563–1.321) P=0.495
Rehospitalization	283 (33.4%)	134 (36.2%)	1.125 (0.916–1.381) P=0.263	1.089 (0.843–1.409) P=0.515
All-cause mortality or rehospitalization	339 (40.0%)	168 (45.4%)	1.190 (0.989–1.432) P=0.065	1.082 (0.858–1.365) P=0.507

HR, hazard ratio; CI, confidence interval. Other abbreviations see in Table 1.
HF with reduced EF was used as a reference against HF with preserved EF when the HRs were calculated.

Table 4. Subgroup Analysis of All-Cause Death for HF Patients With Reduced EF vs Preserved EF

Subgroup	n	HR reduced EF vs preserved EF	95%CI
Age			
≥65 years	804	0.949	0.655–1.375
<65 years	413	1.253	0.540–2.909
Gender			
Male	806	0.878	0.576–1.339
Female	411	0.995	0.548–1.806
Etiology			
Ischemic	425	0.919	0.540–1.564
Non-ischemic	792	0.946	0.602–1.487
Hypertension			
Hypertension	677	0.949	0.583–1.544
No hypertension	534	1.007	0.612–1.657
Diabetes			
Diabetes	385	0.607	0.321–1.147
No diabetes	831	1.057	0.704–1.588
Medication use at discharge			
ACE inhibitor/ARB	970	0.879	0.555–1.390
No ACE inhibitor/ARB	247	1.011	0.598–1.709
β-blocker	708	0.914	0.543–1.540
No β-blocker	509	0.957	0.606–1.512
Spironolactone	686	1.257	0.678–2.234
No spironolactone	531	0.835	0.550–1.268

Abbreviations see in Tables 1–3.
HF with reduced EF was used as a reference against HF with preserved EF when the HRs were calculated.

patients with reduced and preserved EF, respectively, which did not differ between groups (P=0.13). The prevalence of cardiac mortality within all-cause mortality was 66% and 59% in patients with reduced EF and preserved EF, respectively, which did not differ between groups (P=0.27). Rehospitalization rates during the same period were 23.7% and 25.7% in reduced and preserved EF, respectively, which also did not differ between groups (P=0.47). The rates of all-cause mortality and rehospitalization within 1 year after discharge in patients with EF between 40% and 50% were 7.0% and 24.8%, respectively, which did not differ from those in other 2 groups.

Figure 2 shows adjusted event-free survival curves and **Table 3** shows unadjusted and adjusted HR of outcomes for patients with reduced (n=847) and preserved EF (n=370). HR with reduced EF was used as a reference against HF with preserved EF when the HR was calculated. There was no significant difference in survival curves free from all-cause death between patients with reduced and preserved EF (adjusted HR 0.930 and 95%CI 0.664–1.303; P=0.675). There were also no significant differences in cardiac death between groups (adjusted HR 0.862; 95%CI 0.563–1.321; P=0.495). The combined all-cause death or rehospitalization free curves did not differ between groups (adjusted HR 1.082 and 95%CI 0.858–1.365; P=0.507).

The results of subgroup analysis for all-cause mortality stratified by age (≥65 vs <65 years), gender (male vs female), etiology (ischemic vs non-ischemic), presence of hypertension, presence of diabetes, and medication use at discharge are shown in **Table 4**. The association between EF and all-cause death in each subgroup was similar to that found on the primary analysis.

Discussion

The present study based on the JCARE-CARD provides a comparison of the clinical characteristics, treatment, and outcomes of HF patients with reduced vs preserved EF encountered in routine clinical practice in Japan. It confirms previous studies that HF with preserved EF is common and accounts for a significant proportion of patients with HF. They have similar in-hospital as well as long-term mortality after discharge to those with reduced EF. Therefore, preserved EF does not readily mean 'good' prognosis. In

Table 5. Cohort Studies for Hospitalized HF Patients With Reduced EF vs Preserved EF

Study/Country	Reference	Year	No.	EF cut-off values (%)	Preserved/ Total (%)	Follow-up	Mortality (P/R, %)	Rehospitalization (P/R, %)
EuroHeart Failure Survey/Europe	5	2004	10701	≥40%	3,148/6,806 (46)	12 weeks	10/12	22/21
Owan/USA	26	2006	6076	≥50%	2,167/4,596 (47)	1 year	29/32	–
Sach Bhatia/Canada	20	2006	9945	>50%	880/2,802 (31)	1 year	22.2/25.5	13.5/16.1
OPTIMIZE/USA	7	2007	48612	≥40%	21,149/41,267 (51)	60±90 days	9.5/9.8	29.2/29.9
JCARE-CARD/Japan (The present study)	–	2009	2675	≥50%	429/1,692 (22)	2.4 years	22.7/17.8	36.2/33.4

P/R, preserved/reduced EF. Other abbreviations see in Table 1.

light of the present findings, effective management strategies need to be established for this subset of HF patients.

HF has been traditionally classified as 'diastolic' or 'systolic', but this nomenclature has become the subject of controversy.[13,14] In the present study, we used the term 'HF with preserved EF' rather than 'diastolic HF' because this terminology has been adopted in the guidelines in American College of Cardiology/American Heart Association[15] and European Society of Cardiology.[16] There is no simple binary division between 'preserved' and 'reduced' EF. Instead there might be a 'border zone' where there is uncertainty. We thus defined EF >50% as 'preserved' and EF <40% as 'reduced' and excluded patients with EF between 40% and 50% from the present analysis.

The prevalence of HF with preserved EF was 26% in the present study, which is consistent with the values ranging 24–55% reported from previous studies and also recent large-scale registries from the USA and Europe.[6,7,17,18] Euro Heart Failure Survey reported that 3,148 out of 6,806 patients (46.3%) had HF and preserved systolic function.[17] The ADHERE database included more than 100,000 patients hospitalized with HF and showed that 50.4% had EF ≥40% and 22.7% had ≥55%.[6,18] In OPTIMIZE-HF registry, including 48,612 patients hospitalized for HF, 41,267 (84.9%) had data for EF or a qualitative LV function assessment and, of the patients with LV function assessed, 21,149 (51.2%) had EF ≥40% or a qualitatively normal/mildly impaired EF.[7] Even though the definitions for preserved EF have varied and the appropriate EF cut-off values have not been established, the previous findings were mostly similar to our present results.

The clinical characteristics of the study patients were also similar to those of the ADHERE and OPTIMIZE-HF.[6,7] HF patients with preserved EF were older, more often female, and more likely to have hypertension (**Table 1**). They were likely to have a hypertensive rather than ischemic etiology. Higher prevalence of HF with preserved EF in elderly patients most likely reflects the effects of aging on myocardial structure, and the high prevalence of cardiac hypertrophy and coronary artery disease in this group of HF patients.[19] HF patients with preserved EF also had higher prevalence of atrial fibrillation, which might be a consequence as well as a precipitating factor for clinical deterioration of HF. Anemia was also prevalent in HF patients with preserved EF than those with reduced EF (**Table 1**). In parallel to higher prevalence of anemia in patients with preserved EF, the hemoglobin concentration was significantly lower in this group (P<0.001). Higher prevalence of anemia in patients with preserved EF was also documented in other previous studies.[20,21] In the sub-analysis of CHARM (Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity) program, lower hemoglobin was associated with greater EF.[21] They speculated that anemia was associated with greater EF as a result of increased cardiac output, reduced systemic vascular resistance and the resultant reduction in the afterload to the heart.[22,23] Although the precise mechanisms responsible for the association between anemia and preserved EF are unclear, it might be an unique clinical feature associated with this type of HF. Chronic renal failure was more prevalent in patients with preserved EF (**Table 1**). However, serum creatinine concentrations were similar between reduced and preserved EF.

Patients with preserved EF were less likely to receive ACE inhibitors, β-blockers, spironolactone, and statins at the time of discharge (**Table 2**), which are also consistent with the previous studies.[2,3,6] These results might reflect a lack of evidence-based strategies for effective medication of this type of HF.

Unadjusted in-hospital mortality rates in patients with preserved EF were higher than those with reduced EF, which, however, were not different after multivariable adjustment. These results are not consistent with those in the ADHERE and the OPTIMIZE-HF.[6,7] The ADHERE study showed that in-hospital mortality was lower in patients with preserved EF compared to that with reduced EF (2.8% vs 3.9%; P=0.005).[6] Similarly, the OPTIMIZE-HF registry reported that the risk of in-hospital mortality was lower in patients with preserved EF (2.9% vs 3.9%; P<0.0001).[7] However, the difference in the survival rate between preserved and reduced EF was quite small (1%) in these studies and HF patients with preserved EF remain at equally high risk for mortality during hospitalization as those with reduced EF. In-hospital outcomes of HF patients might be determined by various factors other than EF, such as the presence of comorbidities. Therefore, further studies are needed to determine the predictors of in-hospital outcomes in patients hospitalized with worsening HF.

The present study showed that the post-discharge long-term survival and rehospitalization as a result of the worsening of HF were also similar between preserved and reduced EF (**Table 3** and **Figure 2**). Further, the association between the long-term outcomes and EF was not affected by age, sex, etiology, comorbidities, and the use of ACE inhibitor or angiotensin receptor blocker (ARB) and β-blocker at discharge (**Table 4**). The OPTIMIZE-HF also showed that patients with preserved EF had similar mortality risk (9.5% vs 9.8%; P=0.459) and rehospitalization rates compared to those with reduced EF. However, the findings from the OPTIMIZE-HF were limited because the follow-up data were collected from a pre-specified subset of patients (only 10%). In addition, the follow-up period was limited to 60–90 days after hospital discharge, which might have been too short to draw any conclusive findings. Therefore, the duration of follow-up in the present study (2.4 years) has extended the findings from OPTIMIZE-HF and contributed new observations and insights. The present

findings are also consistent with the study by Bhatia among 2,802 patients hospitalized with new-onset HF, which showed that the post-discharge survival of patients with HF and preserved EF was similar to those with reduced EF.[20] However, that study was also limited in that only 42% of potentially eligible patients had a documented assessment of LV function and it drew from only a single province in Canada. Other community-based study also demonstrated comparable 6-month mortality rates in patients with systolic and diastolic dysfunction.[24] Although the JCARE-CARD data are consistent with earlier observations in patients with preserved EF, it should be noted that they were followed up for a longer period of time (**Table 5**).[5,7,20,26] Even though other studies reported more favorable survival in patients with preserved EF, its difference was even small.[1,25,26]

Despite the risk for long-term adverse outcomes, sufficient data are lacking to prove the effective treatment strategies for HF patients with preserved EF. Current HF guideline recommendations include control of blood pressure in hypertension, ventricular rate control in atrial fibrillation, and use of diuretics to control pulmonary congestion and peripheral edema for patients with preserved EF.[15,16] The CHARM study observed a reduction in HF hospitalizations for HF patients and preserved EF who were treated with the ARB candesartan in addition to standard background therapy.[27] On the contrary, recent clinical trial I-PRESERVE (Irbesartan in Patients with Heart Failure and Preserved Ejection Fraction) could not confirm the clinical benefits of ARB irbesartan in HF with preserved EF.[28] In the JCARE-CARD, HF patients with preserved EF were less likely to be treated with an ACE inhibitor or ARB and β-blockers than those with reduced EF (**Table 2**). Despite the lack of data to support the efficacy of these drugs, they might be potentially beneficial in patients with HF and preserved EF who also have other indications for these agents, such as coronary artery disease, diabetes mellitus, or hypertension. Given the high post-discharge clinical event rate and the lack of proven medical therapies for this type of HF, there is a clear need to establish the effective management strategies.

There are several limitations which should be acknowledged in the present study. First, the present observations included only hospitalized patients with worsening HF, a population known to be at increased risk of adverse outcomes including mortality and rehospitalization.[29,30] By using the criteria regarding their symptoms and signs sufficiently severe to be hospitalized for HF, we could enroll patients with reasonably uniform status on admission. Second, EF was not assessed in 332 patients (12.4%), and these patients were excluded from the analysis. These values are similar to those in the OPTIMIZE-HF registry (15%).[7] However, they are lower than the values in Euro Heart failure survey (approximately 50%).[5] Third, JCARE-CARD is not a prospective randomized trial, and despite covariate adjustment, other measured and unmeasured factors might have influenced outcomes. We could not completely exclude other unmeasured factors that might also affect outcomes. Fourth, the data were dependent on the accuracy of documentation and abstraction by individual hospitals and cardiologists that participated in this study. However, it is not the objective of this survey to restrict enrollment to the narrowly defined population of HF usually included in clinical trials, but rather to include a broad range of patients reflecting the current reality of clinical practice. Finally, we did not have the detailed information regarding the causes of death in our study patients. Further studies focusing on this crucial issue are clearly needed in HF patients with reduced and preserved EF.

Conclusion

In conclusion, preserved EF was present in a substantial proportion of hospitalized patients with worsening HF in the large unselected registry in Japan. Although patients with HF and preserved EF differ significantly from those with reduced EF, both groups experience similar rates of mortality and rehospitalization as a result of worsening HF. Given the high risk of adverse clinical events and the lack of a sufficient evidence to guide the treatment, clinical trials are critically needed to identify the effective management strategies for this type of patients with HF.

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References

1. Hogg K, Swedberg K, McMurray J. Heart failure with preserved left ventricular systolic function; epidemiology, clinical characteristics, and prognosis. *J Am Coll Cardiol* 2004; **43:** 317–327.
2. Philbin EF, Rocco TA Jr, Lindenmuth NW, Ulrich K, Jenkins PL. Systolic versus diastolic heart failure in community practice: Clinical features, outcomes, and the use of angiotensin-converting enzyme inhibitors. *Am J Med* 2000; **109:** 605–613.
3. Tsutsui H, Tsuchihashi M, Takeshita A. Mortality and readmission of hospitalized patients with congestive heart failure and preserved versus depressed systolic function. *Am J Cardiol* 2001; **88:** 530–533.
4. Smith GL, Masoudi FA, Vaccarino V, Radford MJ, Krumholz HM. Outcomes in heart failure patients with preserved ejection fraction: Mortality, readmission, and functional decline. *J Am Coll Cardiol* 2003; **41:** 1510–1518.
5. Lenzen MJ, Scholte op Reimer WJ, Boersma E, Vantrimpont PJ, Follath F, Swedberg K, et al. Differences between patients with a preserved and a depressed left ventricular function: A report from the EuroHeart Failure Survey. *Eur Heart J* 2004; **25:** 1214–1220.
6. Yancy CW, Lopatin M, Stevenson LW, De Marco T, Fonarow GC. Clinical presentation, management, and in-hospital outcomes of patients admitted with acute decompensated heart failure with preserved systolic function: A report from the Acute Decompensated Heart Failure National Registry (ADHERE) Database. *J Am Coll Cardiol* 2006; **47:** 76–84.
7. Fonarow GC, Stough WG, Abraham WT, Albert NM, Gheorghiade M, Greenberg BH, et al. Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: A report from the OPTIMIZE-HF Registry. *J Am Coll Cardiol* 2007; **50:** 768–777.
8. Ogawa M, Tanaka F, Onoda T, Ohsawa M, Itai K, Sakai T, et al. A community based epidemiological and clinical study of hospitalization of patients with congestive heart failure in Northern Iwate, Japan. *Circ J* 2007; **71:** 455–459.
9. Kawashiro N, Kasanuki H, Ogawa H, Matsuda N, Hagiwara N. Clinical characteristics and outcome of hospitalized patients with congestive heart failure: Results of the HIJC-HF registry. *Circ J* 2008; **72:** 2015–2020.
10. Tsuchihashi M, Tsutsui H, Kodama K, Kasagi F, Takeshita A. Clinical characteristics and prognosis of hospitalized patients with congestive heart failure: A study in Fukuoka, Japan. *Jpn Circ J* 2000; **64:** 953–959.
11. Tsuchihashi M, Tsutsui H, Kodama K, Kasagi F, Setoguchi S, Mohri M, et al. Medical and socioenvironmental predictors of hospital readmission in patients with congestive heart failure. *Am Heart J* 2001; **142:** E7.
12. Tsutsui H, Tsuchihashi-Makaya M, Kinugawa S, Goto D, Takeshita

A. Clinical characteristics and outcome of hospitalized patients with heart failure in Japan: Rationale and design of Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD). *Circ J* 2006; **70:** 1617–1623.
13. Zile MR. Heart failure with preserved ejection fraction: Is this diastolic heart failure? *J Am Coll Cardiol* 2003; **41:** 1519–1522.
14. Burkhoff D, Maurer MS, Packer M. Heart failure with a normal ejection fraction: Is it really a disorder of diastolic function? *Circulation* 2003; **107:** 656–658.
15. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, et al. 2009 focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: Developed in collaboration with the International Society for Heart and Lung Transplantation. *Circulation* 2009; **119:** e391–e479.
16. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology: Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *Eur Heart J* 2008; **29:** 2388–2442.
17. Cleland JG, Swedberg K, Follath F, Komajda M, Cohen-Solal A, Aguilar JC, et al. The EuroHeart Failure survey programme--a survey on the quality of care among patients with heart failure in Europe. Part 1: Patient characteristics and diagnosis. *Eur Heart J* 2003; **24:** 442–463.
18. Sweitzer NK, Lopatin M, Yancy CW, Mills RM, Stevenson LW. Comparison of clinical features and outcomes of patients hospitalized with heart failure and normal ejection fraction (> or =55%) versus those with mildly reduced (40% to 55%) and moderately to severely reduced (<40%) fractions. *Am J Cardiol* 2008; **101:** 1151–1156.
19. Wei JY. Age and the cardiovascular system. *N Engl J Med* 1992; **327:** 1735–1739.
20. Bhatia RS, Tu JV, Lee DS, Austin PC, Fang J, Haouzi A, et al. Outcome of heart failure with preserved ejection fraction in a population-based study. *N Engl J Med* 2006; **355:** 260–269.
21. O'Meara E, Clayton T, McEntegart MB, McMurray JJ, Lang CC, Roger SD, et al. Clinical correlates and consequences of anemia in a broad spectrum of patients with heart failure: Results of the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) Program. *Circulation* 2006; **113:** 986–994.
22. Anand IS, Chandrashekhar Y, Wander GS, Chawla LS. Endothelium-derived relaxing factor is important in mediating the high output state in chronic severe anemia. *J Am Coll Cardiol* 1995; **25:** 1402–1407.
23. Katz SD, Rao R, Berman JW, Schwarz M, Demopoulos L, Bijou R, et al. Pathophysiological correlates of increased serum tumor necrosis factor in patients with congestive heart failure: Relation to nitric oxide-dependent vasodilation in the forearm circulation. *Circulation* 1994; **90:** 12–16.
24. Bursi F, Weston SA, Redfield MM, Jacobsen SJ, Pakhomov S, Nkomo VT, et al. Systolic and diastolic heart failure in the community. *JAMA* 2006; **296:** 2209–2216.
25. Vasan RS, Larson MG, Benjamin EJ, Evans JC, Reiss CK, Levy D. Congestive heart failure in subjects with normal versus reduced left ventricular ejection fraction: Prevalence and mortality in a population-based cohort. *J Am Coll Cardiol* 1999; **33:** 1948–1955.
26. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. *N Engl J Med* 2006; **355:** 251–259.
27. Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: The CHARM-Preserved Trial. *Lancet* 2003; **362:** 777–781.
28. Massie BM, Carson PE, McMurray JJ, Komajda M, McKelvie R, Zile MR, et al. Irbesartan in patients with heart failure and preserved ejection fraction. *N Engl J Med* 2008; **359:** 2456–2467.
29. de Giuli F, Khaw KT, Cowie MR, Sutton GC, Ferrari R, Poole-Wilson PA. Incidence and outcome of persons with a clinical diagnosis of heart failure in a general practice population of 696,884 in the United Kingdom. *Eur J Heart Fail* 2005; **7:** 295–302.
30. Tsutsui H, Tsuchihashi-Makaya M, Kinugawa S, Goto D, Takeshita A. Characteristics and outcomes of patients with heart failure in general practices and hospitals: Japanese Cardiac Registry of Heart Failure in General Practice (JCARE-GENERAL). *Circ J* 2007; **71:** 449–454.