Clinical Characteristics, Management, and Outcomes of Japanese Patients Hospitalized for Heart Failure With Preserved Ejection Fraction
— A Report From the Japanese Heart Failure Syndrome With Preserved Ejection Fraction (JASPER) Registry —

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Background: Despite the specific characteristics of heart failure with preserved ejection fraction (HFpEF) having been demonstrated predominantly from registries in Western countries, important international differences exist in terms of patient characteristics, management and medical infrastructure between Western and Asian countries.

Methods and Results: We performed nationwide registration of consecutive Japanese hospitalized HFpEF patients with left ventricular EF ≥50% from 15 sites between November 2012 and March 2015. Follow-up data were obtained up to 2 years post-discharge. A total of 535 patients were registered. The median age was 80 years and 50% were female. The most common comorbid conditions were hypertension (77%) and atrial fibrillation (AF: 62%), but body mass index was relatively low. In-hospital mortality rate was 1.3% and the median length of hospitalization was 16 days. By 2 years post-discharge, 40.8% of patients had all-cause death or HF hospitalization. Approximately one-half of deaths had a cardiac cause. Lower serum albumin on admission was one of the strongest independent determinants of worse clinical outcome.

Conclusions: Japanese HFpEF patients were less obese, but had a substantially higher prevalence of AF and lower incidence of subsequent events compared with previous reports. Our findings indicated that specific preventative and therapeutic strategies focusing on AF and nutritional status might need to be considered for Japanese hospitalized patients with HFpEF.

Key Words: Albumin; Epidemiology; Heart failure with preserved ejection fraction; Japan; Prognosis

Received January 19, 2018; revised manuscript received February 13, 2018; accepted February 21, 2018; released online March 23, 2018

This paper was presented at the 82nd Annual Scientific Meeting of the Japanese Circulation Society, Late Breaking Cohort Studies 2-1 (March 24, 2018, Osaka, Japan)

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exist in patients' characteristics, clinical practice patterns and healthcare resources and expenditure, particularly between Western and Asian countries. Notably, Japanese patients hospitalized for HF have a substantially lower prevalence of ischemic heart disease (IHD), obesity and COPD, and longer length of hospital stay than US patients. These racial and geographical differences may influence clinical outcomes. Furthermore, the recommended management for HFrEF patients focuses on the appropriate treatment of comorbid conditions because of a lack of specific medication that can improve the outcomes for HFrEF patients in contrast to those for HFrEF patients. From this point of view, physicians need to know the region-specific clinical characteristics, management, and outcomes of HFrEF patients in each country; however, these have not been fully elucidated in Asia, especially in Japan. Several previous reports have presented epidemiological information of hospitalized HFrEF patients with comparison to HFrEF, but patients in those studies were registered before relatively recent Japanese and Western HF guidelines published in 2011–2012. Furthermore, the previous studies other than the Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD) in Japanese hospitalized HFrEF patients were retrospective and/or single center studies and had relatively small sample sizes (n=73–169, JCARE-CARD [n=429]). Strong prognostic determinants of subsequent HF-specific adverse events (death and HF admission) also have not been fully identified in Japanese hospitalized HFrEF patients in a larger study population, even in JCARE-CARD.

Accordingly, we investigated the clinical demographics, treatment, and long-term outcomes, including important prognostic determinants, in Japanese hospitalized HFrEF patients using data from a recently registered HFrEF-specific nationwide cohort study in Japan, the Japanese Heart Failure Syndrome with Preserved Ejection Fraction (JASPER) registry.

Methods

Study Design

The JASPER registry is a multicenter, observational, prospective cohort that includes consecutive patients aged ≥20 years requiring hospitalization with a diagnosis of acute HF according to the Framingham criteria by at least 2 experienced cardiologists, with preserved left ventricular (LV) systolic function defined as LVEF ≥50% by the modified Simpson method or LV fractional shortening ≥25% by echocardiography. Patients with acute coronary syndrome, receiving hemodialysis or with a history of heart transplantation were excluded.

The patients' demographic data including comorbid conditions, clinical signs, laboratory and echocardiographic data, in-hospital treatment including oral and intravenous medications, and length of hospital stay were obtained. Regarding the precipitating factors for HF admission, we used the Electronic Data Capture (EDC) system for collecting the clinical data from each site. Each site could select individual precipitating factors from a dropdown list on the EDC system. Thus, expert cardiologists at each site chose the most appropriate precipitating factor from these categories based on their clinical judgment. Mortality was defined as death from any cause, death from cardiovascular (CV) causes including sudden cardiac death (SCD) and death from worsening HF, myocardial infarction, cerebrovascular accident or other CV disease, and death from non-CV cause. Death was considered as SCD unless a specific CV other than SCD or non-CV cause was identified by the primary physician.

Follow-up was performed at discharge and at 12 and 24 months after discharge by direct contact with patients or their physicians at the hospital or outpatient clinic, telephone interview of patients or, if deceased, of family members, and by mail, by dedicated coordinators and investigators. In this study, because patient information was anonymized and de-identified prior to analyses, written informed consent was not obtained from each patient. However, we publicized the study by posting a summary of the protocol (with an easily understood description) on the website of the National Cerebral and Cardiovascular Center; the notice clearly informed patients of their right to refuse enrolment. These procedures for informed consent and enrolment were in accordance with the detailed regulations regarding informed consent described in the guidelines, and this study, including the procedure for enrolment, was approved by the Institutional Review Board of each site, and registered under the Japanese UMIN Clinical Trials Registration (UMIN000010601).

Statistical Analysis

Continuous variables are presented as mean±SD when normally distributed, and as median and interquartile range (IQR) when non-normally distributed. Comparisons of parameters across atrial fibrillation (AF) status groups were made by Kruskal-Wallis test for continuous variables, and by chi-squared test or Fisher’s exact test for dichotomous variables, when appropriate.

The cumulative incidence of the composite of all-cause death and HF rehospitalization, CV death, non-CV death and HF rehospitalization was estimated using Kaplan-Meier curves.

The association between parameters and the composite of all-cause death and HF readmission was assessed by Cox proportional hazards regression. Univariate factors that had a value of P<0.05 were identified according to the number of events. Finally, these factors were entered into the multivariate model to assess the independent prognostic determinants on admission of the composite of all-cause death and HF rehospitalization. Moreover, stepwise selection with a P-value of 0.10 for backward elimination was used to select the best predictive model in the total population.

All tests were 2-tailed, and a value of P<0.05 was considered statistically significant. All analyses were performed with Stata MP64 version 15 (StataCorp, College Station, TX, USA).

Results

Baseline Characteristics, Treatment and In-Hospital Death in JASPER and Comparison With HFrEF Registries in the USA

A total of 535 consecutive hospitalized HFrEF patients from 15 university or teaching hospitals were registered in the JASPER registry. Table 1 shows their baseline characteristics. Median age was 80 years and 50% were female. The prevalence of hypertension, IHD and AF were 77%, 28% and 62%, respectively. Median B-type natriuretic peptide (BNP) level was 414 pg/mL on admission. Intravenous
### Table 1. Baseline Patient Characteristics on Admission, and In-Hospital Treatment and Death of Patients in the JASPER Registry

| Variables                                    | Overall (n=535) | Missing |
|----------------------------------------------|----------------|---------|
| Age, years                                   | 80 (73–84)     | 0 (0)   |
| Female                                       | 267 (50.0)     | 0 (0)   |
| BMI, kg/m²                                    | 23.9±4.7       | 19 (3.5) |
| NYHA functional class on admission           |                | 22 (4.1) |
| I                                            | 4 (0.7)        |         |
| II                                           | 110 (20.6)     |         |
| III                                          | 212 (39.6)     |         |
| IV                                           | 187 (35.0)     |         |
| NYHA functional class at discharge           |                | 53 (9.9) |
| I                                            | 183 (34.2)     |         |
| II                                           | 269 (50.3)     |         |
| III                                          | 29 (5.4)       |         |
| IV                                           | 1 (0.4)        |         |
| Vital signs on admission                     |                |         |
| Heart rate, beats/min                        | 80 (66–100)    | 0 (0)   |
| SBP, mmHg                                     | 147 (124–171)  | 0 (0)   |
| DBP, mmHg                                     | 76 (64–92)     | 4 (0.7) |
| Vital signs at discharge                     |                |         |
| Heart rate, beats/min                        | 66 (60–74)     | 10 (1.9)|
| SBP, mmHg                                     | 113 (102–124)  | 9 (1.7) |
| DBP, mmHg                                     | 60 (53–68)     | 10 (1.9)|
| Past history                                 |                |         |
| Smoking                                      | 237 (44.3)     | 18 (3.4)|
| Prior HF admission                           | 194 (36.3)     | 18 (3.4)|
| Prior MI                                     | 66 (12.3)      | 7 (1.3) |
| CAD                                          | 148 (27.7)     | 11 (2.1)|
| AF                                           | 329 (61.5)     | 6 (1.1) |
| Diabetes mellitus                            | 204 (38.1)     | 3 (0.6) |
| Hypertension                                 | 413 (77.2)     | 2 (0.4) |
| Dyslipidemia                                  | 226 (42.2)     | 4 (0.8) |
| CVA                                          | 124 (23.2)     | 10 (1.9)|
| PAD                                          | 55 (10.3)      | 23 (4.3)|
| CKD                                          | 272 (50.8)     | 2 (0.4) |
| COPD/asthma                                   | 58 (10.8)      | 11 (2.1)|
| Sleep apnea syndrome                         | 44 (8.2)       | 59 (11.0)|
| Depression                                   | 8 (1.5)        | 10 (1.9)|
| Liver disease                                 | 35 (6.5)       | 4 (0.8) |
| Clinical signs                                |                |         |
| Breathlessness                                | 486 (90.8)     | 9 (1.7) |
| Elevated JVP                                  | 242 (45.2)     | 64 (12.0)|
| Lower extremity edema                        | 381 (71.2)     | 5 (0.9) |
| Laboratory data on admission                 |                |         |
| Sodium, mEq/L                                | 141 (138–142)  | 0 (0)   |
| BUN, mg/dL                                    | 22 (16–31)     | 0 (0)   |
| Creatinine, mg/dL                            | 1.04 (0.76–1.47)| 0 (0) |
| Hemoglobin, g/dL                             | 11.2±2.2       | 0 (0)   |
| BNP, pg/mL                                    | 414 (225–681)  | 9 (1.7) |
| Troponin T, ng/dL                            | 0.032 (0.020–0.055)| 308 (57.6)|
| Potassium, mEq/L                             | 4.2±0.7        | 0 (0)   |
| White blood cell count, /μL                  | 6,400 (5,000–8,600)| 0 (0) |
| C-reactive protein, mg/dL                    | 0.41 (0.13–1.40)| 8 (1.5) |
| Albumin, g/dL                                 | 3.7 (3.3–4.0)  | 31 (5.8) |
| Total cholesterol, mg/dL                     | 157±38         | 79 (14.8)|
| Total bilirubin, mg/dL                       | 0.7 (0.5–1.0)  | 6 (1.1) |

(Table 1 continued the next page.)
compared with the published US HFpEF registries. The prevalence of IHD, diabetes mellitus and COPD were lower, and that of AF and cerebrovascular accident were higher in Japanese patients than in US patients. Japanese patients had higher sodium levels and lower serum creatinine and BNP levels compared with US patients. More than 60% of Japanese patients, but only 18% of US patients, were treated with intravenous vasodilators regardless of similar systolic blood pressure (SBP) on admission. Hospital diuretics were frequently used in 81% of HFpEF patients, and 60% were treated with vasodilators (Table 1). A total of 7 patients (1.3%: 5 with cardiac cause and 2 with non-cardiac cause) died during hospitalization for a median of 16 days (Table 1).

A comparison of patients’ characteristics and in-hospital death between the JASPER and US HFpEF registries is shown in Table 2. Japanese hospitalized HFpEF patients were older, less obese, and had a lower rate of female sex compared with the published US HFpEF registries. The prevalence of IHD, diabetes mellitus and COPD were lower, and that of AF and cerebrovascular accident were higher in Japanese patients than in US patients. Japanese patients had higher sodium levels and lower serum creatinine and BNP levels compared with US patients. More than 60% of Japanese patients, but only 18% of US patients, were treated with intravenous vasodilators regardless of similar systolic blood pressure (SBP) on admission. Hospital
Baseline Characteristics Across AF Status

Because of the higher prevalence of AF in Japanese patients than in US patients, we compared the patients’ characteristics among AF status stratified by AF history and rhythm (AF or sinus rhythm) on admission. Patients with an AF history had a higher prevalence of prior HF admission with higher prescription rates of loop diuretics, mineral corticoid receptor antagonists, digitalis, and anticoagulation agents, and tended to have a higher frequency of dietary non-compliance among the precipitating factors for HF admission than those without (Table 3, Figure 2B). Patients with no AF history and in sinus rhythm on admission had higher SBP on admission with smaller left atrial size and stay was substantially longer and the in-hospital death rate was lower in Japan than in the USA. Japanese patients were more frequently prescribed angiotensin-receptor blockers and mineral corticoid antagonists at discharge than US patients registered to OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure) (Figure 1). Regarding precipitating factors for HF admission, dietary non-compliance was more frequently observed, and medication non-compliance and renal failure were less frequently observed in Japanese patients than in US patients registered to GWTG-HF (Get With The Guidelines-Heart Failure) (Figure 2A).

### Table 2. Comparison of HF Registries for Hospitalized HfPEF Patients

| Variables | JASPER | ADHERE | OPTIMIZE-HF | GWTG-HF |
|-----------|--------|--------|-------------|---------|
| No. of patients | 535 | 26,322 | 10,072 | 40,354 |
| EF criteria, % | ≥50 | ≥40 | >50 | ≥50 |
| Age, years | 80 (73–84) | 73.9±13.2 | 75.6±13.1 | 78 (67–85) |
| Female, % | 50.0 | 62 | 68 | 63 |
| BMI, kg/m² | 23.9±4.7 | – | – | 29 (24–35) |
| NYHA functional class, % | | | | |
| III | 39.6 | – | 62 | – |
| IV | 35.0 | 34 | 44 | – |
| Heart rate, beats/min | 80 (66–100) | 86.8±22.0 | 84±21 | 80 (68–94) |
| SBP, mmHg | 147 (124–171) | 152.5±32.7 | 150±33 | 145 (125–167) |
| DBP, mmHg | 76 (64–92) | 78.7±20.6 | 75±19 | – |
| Past history, % | | | | |
| Prior MI | 12.3 | 24 | – | – |
| CAD | 27.7 | 50 | 32 | 44 |
| AF | 61.5 | 21 | 32 | 34 |
| Diabetes mellitus | 38.1 | 45 | 41 | 46 |
| Hypertension | 77.2 | 77 | 77 | 80 |
| Dyslipidemia | 42.2 | – | – | 43 |
| CVA | 23.2 | – | – | 15 |
| PAD | 10.3 | 17 | – | 11.9 |
| CKD | 50.8 | 26 | – | 52 |
| COPD/asthma | 10.8 | 31 | – | 33 |
| Laboratory data | | | | |
| Sodium, mEq/L | 141 (138–142) | – | 137.8±4.8 | 138 (136–141) |
| BUN, mg/dL | 22 (16–31) | 29.3±19.3 | – | – |
| Creatinine, mg/dL | 1.04 (0.76–1.47) | 1.7±1.5 | 1.2 (1.0–1.8) | 1.3 (1.0–1.9) |
| Hemoglobin, g/dL | 11.2±2.2 | – | 11.8±2.0 | 11.5 (10.2–12.9) |
| BNP, pg/mL | 414 (225–681) | – | 537 (287–997) | 551 (271–1,081) |
| Troponin T, ng/dL | 0.032 (0.020–0.055) | – | – | 0.05 (0.02–0.10) |
| Initial treatment, % | | | | |
| Intravenous diuretics | 80.6 | 91 | – | – |
| Vasodilators | 60.4 | 18 | – | – |
| Nitrates | 29.2 | 12 | – | – |
| Carperitide | 45.8 | – | – | – |
| Inotropes | 4.1 | 8 | – | – |
| Dobutamine | 3.4 | 3 | – | – |
| PDE-III inhibitors | 1.1 | 1 | – | – |
| In-hospital death, n (%) | 1.3 | 2.8 | 2.9 | 2.5 |
| Length of hospital stay, median (IQR) days | 16 (11–23) | 4.9 (3.1–7.6) | – | – |

ADHERE, Acute Decompensated Heart Failure National Registry; EF, ejection fraction; GWTG-HF, Get With the Guidelines-Heart Failure; HfPEF, HF with preserved ejection fraction; OPTIMIZE-HF, Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure. Other abbreviations as in Table 1.
Figure 1. Medications on admission and at discharge of patients with heart failure with preserved ejection fraction in Japan (JASPER) or the USA (OPTIMIZE-HF). ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; JASPER, Japanese Heart Failure Syndrome with Preserved Ejection Fraction; MRA, mineral corticoid-receptor antagonist; OPTIMIZE-HF, Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure.

Figure 2. Precipitating factors for heart failure admission in Japan and the USA. (A) JASPER and GWTG-HF; (B) across AF status. AF, atrial fibrillation; GWTG-HF, Get With the Guidelines-Heart Failure; JASPER, Japanese Heart Failure Syndrome with Preserved Ejection Fraction; SR, sinus rhythm.
| Variables                      | No history of AF | History of AF | P value  |
|--------------------------------|------------------|---------------|----------|
| **Age, years**                 |                  |               |          |
|                               | 79 (69–84)       | 83 (76–87)    | 0.033    |
| **Female**                     | 91 (50.6)        | 11 (55.0)     | 0.71     |
| **BMI, kg/m²**                 | 23.7 (21.0–26.9) | 23.5 (21.7–25.0) | 0.86   |
| **NYHA functional class**      |                  |               | 0.23     |
| I                              | 0 (0)            | 1 (2.4)       |          |
| II                             | 28 (16.4)        | 6 (14.3)      |          |
| III                            | 72 (42.1)        | 21 (50.0)     |          |
| IV                             | 71 (41.5)        | 14 (33.3)     |          |
| **Heart rate, beats/min**      |                  |               | <0.001   |
|                               | 75 (64–93)       | 115 (78–135)  |          |
| **SBP, mmHg**                  |                  |               | <0.001   |
|                               | 160 (129–190)    | 134 (114–160) |          |
| **DBP, mmHg**                  |                  |               | 0.66     |
|                               | 75 (61–92)       | 79 (69–102)   |          |
| **Past history**               |                  |               |          |
| Smoking                        | 77 (44.3)        | 19 (44.2)     |          |
| Prior HF admission             | 46 (26.9)        | 23 (53.5)     | <0.001   |
| Prior MI                       | 32 (18.1)        | 5 (11.6)      | 0.11     |
| CAD                            | 61 (35.1)        | 11 (26.8)     | 0.21     |
| Diabetes mellitus              | 72 (40.5)        | 21 (47.7)     | 0.73     |
| Hypertension                   | 145 (80.6)       | 33 (75.0)     | 0.14     |
| Dyslipidemia                   | 92 (51.7)        | 15 (34.1)     | <0.001   |
| CVA                            | 31 (17.6)        | 12 (29.3)     | 0.065    |
| PAD                            | 17 (9.7)         | 6 (14.3)      | 0.46     |
| CKD                            | 97 (53.9)        | 25 (56.8)     | 0.030    |
| COPD/Asthma                    | 22 (12.3)        | 6 (14.3)      | 0.38     |
| Sleep apnea syndrome           | 16 (9.9)         | 4 (10.3)      | 0.84     |
| **Clinical signs**             |                  |               |          |
| Breathlessness                 | 162 (91.5)       | 41 (95.4)     | 0.51     |
| Elevated JVP                   | 66 (42.3)        | 23 (57.5)     | 0.013    |
| Lower extremity edema          | 123 (68.7)       | 34 (79.1)     | 0.28     |
| **Laboratory data on admission**|                  |               |          |
| Sodium, mEq/L                  | 141 (138–142)    | 140 (138–142) | 0.94     |
| BUN, mg/dL                     | 22 (16–35)       | 23 (17–34)    | 0.38     |
| Creatinine, mg/dL              | 1.2 (0.7–1.9)    | 1.0 (0.8–1.6) | 0.12     |
| BNP, pg/mL                     | 455 (274–847)    | 424 (203–641) | 0.005    |
| Hemoglobin, g/dL               | 10.8 (9.4–12.7)  | 10.9 (9.9–11.8)| 0.63  |
| **Echocardiography**           |                  |               |          |
| LVEF, %                        | 60 (54–65)       | 59 (52–65)    | 0.023    |
| LAD, mm                        | 42 (37–46)       | 47 (42–50)    | <0.001   |
| LVDD, mm                       | 48 (43–52)       | 46 (42–51)    | 0.41     |
| LVPWD, mm                      | 11 (9–12)        | 11 (9–12)     | 0.27     |
| LVIVSD, mm                     | 11 (10–13)       | 11 (9–12)     | 0.24     |
| LVMI, g/m²                     | 119 (100–149)    | 112 (91–134)  | 0.070    |
| E wave, cm/s                   | 90 (68–105)      | 101 (84–117)  | <0.001   |
| DcT, ms                        | 200 (159–247)    | 207 (171–265) | <0.001   |
| e’ (septum), cm/s              | 4.8 (3.8–6.8)    | 5.0 (3.7–5.6) | <0.001   |
| TRPG, mmHg                     | 36 (27–43)       | 35 (27–45)    | 0.45     |
| IVCD, mm                       | 19 (14–22)       | 22 (17–24)    | 0.005    |
| **Medications before admission**|                  |               |          |
| ACEIs/ARBs                     | 96 (53)          | 26 (59)       | 0.68     |
| β-blockers                     | 71 (39)          | 26 (59)       | 0.074    |
| Loop diuretics                 | 76 (42)          | 26 (59)       | <0.001   |
| MRAs                            | 21 (12)          | 12 (27)       | 0.046    |
| Digitalis                      | 6 (3)            | 4 (9)         | 0.29     |
| Anticoagulation                | 15 (8)           | 33 (75)       | <0.001   |

Values are mean±standard deviation, median (IQR) or percentages. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; LVMI, left ventricular mass index; MRA, mineral corticoid-receptor antagonist; SR, sinus rhythm. Other abbreviations as in Tables 1, 2.
Long-Term Clinical Outcomes and Mode of Death

During a median follow-up period of 731 (IQR 552–813) days, 476 (94.4%) and 363 (72.0%) patients were successfully followed up at 1 year and 2 years after discharge, respectively (Figure 3). Among them, 17.9%, 7.6%, 2.9%, 4.6% and 10.3% of patients experienced all-cause death or HF hospitalization, all-cause death, CV death, non-CV death and HF hospitalization at 1-year post-discharge, respectively (Figure 3). At 2 years post-discharge, 40.8%, 20.9%,
10.5%, 10.5% and 23.1% of patients had all-cause death or HF hospitalization, all-cause death, CV death, non-CV death and HF hospitalization at 1-year post-discharge, respectively (Figure 3). Figure 4 shows the mode of death: almost half of deaths had a cardiac cause, and 24% and 21% of CV deaths were SCD and HF deaths, respectively.

**Determinants of Long-Term Death or HF Hospitalization**

Multivariate Cox regression analyses demonstrated that lower SBP and lower serum albumin level on admission, and NYHA class III/IV and plasma BNP level at discharge were independently associated with the post-discharge composite outcome of all-cause death and HF admission in either covariate selection (Table 4).

**Discussion**

The JASPER registry provides the clinical characteristics, in-hospital treatment, and outcomes of Japanese hospitalized HFpEF patients. The major findings of our study were as follows: (1) in contrast to US hospitalized HFpEF patients, Japanese patients had a substantially higher prevalence of AF but lower prevalences of obesity, IHD, diabetes mellitus, COPD and renal insufficiency; (2) the clinical presentation of Japanese hospitalized HFpEF patients might be mostly characterized by uncontrolled hypertension and flush pulmonary edema without AF, or AF with repeated HF admissions; (3) Japanese HFpEF patients had longer hospital stay and lower in-hospital death rate than US patients; (4) approximately 40% of HFpEF patients experienced adverse events, including death or HF hospitalization, within 2 years post-discharge, and half of them died of CV causes; and (5) lower SBP and lower serum albumin level on admission, and NYHA class III/IV and the plasma BNP level at discharge were powerful and robust determinants of long-term death and HF hospitalization.

Large-scale clinical trials and real-world registries predominantly from Western countries have demonstrated that the main features of HFpEF patients are advanced age and female sex, and these patients have multiple comorbid conditions, including obesity or overweight, systemic hypertension, type 2 diabetes mellitus and renal insufficiency. Of them, obesity/overweight has reached epidemic proportions in patients with HFpEF, and its prevalence is surprisingly high at around 85%. Shah et al recently proposed the emerging mechanisms for the development of HFpEF. Systemic inflammation, mainly caused by these predominant comorbidities, may affect myocardial remodeling and dysfunction in HFpEF through an enhanced endothelium-cardiomyocyte signaling cascade with coronary microvascular endothelial dysfunction. Furthermore, obese HFpEF patients show interesting pathophysiological features such as greater biventricular remodeling, volume overload, worse exercise capacity, more profound hemodynamic instability, and impaired pulmonary vasodilation. In contrast to these findings, our Japanese HFpEF patients had markedly lower BMI (mean 23.9 kg/m² in JASPER vs. median 29 kg/m² in GWTG-HF), but the prevalence of AF was 3-fold higher in JASPER (61.5%) when compared with US hospitalized HFpEF cohorts (21–34%).

Although the actual reason for the marked difference in the prevalence of AF between JASPER and the US HFpEF registries is unclear, we can speculate it is based in the lower prevalence of obesity, IHD, diabetes mellitus, COPD and renal insufficiency, all of which have been recently considered as major/emerging risk factors for developing HFpEF. As a consequence, AF could become a relatively key comorbidity for HFpEF development in Japanese patients compared with US patients. Because AF precedes, is present concurrently with, or occurs subsequent to the onset of HFpEF, it may play important roles in the development and maintenance of HFpEF, especially in Japanese patients. The hospitalized HFpEF patients in this study could be characterized by the following 3 phenotypes after comparison of clinical characteristics across AF status and precipitating factors for HF admission: (1) uncontrolled hypertension with flush pulmonary edema without AF, (2) sudden onset of AF, and (3) AF with repeated HF admissions. Thus, AF and hypertension might be the main therapeutic targets for the prevention of HFpEF development and worsening HF in Japanese patients. In addition, dietary non-compliance was the most frequent precipitating factor for HF admission in this cohort (24.5% of all precipitating factors). Optimizing patient education and disease management strategies based on these population-specific precipitating factors for HF admission could lead to prevention of worsening HF. Future studies should focus on testing interventions targeting these contributing factors.

The overall absolute rate of in-hospital death for patients with HFpEF in the present study (1.3%) differed from that reported in the OPTIMIZE-HF (2.9%), ADHERE (2.8%) and GWTG-HF (2.5%) cohorts, despite the longer hospital stay for Japanese patients. These differences were largely related to differences in the cohorts' characteristics, treatment, and the setting of the study, including the enrolment period as well as the definition of HFpEF. Nevertheless, a recent report from Singapore showed similar findings regarding in-hospital death (1.2%). In terms of long-term clinical outcomes, our study revealed that HFpEF in Japanese is not always a benign entity, having a 2-year mortality rate of 20.9%. The JCARE-CARD registry reported a similar mortality of approximately 19% after a mean follow-up of 2.4 years. The 2-year all-cause mortality rate of Singapore hospitalized patients with HFpEF was higher at 26.6%. Despite the differences in the studies, mortality rates remain high in Asian HFpEF patients. On the other hand, around half of hospitalized US HFpEF patients registered to GWTG-HF died during the 2 years after admission. In addition, the
composite event of all-cause death or HF hospitalization at 2 years occurred more frequently in these US HFpEF patients (≈85%) when compared with Japanese patients (40.8%). However, these event rates were estimated in a limited US population that was registered to GWTG-HF linked to the Medicare database (≥65 years old). As a consequence, the relatively older age of the US patients (median, 82 years) than of the Japanese patients (median, 80 years) could have contributed to the subsequent event rates. Other differences in the patient populations, such as

| Variables                        | Univariable analysis | Multivariable analysis (significant covariates in univariate analyses) | Multivariable analysis (stepwise selection) |
|----------------------------------|----------------------|------------------------------------------------------------------------|---------------------------------------------|
|                                  | HR (95% CI)          | P value                                                                | HR (95% CI)                                 |
|                                  |                      |                                                                        | P value                                      |
|                                  |                      |                                                                        |                                             |
| Age                              | 1.03 (1.01–1.05)     | 0.002                                                                  | 1.00 (0.98–1.02)                             | 0.64 NS                                     |
| Female                           | 1.00 (0.73–1.36)     | 0.99                                                                   | NS                                           | NS                                          |
| BMI                              | 0.95 (0.92–0.99)     | 0.015                                                                  | 1.00 (0.96–1.05)                             | 0.85 NS                                     |
| NYHA class IV on admission       | 0.84 (0.60–1.16)     | 0.29                                                                   | NS                                           | NS                                          |
| NYHA class III or IV at discharge| 3.19 (1.92–5.30)     | <0.001                                                                 | 2.77 (1.51–5.07)                             | 0.001 1.01 (1.00–1.02)                     |
| Heart rate on admission          | 1.00 (0.996–1.007)   | 0.63                                                                   | NS                                           | NS                                          |
| Heart rate at discharge          | 1.01 (1.00–1.02)     | 0.18                                                                   | NS                                           | NS                                          |
| SBP on admission                 | 0.99 (0.988–0.997)   | 0.001                                                                  | 0.99 (0.99–1.00)                             | 0.026 0.99 (0.99–1.000)                     |
| SBP at discharge                 | 0.99 (0.98–1.00)     | 0.14                                                                   | NS                                           | NS                                          |
| Prior HF admission               | 1.88 (1.38–2.56)     | <0.001                                                                 | 1.33 (0.87–2.02)                             | 0.19 NS                                     |
| Prior MI                         | 1.39 (0.92–2.12)     | 0.121                                                                  | NS                                           | NS                                          |
| CAD                              | 1.23 (0.88–1.71)     | 0.22                                                                   | NS                                           | NS                                          |
| AF                               | 1.40 (1.00–1.95)     | 0.051                                                                  | 0.96 (0.62–1.49)                             | 0.85 NS                                     |
| Diabetes                         | 0.97 (0.70–1.33)     | 0.84                                                                   | NS                                           | NS                                          |
| Hypertension                     | 0.94 (0.65–1.34)     | 0.72                                                                   | NS                                           | NS                                          |
| Dyslipidemia                     | 0.68 (0.49–0.93)     | 0.017                                                                  | 1.23 (0.78–1.95)                             | 0.37 NS                                     |
| CVA                              | 1.50 (1.07–2.09)     | 0.018                                                                  | 1.30 (0.84–2.01)                             | 0.24 NS                                     |
| PAD                              | 1.49 (0.95–2.31)     | 0.080                                                                  | NS                                           | NS                                          |
| CKD                              | 1.08 (0.80–1.47)     | 0.61                                                                   | NS                                           | NS                                          |
| COPD/asthma                      | 1.54 (0.99–2.39)     | 0.056                                                                  | NS                                           | NS                                          |
| Depression                       | 0.76 (0.19–3.06)     | 0.70                                                                   | NS                                           | NS                                          |
| Liver disease                    | 1.08 (0.58–1.99)     | 0.81                                                                   | NS                                           | NS                                          |
| Sodium on admission              | 0.95 (0.92–0.98)     | <0.001                                                                 | 0.96 (0.91–1.00)                             | 0.068 0.96 (0.92–1.00)                      |
| Sodium at discharge              | 0.94 (0.91–0.98)     | 0.002                                                                  | NS                                           | NS                                          |
| BUN on admission                 | 1.009 (1.002–1.016)  | 0.014                                                                  | NS                                           | NS                                          |
| BUN at discharge                 | 1.02 (1.01–1.02)     | <0.001                                                                 | 1.01 (1.00–1.02)                             | 0.050 NS                                    |
| Creatinine on admission          | 1.15 (0.99–1.34)     | 0.061                                                                  | NS                                           | NS                                          |
| Creatinine at discharge          | 1.20 (1.04–1.38)     | 0.012                                                                  | NS                                           | NS                                          |
| Hemoglobin on admission          | 0.90 (0.84–0.97)     | 0.004                                                                  | NS                                           | NS                                          |
| Hemoglobin at discharge          | 0.84 (0.77–0.92)     | <0.001                                                                 | 0.94 (0.83–1.06)                             | 0.30 NS                                     |
| Log BNP on admission             | 1.21 (1.01–1.44)     | 0.035                                                                  | NS                                           | NS                                          |
| Log BNP at discharge             | 1.61 (1.35–1.92)     | <0.001                                                                 | 1.35 (1.09–1.68)                             | 0.006 1.34 (1.08–1.65)                      | 0.007 |
| Potassium on admission           | 1.29 (1.03–1.62)     | 0.027                                                                  | 0.92 (0.64–1.31)                             | 0.64 NS                                     |
| Potassium at discharge           | 1.01 (0.75–1.37)     | 0.94                                                                   | NS                                           | NS                                          |
| CRP on admission                 | 1.05 (1.00–1.09)     | 0.049                                                                  | NS                                           | NS                                          |
| CRP at discharge                 | 1.13 (1.03–1.24)     | 0.009                                                                  | 0.96 (0.85–1.09)                             | 0.54 NS                                     |
| Albumin on admission             | 0.44 (0.31–0.63)     | <0.001                                                                 | 0.56 (0.35–0.90)                             | 0.016 0.51 (0.33–0.70)                      | 0.002 |
| Albumin at discharge             | 0.47 (0.34–0.68)     | <0.001                                                                 | NS                                           | NS                                          |
| Total cholesterol on admission   | 1.00 (0.99–1.00)     | 0.75                                                                   | NS                                           | NS                                          |
| Total bilirubin on admission     | 1.10 (0.85–1.42)     | 0.45                                                                   | NS                                           | NS                                          |
| LVEF                             | 1.00 (0.98–1.02)     | 0.94                                                                   | NS                                           | NS                                          |
| Use of ACEIs or ARBs at discharge| 0.71 (0.52–0.99)     | 0.042                                                                  | 0.96 (0.61–1.51)                             | 0.85 NS                                     |
| Use of β-blockers at discharge   | 1.29 (0.93–1.80)     | 0.132                                                                  | NS                                           | NS                                          |
| Use of MRAs at discharge         | 1.22 (0.89–1.69)     | 0.22                                                                   | NS                                           | NS                                          |
| Use of loop diuretics at discharge| 1.30 (0.90–1.90)     | 0.163                                                                  | NS                                           | NS                                          |
| Use of statins at discharge      | 0.57 (0.39–0.82)     | 0.002                                                                  | 0.60 (0.36–1.01)                             | 0.055 NS                                    |

CI, confidence interval; CRP, C-reactive protein; HR, hazard ratio; NS, not selected. Other abbreviations as in Tables 1–3.
Hospitalized HFpEF in Japan

ethnicity and medical culture, may also have contributed to these modest differences in in-hospital and long-term mortality rates between Asian and Western countries. The rate of CV death has been reported to be approximately 50–60% in HFpEF patients,\(^\text{19,39}\) and our study showed similar findings for the rate of CV death (51.8%) and mode of CV death in JASPER to those in the I-PRESERVE and CHARM-Preserved trials.\(^\text{39}\)

It should be noted that a lower serum albumin level was one of the most powerful predictors of outcome in this HFpEF patients. Hypoalbuminemia in HF is probably from multiple causes, including malnutrition, inflammation, reduced synthesis because of hepatic congestion, hemodilution, and impaired anabolic–catabolic balance.\(^\text{40}\) Pathophysiologically, severe hypoalbuminemia accelerates fluid retention and systemic edema through a decline in plasma oncotic pressure, which may result in further progression of cardiac and renal impairment accompanied by diuretic resistance in HF patients.\(^\text{41}\) Importantly, the determinants of clinical outcome differ between HFpEF and HFrEF,\(^\text{37}\) and hypoalbuminemia would be an important strong prognostic determinant in HFpEF patients especially.\(^\text{42,43}\) These reports support our findings, and serum albumin could be an important nutritional marker. Accordingly, prospective investigations of the potential preventative or therapeutic role of nutritional intervention for hypoalbuminemia in HFpEF patients are warranted.

Study Limitations

Although consecutive hospitalized HFpEF patients were registered from 16 nationwide sites in JASPER, the sample size was relatively smaller than those in previous reports predominantly from Western countries despite being the largest sample size in Japan. Because JASPER is a registry specifically focusing on HFpEF, and therefore HFpEF patients were not simultaneously registered, we could not compare the characteristics and outcomes between these HF phenotypes. In Table 3, patients who were categorized as having no history of AF and AF on admission had an enlarged left atrial dimension similar to those with the history of AF. We tried to obtain each patient’s history as appropriate; however, it would be difficult to determine AF history without ECG evidence. Thus, these patients might have a history of AF. Finally, only 72.0% of patients were successfully followed up at 2 years after discharge, leading to a substantial selection bias, despite there being no statistically difference regarding baseline characteristics related to long-term adverse events across the follow-up status (Table S1).

In conclusion, our analyses revealed that Japanese hospitalized HFpEF patients had a substantially higher prevalence of AF but a lower prevalence of obesity, IHD, diabetes mellitus, COPD and renal insufficiency, a longer hospital stay and lower subsequent event rates compared with US patients. Lower serum albumin level was one of the most powerful independent and robust determinants of long-term death and HF hospitalization. These findings indicated that specific preventative and therapeutic strategies focusing on AF and nutritional status might need to be considered for Japanese patients hospitalized with HFpEF.

Acknowledgments

The authors are grateful for the contributions of all the investigators, clinical research coordinators, data managers, and laboratory techni-
ment of heart failure: executive summary: A report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation 2013; 128: 1810–1852.

15. Greene SJ, Fonarow GC, Solomon SD, Subacius H, Maggioni AP, Bohm M, et al. Global variation in clinical profile, management, and post-discharge outcomes among patients hospitalized for worsening chronic heart failure: Findings from the ASTRONAUT trial. Eur J Heart Fail 2015; 17: 591–600.

16. Kristensen SL, Martinez F, Jhund PS, Arango JL, Belohlavek J, Boytsov S, et al. Geographic variations in the PARADIGM-HF heart failure trial. Eur Heart J 2016; 37: 3167–3174.

17. Sato N, Kajimoto K, Keida T, Mizuno M, Minami Y, Yumino D, et al. Clinical features and outcome in hospitalized heart failure in Japan (from the ATTEND Registry). Circ J 2013; 77: 944–951.

18. Abraham WT, Fonarow GC, Albert NM, Stough WG, Gheorghianti M, Gromberg BH, et al. Predictors of in-hospital mortality in patients hospitalized for heart failure: Insights from the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF). J Am Coll Cardiol 2008; 52: 347–356.

19. Lee R, Chan SP, Chan YH, Wong J, Lau D, Ng K. Impact of race on morbidity and mortality in patients with congestive heart failure: A study of the multicultural population in Singapore. Int J Cardiol 2009; 134: 422–425.

20. Redfield MM. Heart failure with preserved ejection fraction. N Engl J Med 2016; 375: 1868–1877.

21. Kaneko H, Suzuki S, Yajima J, Okawa Y, Sagara K, Otsuka T, et al. Clinical characteristics and long-term clinical outcomes of Japanese heart failure patients with preserved versus reduced left ventricular ejection fraction: A prospective cohort of Shinken Database 2004–2011. J Cardiol 2013; 62: 102–109.

22. Satomura H, Wada H, Sakakura K, Kubo N, Ikeda N, Sugawara Y, et al. Congestive heart failure in the elderly: Comparison between reduced ejection fraction and preserved ejection fraction. J Cardiol 2012; 59: 215–219.

23. Setoguchi M, Hashimoto Y, Sasaoka T, Ashikaga T, Isobe M. Risk factors for rehospitalization in heart failure with preserved ejection fraction compared with reduced ejection fraction. Heart Vessels 2015; 30: 595–603.

24. Hamaguchi S, Kinugawa S, Sobirin MA, Goto D, Tsuchihashi-Makaya M, Yamada S, et al. Mode of death in patients with heart failure and reduced vs. preserved ejection fraction: Report from the registry of hospitalized heart failure patients. Circ J 2012; 76: 1662–1669.

25. JCS Joint Working Group. Guidelines for treatment of acute heart failure (JCS 2011): Digest version. Circ J 2013; 77: 2157–2201.

26. McMurray JJ, Adamopoulos S, Anker SD, Aurichio A, Bohm M, Dickstein K, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2012; 14: 803–869.

27. McKee PA, Castelli WP, McNamara PM, Kannel WB. The natural history of congestive heart failure: The Framingham study. N Engl J Med 1971; 285: 1441–1446.

28. West R, Liang L, Fonarow GC, Kociol R, Mills RM, O’Connor CM, et al. Characterization of heart failure patients with preserved ejection fraction: A comparison between ADHERE-US registry and ADHERE-International registry. Eur J Heart Fail 2011; 13: 945–952.

29. Haas M, Kitzman DW, Anand IS, Miller A, Zile MR, Massie BM, et al. Body mass index and adverse cardiovascular outcomes in heart failure patients with preserved ejection fraction: Results from the Irbesartan in Heart Failure with Preserved Ejection Fraction (I-PRESERVE) trial. Circ Heart Fail 2011; 4: 324–331.

30. Dhingra A, Garg A, Kaur S, Chopra S, Batra JS, Pandey A, et al. Epidemiology of heart failure with preserved ejection fraction. Curr Heart Fail Rep 2014; 11: 354–365.

31. Shah SJ, Kitzman DW, Borlaug BA, van Heerbeeck I, Zile MR, Kass DA, et al. Phenotype-specific treatment of heart failure with preserved ejection fraction: A multiorgan roadmap. Circulation 2016; 134: 73–90.

32. Obokata M, Reddy YNV, Pilsaru SV, Melenovsky V, Borlaug BA. Evidence supporting the existence of a distinct obese phenotype of heart failure with preserved ejection fraction. Circulation 2017; 136: 6–19.

33. Zakeri R, Chamberlain AM, Roger VL, Redfield MM. Temporal relationship and prognostic significance of atrial fibrillation in heart failure patients with preserved ejection fraction: A community-based study. Circulation 2013; 128: 1085–1093.

34. McAlister FA, Lawson FM, Teo KK, Armstrong PW. A systematic review of randomized trials of disease management programs in heart failure. Am J Med 2001; 110: 378–384.

35. Heart Failure Society Of America. HFSA 2006 comprehensive heart failure practice guideline. J Card Fail 2006; 12: e1–e2.

36. Hunt SA, Baker DW, Chin MH, Cinquegrani MP, Feldman AM, Francis GS, et al. ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: Executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to revise the 1995 Guidelines for the Evaluation and Management of Heart Failure). J Am Coll Cardiol 2001; 38: 2101–2113.

37. Yap J, Sim D, Lim CP, Chia SY, Go YY, Jaffeearlly FR, et al. Predictors of two-year mortality in Asian patients with heart failure and preserved ejection fraction. Int J Cardiol 2015; 183: 33–38.

38. Shah KS, Xu H, Matsouaka RA, Bhatt DL, Heidenreich PA, Hernandez AF, et al. Heart failure with preserved, borderline, and reduced ejection fraction: 5-year outcomes. J Am Coll Cardiol 2017; 70: 2476–2486.

39. Chan MM, Lam CS. How do patients with heart failure with preserved ejection fraction die? Eur J Heart Fail 2013; 15: 604–613.

40. Anker SD, Chua TP, Ponikowski P, Harrington D, Swan JW, Kox WJ, et al. Hormonal changes and catechol/anabolic imbalance in chronic heart failure and their importance for cardiac cachexia. Circulation 1997; 96: 526–534.

41. Arques S, Ambrosi P. Human serum albumin in the clinical syndrome of heart failure. J Card Fail 2011; 17: 451–458.

42. Tsuji K, Sakata Y, Nochioka K, Miura M, Yamauchi T, Onose T, 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 2017; 19: 1258–1269.

43. Liu M, Chan CP, Yan BF, Zhang Q, Lam YY, Li RJ, et al. Albumin levels predict survival in patients with heart failure and preserved ejection fraction. Eur J Heart Fail 2012; 14: 39–44.

Supplementary Files

Supplementary File 1

Appendix S1

Table S1. Comparison of baseline characteristics related to long-term adverse events across the follow-up status

Please find supplementary file(s): http://dx.doi.org/10.1253/circj.CJ-18-0073