ORIGINAL RESEARCH

Sex Differences in Heart Failure With Preserved Ejection Fraction

Yohei Sotomi, MD, PhD; Shungo Hikoso, MD, PhD; Daisaku Nakatani, MD, PhD; Hiroya Mizuno, MD, PhD; Katsuki Okada, MD, PhD; Tomoharu Dohi, MD, PhD; Tetsuhiisa Kitamura, MD, MSc, DrPH; Akihiro Sunaga, MD; Hirota Kida, MAS; Bolrathanak Oeun, MD; Taiki Sato, MD; Sho Komukai, MD, PhD; Shunsuke Tamaki, MD, PhD; Masamichi Yano, MD, PhD; Takaharu Hayashi, MD, PhD; Akito Nakagawa, MD, PhD; Yusuke Nakagawa, MD, PhD; Yoshio Yasumura, MD, PhD; Takahisa Yamada, MD, PhD; Yasushi Sakata, MD, PhD; on behalf of the PURSUIT-HFpEF Investigators*

BACKGROUND: The female preponderance in heart failure with preserved ejection fraction (HFpEF) is a distinguishing feature of this disorder, but the association of sex with degree of diastolic dysfunction and clinical outcomes among individuals with HFpEF remains unclear.

METHODS AND RESULTS: We conducted a prospective, multicenter, observational study of patients with HFpEF (PURSUIT-HFpEF [Prospective Multicenter Observational Study of Patients with Heart Failure with Preserved Ejection Fraction]: UMIN000021831). Between 2016 and 2019, 871 patients were enrolled from 26 hospitals (follow-up: 399±349 days). We investigated sex-related differences in diastolic dysfunction and postdischarge clinical outcomes in patients with HFpEF. The echocardiographic end point was diastolic dysfunction according to American Society of Echocardiography/European Association of Cardiovascular Imaging criteria. The clinical end point was a composite of all-cause death and heart failure readmission. Women accounted for 55.2% (481 patients) of the overall cohort. Compared with men, women were older and had lower prevalence rates of hypertension, coronary artery disease, and chronic kidney disease. Women had diastolic dysfunction more frequently than men (52.8% versus 32.0%, \( P < 0.001 \)). The incidence of the clinical end point did not differ between women and men (women 36.1/100 person-years versus men 30.5/100 person-years, \( P = 0.336 \)). Female sex was independently associated with the echocardiographic end point (adjusted odds ratio, 2.839; 95% CI, 1.884–4.278; \( P < 0.001 \)) and the clinical end point (adjusted hazard ratio, 1.538; 95% CI, 1.143–2.070; \( P = 0.004 \)).

CONCLUSIONS: Female sex was independently associated with the presence of diastolic dysfunction and worse clinical outcomes in a cohort of elderly patients with HFpEF. Our results suggest that a sex-specific approach is key to investigating the pathophysiology of HFpEF.

REGISTRATION: URL: https://upload.umin.ac.jp; Unique identifier: UMIN000021831.

Key Words: diastolic dysfunction ■ heart failure ■ preserved left ventricular function ■ prognosis ■ sex

Epidemiological studies have established that patients with heart failure with preserved ejection fraction (HFpEF) are more likely to be female than male. Women accounted for only 20% to 25% of subjects in clinical trials evaluating heart failure with reduced ejection fraction,\(^1\)\(^–\)\(^3\) whereas in clinical trials assessing HFpEF, women account for as many as 50% to 60% of the trial cohort.\(^4\)\(^,\)\(^5\) Female sex predominance is one of the strongest distinguishing features of HFpEF compared with heart failure with...
The immune system and inflammation have been thought to be central to the development of HFpEF. Several comorbidities, including hypertension, diabetes mellitus, atrial fibrillation, obesity, and ischemia, are known to be associated with development and prognosis of HFpEF. Inflammation driven by such comorbidities may be a fundamental mechanism causing myocardial dysfunction. Impacts of the comorbidities differ between women and men. For instance, hypertension increases the risk of heart failure (HF) by 3× in women, compared with 2× in men. Diabetes mellitus has a more pronounced effect on HF in women, increasing the HF risk 5× in women compared with 2.4× in men. Atrial fibrillation increases the risk of HF hospitalization 1.63× in women as compared with 1.37× in men. Women have stronger immune responses than men, which may contribute to the different impacts on the development of diastolic dysfunction and subsequent clinical outcomes between the sexes.

Exploring mechanisms behind the sex differences in HFpEF may help us to understand underlying HFpEF pathophysiology and to identify more specific therapeutic approaches. The purpose of the present study was to assess sex differences in the prevalence of diastolic dysfunction and clinical outcomes in HFpEF.

METHODS

Our study data will not be made available to other researchers for purposes of reproducing the results because of institutional review board restrictions.

Study Patients

The PURSUIT-HFpEF (Prospective Multicenter Observational Study of Patients with Heart Failure with Preserved Ejection Fraction) study is a prospective, multicenter, observational study in which collaborating hospitals in Osaka record clinical, echocardiographic, and outcome data of patients with acute decompressed heart failure with preserved left ventricular ejection fraction (≥50%) (UMIN-CTR [University Hospital Medical Information Network Clinical Trials Registry] ID: UMIN000021831). Consecutive patients with acute decompressed heart failure and preserved ejection fraction were prospectively registered and agreed to be followed up for collection of outcome data. Acute decompressed heart failure was diagnosed on the basis of the following criteria: (1) clinical symptoms and signs according to the Framingham Heart Study criteria; and (2) serum NT-proBNP (N-terminal pro-B-type natriuretic peptide) level of ≥400 pg/mL or BNP (brain natriuretic peptide) level of ≥100 pg/mL. All patients provided written informed consent for participation in this study. The study protocol was approved by the ethics committee of each participating hospital. This study conformed to the ethical guidelines outlined in the Declaration of Helsinki.

Details of the data collection have been described elsewhere. In brief, basic patient characteristics, echocardiography, laboratory tests, and lists of medications were obtained on admission, at discharge, and at each annual follow-up time point. We used laboratory data and echocardiography data at the time of discharge (in stable condition after treatment of acute decompressed heart failure) in this analysis.

Study Design and End Points

The present study aimed to assess the frequency of diastolic dysfunction in women and men and to investigate the sex-related differences in causes of diastolic dysfunction and clinical outcomes in HFpEF.
dysfunction and prognostic predictors for postdischarge clinical outcomes in patients with HFpEF. Sex, systemic inflammation represented by C-reactive protein, and various basic comorbidities were comprehensively evaluated in order to estimate their impacts on diastolic dysfunction and postdischarge clinical outcome.

The echocardiographic end point was diastolic dysfunction. Based on the echocardiographic data obtained at discharge, diastolic dysfunction was diagnosed according to the American Society of Echocardiography and European Association of Cardiovascular Imaging (ASE/EACVI) guidelines for diastolic function assessment. The 4 recommended variables for identifying diastolic dysfunction and their abnormal cutoff values are: septal e’ <7 cm/s or lateral e’ <10 cm/s, average E/e’ ratio >14, left atrial volume index >34 mL/m², and peak tricuspid valve regurgitation velocity >2.8 m/s. Only patients with all 4 criteria available were analyzed. Left ventricular diastolic dysfunction was diagnosed if >50% of the parameters met these cutoff values.

The clinical end point was a composite of all-cause death and heart failure readmission. All patients were followed up in each hospital after discharge. Survival data were obtained by dedicated coordinators and investigators by direct contact with patients and their physicians at the hospital or in an outpatient setting or by a telephone interview with their families or by mail. In the present analysis, we analyzed all available clinical follow-up data up to the end of 2019.

Statistical Analysis
Data are presented with listwise deletion. Categorical variables are expressed as counts (percentages) and compared with the chi-square test or Fisher’s exact test. Continuous variables are expressed as mean (SD) or median (interquartile range) and compared using Student t test or the Mann–Whitney U test as appropriate. The clinical end point (a composite of all-cause death and heart failure readmission) was assessed according to sex in a time-to-first-event fashion with the Kaplan–Meier method and compared with the log-rank test. Impact of female sex on the echocardiographic and clinical end points was assessed with a binary logistic regression model and the Cox proportional hazards model, respectively. Sex was the variable of interest and the other covariates in the models were as follows: C-reactive protein, age, anemia (hemoglobin level <12 g/DL in women and <13 g/ Dl in men according to the World Health Organization definition), hypertension, diabetes mellitus, dyslipidemia, coronary artery disease, chronic kidney disease, atrial fibrillation, obesity (body mass index ≥25), and cholinesterase. These covariates were chosen based on the clinical consensus and our previous reports. Because we aimed to investigate the fundamental sex-related pathophysiology, we included only basic characteristics in the covariates. However, as a sensitivity analysis, we additionally constructed a Cox proportional hazards model for the clinical end point that included the aforementioned comorbidities and postdischarge medications with prescription rates that were significantly different between women and men. The presence of a statistically significant interaction between sex and the model covariates was tested by the Wald test. An interaction term between each covariate and sex was included in the multivariable models to identify sex-related differences in predictors of the echocardiographic and clinical end points. Adjusted probability curves in women and men were created with this model. The proportional hazards assumption of sex for the clinical end point was confirmed by Schoenfeld residuals (P=0.67). The influence of these factors on the echocardiographic and clinical end points were also assessed in women and men separately in order to investigate the sex differences in causes and prognostic factors of HFpEF. As additional analyses, we evaluated the association between the aforementioned covariates and individual components of the clinical end point. The Cox proportional hazards model was used for all-cause death. The Fine and Gray model was used for heart failure readmission considering all-cause death as a competing risk. A P<0.05 was considered statistically significant. The significance level for subgroup analysis (women and men) was 0.025 after adjustment for multiplicity using the Bonferroni correction. All analyses were undertaken using SPSS 24.0 (IBM Corporation, Armonk, NY) or R software (version 3.6.2; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS
Study Subjects
Between June 2016 and December 2019, 871 patients were enrolled from 26 hospitals. Mean follow-up duration was 399±349 days. Patients’ characteristics are tabulated in Table 1. Of 871 patients enrolled, 481 (55.2%) were women and 389 (44.7%) were men. A single patient with missing sex data was excluded from the entire analysis. Compared with men, women were older; had lower prevalence rates of hypertension, coronary artery disease, and chronic kidney disease; and were less commonly smokers. The level of C-reactive protein was lower in women than in men. There was no significant difference in body mass index, NT-proBNP, or prevalence of dyslipidemia, diabetes mellitus, or atrial fibrillation. During hospitalization, a diagnosis of cardiac...
Table 1. **Patient Characteristics**

| Variable                                                                 | Women          | Men            | P Value   |
|--------------------------------------------------------------------------|----------------|----------------|-----------|
| Number                                                                   | 481*           | 389*           | <0.001    |
| Age, y                                                                   | 82.23 (8.63)   | 79.75 (8.93)   | 0.124     |
| Body mass index                                                          | 21.73 (4.82)   | 22.19 (3.80)   | 0.001     |
| Body weight, kg                                                          | 47.77 (11.81)  | 58.92 (11.49)  | <0.001    |
| Obesity (body mass index ≥25)                                            | 90 (19.0)      | 82 (21.4)      | 0.387     |
| Systolic blood pressure, mm Hg                                           | 118.61 (18.12) | 119.44 (17.88) | 0.502     |
| Diastolic blood pressure, mm Hg                                          | 66.20 (11.91)  | 65.34 (12.01)  | 0.296     |
| Heart rate, bpm                                                          | 72.56 (13.47)  | 70.09 (13.13)  | 0.007     |
| NYHA class                                                               |                |                | 0.011     |
| NYHA I                                                                   | 153 (32.4)     | 155 (40.4)     |           |
| NYHA II                                                                  | 268 (56.8)     | 207 (53.9)     |           |
| NYHA III                                                                 | 43 (9.1)       | 17 (4.4)       |           |
| NYHA IV                                                                  | 8 (1.7)        | 5 (1.3)        |           |
| Frail†                                                                   | 186 (38.8)     | 73 (16.8)      | <0.001    |
| HFA-PEFF score                                                           |                |                | 0.758     |
| Low (0–1)                                                                | 6 (1.3)        | 4 (1.1)        |           |
| Intermediate (2–4)                                                       | 132 (29.0)     | 115 (31.3)     |           |
| High (5–6)                                                               | 317 (69.7)     | 248 (67.6)     |           |
| History                                                                  |                |                |           |
| Hypertension                                                             | 395 (82.5)     | 340 (87.6)     | 0.037     |
| Dyslipidemia                                                             | 207 (43.3)     | 149 (38.7)     | 0.186     |
| Diabetes mellitus                                                        | 149 (31.2)     | 138 (35.9)     | 0.147     |
| Anemia                                                                   | 330 (68.8)     | 284 (73.4)     | 0.136     |
| Atrial fibrillation                                                      | 178 (37.2)     | 153 (39.3)     | 0.528     |
| Persistent atrial fibrillation                                           | 145 (81.9)     | 128 (85.9)     | 0.388     |
| Paroxysmal atrial fibrillation                                           | 32 (18.1)      | 21 (14.1)      |           |
| Congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke or transient ischemic attack, vascular disease, age 65–74 years, sex category score | 5.27 (1.16) | 4.46 (1.23) | <0.001 |
| Congestive heart failure, hypertension, age > 75 years, diabetes mellitus, previous stroke score | 3.24 (1.06) | 3.32 (1.04) | 0.265 |
| Smoking                                                                  |                |                | <0.001    |
| Nonsmoker                                                                | 392 (82.7)     | 144 (37.8)     |           |
| Current smoker                                                           | 26 (5.5)       | 61 (16.0)      |           |
| Past smoker                                                              | 56 (11.8)      | 176 (46.2)     |           |
| Bleeding                                                                 | 17 (3.6)       | 22 (5.8)       | 0.139     |
| Prior hospitalization for heart failure                                  | 116 (24.7)     | 97 (25.6)      | 0.811     |
| Hypertrophic cardiomyopathy                                              | 20 (4.3)       | 12 (3.2)       | 0.471     |
| Secondary cardiomyopathy                                                | 8 (1.7)        | 5 (1.3)        | 0.782     |
| Family history of heart failure                                         | 27 (6.2)       | 9 (2.6)        | 0.016     |
| Atrioventricular block                                                  | 33 (7.0)       | 35 (9.2)       | 0.254     |
| Sick sinus syndrome                                                      | 41 (8.8)       | 23 (6.1)       | 0.152     |
| Pacemaker implantation                                                  | 42 (8.8)       | 26 (6.7)       | 0.310     |
| Pericardial disease                                                      | 5 (1.1)        | 5 (1.3)        | 0.760     |
| Coronary artery disease                                                 | 57 (12.1)      | 93 (24.2)      | <0.001    |
| Percutaneous coronary intervention                                       | 44 (9.2)       | 75 (19.4)      | <0.001    |
| Coronary artery bypass graft                                            | 10 (2.1)       | 21 (5.4)       | 0.010     |
| Myocardial infarction                                                   | 17 (3.6)       | 48 (12.6)      | <0.001    |
| Open heart surgery                                                       | 35 (7.3)       | 29 (7.5)       | >0.999    |

(Continued)
Amyloidosis was made in 5 patients (women 0/481 [0%] versus men 5/389 [1.3%], \( P = 0.013 \)). Medications at discharge are presented in Table 2. Angiotensin II receptor blockers, calcium channel blockers, and antiplatelet drugs were more frequently used in men than in women.

### Echocardiographic End Point

The echocardiographic data in the present cohort were overall in the normal range, except for left atrial parameters and left ventricular mass (Table 3).\(^\text{19}\) The left atrial parameters and left ventricular mass were substantially larger than the normal values of the Japanese cohort.\(^\text{19}\) A total of 595 patients had enough echocardiographic data for the assessment of diastolic dysfunction at discharge. Of these patients, 261 (43.9%) had diastolic dysfunction according to the ASE/EACVI criteria at discharge. Its prevalence was significantly higher in women than in men (179 [52.8%] versus 82 [32.0%], \( P < 0.001 \)). In the overall cohort, female sex, anemia, and obesity were independent factors associated with diastolic dysfunction (Figure 1). In women, anemia was a unique and significant associated factor, whereas in men, there was no significant independent factor associated with diastolic dysfunction. However, the sex subgroup analysis did not show significant interactions between the effect of the individual factors and sex (Figure S1).

### Clinical End Point

The clinical end point of all-cause death or heart failure readmission occurred in 265 patients (30.5%) during the follow-up period. The incidence of the clinical end point did not differ between women and men (women 36.1/100 person-years versus men 30.5/100 person-years, \( P = 0.336 \)) (Table 4). Kaplan-Meier curves and adjusted probability curves stratified by sex are presented in Figure 2. In the overall cohort, female sex, age, coronary artery disease, chronic kidney disease, and cholinesterase were independently associated with the clinical end point (Figures 2B and 3). Female sex was independently associated with increased risk of the clinical end point, which was mainly driven by the association with heart failure readmission (Table S1). Chronic kidney disease and cholinesterase were significantly associated with the clinical end point both in women and men, whereas coronary artery disease was an independent predictor only in women, although there were no significant interactions between the effect of the individual factors and sex (Figure S2). As a sensitivity analysis, we additionally constructed a Cox proportional hazards model including postdischarge medications (Figure S3). The result was consistent with the main analysis.

---

### Table 1. Continued

| Variable                        | Women | Men    | \( P \) Value |
|---------------------------------|-------|--------|---------------|
| Peripheral artery disease       | 18 (3.9) | 30 (8.0) | 0.011         |
| Chronic kidney disease          | 163 (34.2) | 177 (46.0) | <0.001        |
| Dialysis                        | 2 (0.4)   | 12 (3.1)   | 0.002         |
| Stroke                          | 62 (13.1) | 59 (15.3)  | 0.375         |
| Liver dysfunction               | 27 (5.6)  | 29 (7.6)   | 0.269         |
| Malignant tumor                 | 39 (8.2)  | 60 (15.7)  | 0.001         |

Laboratory data

|                      | Women | Men     | \( P \) Value |
|----------------------|-------|---------|---------------|
| Hemoglobin, g/dL     | 11.2 (1.96) | 11.7 (2.09) | <0.001       |
| Hemoglobin A1c, %    | 6.15 (0.90) | 6.14 (0.89) | 0.979       |
| Creatinine, mg/dL    | 1.00 [0.80, 1.40] | 1.20 [1.00, 1.70] | <0.001     |
| Estimated glomerular filtration rate, mL/min per 1.73 m\(^2\) | 41.89 (18.66) | 43.89 (21.52) | 0.146       |
| High-density lipoprotein, mg/dL | 45.36 (11.69) | 42.53 (13.16) | 0.002       |
| Low-density lipoprotein, mg/dL | 96.92 (28.95) | 92.09 (31.34) | 0.029       |
| Total cholesterol, mg/dL     | 165.43 (35.37) | 155.94 (35.03) | <0.001     |
| Triglyceride, mg/dL        | 108.00 (45.91) | 103.45 (48.57) | 0.186       |
| Cholinesterase, IU/L       | 221.84 (69.55) | 204.58 (65.85) | 0.001       |
| C-reactive protein, mg/dL   | 0.27 [0.11, 0.75] | 0.31 [0.13, 1.16] | 0.036       |
| NT-proBNP, pg/mL          | 1090 (481, 2340) | 1090 (489, 2590) | 0.955       |

Data with listwise deletion are expressed as mean (SD), median [interquartile range], or number (percentage).

* A single patient with missing sex data was excluded from the entire analysis. HFA-PEFF indicates Heart Failure Association-pretest assessment, echocardiography and natriuretic peptide, functional testing, final etiology; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.

† Frail was defined as the clinical frailty scale score \( \geq 5 \). HFA-PEFF score is a diagnostic scoring system for heart failure with preserved ejection fraction recommended by the Heart Failure Association of the European Society of Cardiology.\(^\text{18}\)
DISCUSSION

The findings of this study can be summarized as follows: In the PURSUIT-HFpEF prospective multicenter East-Asian HFpEF registry, (1) women accounted for 55.2% of the overall cohort; (2) women had echocardiographic diastolic dysfunction more frequently than men; (3) female sex was independently associated with the presence of echocardiographic diastolic dysfunction; (4) crude incidence of the clinical end point at all-cause death or heart failure readmission did not differ between women and men; (5) however, after multivariable adjustment, female sex was independently associated with increased risk of the clinical end point; and (6) there were no significant interactions between sex and the effects of comorbidities on echocardiographic and clinical end points.

Diastolic Dysfunction in Women

Female sex was independently associated with diastolic dysfunction. This primary finding is supported by several previous studies. A cross-sectional study was conducted to examine sex differences in cardiometabolic profiles and exercise hemodynamic profiles among individuals with HFpEF. This cross-sectional study included 295 participants who met hemodynamic criteria for HFpEF based on invasive cardio-pulmonary exercise testing results. They examined sex differences in hemodynamic parameters during exercise with right heart catheterization. Exercise capacity was similar in men and women, but women had worse biventricular systolic reserve and diastolic reserve even after multivariable adjustment. The impaired diastolic reserve in women is not the same but correlated with diastolic dysfunction on echocardiography. Another study evaluated a total of 161 subjects using invasive hemodynamic and echocardiographic approaches. Compared with men, women had a higher pulmonary capillary wedge pressure indexed to peak exercise workload and lower systemic and pulmonary arterial compliance at exercise. Women had higher mitral inflow velocity to diastolic mitral annular velocity at early filling ratios at rest and peak exercise, along with a higher ejection fraction and smaller ventricular dimensions.

There was the entity of HFpEF without the echocardiographic diastolic dysfunction in the present study. This entity was more common in men than in women (68% in men versus 47% in women, P<0.001). Majority of this cohort may show impaired hemodynamics if they perform functional testing (eg, exercise stress echocardiography, invasive hemodynamic tests at rest and with exercise), because all participants were diagnosed with acute decompensated heart failure at the time of hospital admission. Given the previous evidence, the potential population with impaired diastolic reserve during exercise but without the evidence of the echocardiographic diastolic dysfunction is presumably larger in women than in men. This would further contribute to the female preponderance in HFpEF. On the other hand, male patients had a higher prevalence of chronic kidney disease (46.0% versus 34.2%, P<0.001) and peripheral artery disease (8.0% versus 3.9%, P=0.011) than female patients did. These extra-cardiac deficits may more prominently affect systemic vascular resistance or abnormalities in peripheral oxygen extraction in men than in women. As for the cardiac function, deficits in contractile reserve rather than left ventricular diastolic dysfunction might play a more important role in men than in women. These points warrant further investigations.

The aforementioned sex-specific cardiac features suggest that a kind of sex-specific pathway exists. A variety of pathways has been thought to be associated with myocyte stiffness, including sex difference in calcium handling, myocardium substrate metabolism, an activated renin-angiotensin-aldosterone system in response to low estrogen, a drop in nitric oxide with menopause, and protein kinase A and extracellular signal-regulated kinase 2 activated by progesterone. Sex-specificity in patients with HFpEF is also likely supported by the heterogeneity with a possible benefit of sacubitril–valsartan seen in women in the PARAGON-HF (Prospective Comparison of Angiotensin Receptor–Nephrilysin Inhibitor with
Table 3. Echocardiographic Data

| Variable                                      | Women          | Men           | P Value |
|-----------------------------------------------|----------------|---------------|---------|
| Number                                        | 481*           | 389*          |         |
| Left atrial diameter, mm                      | 43.98 (8.67)   | 44.34 (8.03)  | 0.546   |
| Left atrial volume index†                     | 58.03 (32.76)  | 51.02 (24.56) | 0.002   |
| Left ventricular diastolic diameter, mm       | 43.87 (8.87)   | 47.84 (8.35)  | <0.001  |
| Left ventricular systolic diameter, mm        | 28.19 (4.83)   | 31.55 (5.89)  | <0.001  |
| Left ventricular ejection fraction², %        | 61.21 (7.70)   | 59.60 (7.76)  | 0.006   |
| Left ventricular fractional shortening, %    | 35.81 (6.03)   | 34.22 (6.78)  | <0.001  |
| Left ventricular outflow tract diameter, mm   | 19.10 (1.97)   | 21.09 (1.91)  | <0.001  |
| Interventricular septum thickness, mm         | 9.72 (2.16)    | 10.35 (2.12)  | <0.001  |
| Left ventricle posterior wall thickness, mm   | 9.66 (2.13)    | 10.33 (1.93)  | <0.001  |
| Left ventricular mass, g                      | 145.5 (56.2)   | 180.4 (55.6)  | <0.001  |
| Left ventricular mass index, g/m²             | 104.4 (35.5)   | 111.3 (33.9)  | 0.006   |
| Relative wall thickness                       | 0.45 (0.11)    | 0.44 (0.11)   | 0.395   |
| Peak A velocity, m/s                          | 0.85 (0.28)    | 0.81 (0.25)   | 0.079   |
| Peak E velocity, m/s                          | 0.87 (0.34)    | 0.82 (0.30)   | 0.012   |
| Deceleration time, s                          | 0.22 (0.07)    | 0.21 (0.07)   | 0.692   |
| E/A ratio                                     | 1.02 (0.65)    | 1.00 (0.60)   | 0.794   |
| lateral a’, m/s                               | 0.08 (0.03)    | 0.09 (0.03)   | 0.062   |
| septal a’, m/s                                | 0.07 (0.02)    | 0.08 (0.02)   | 0.006   |
| lateral e’, m/s                               | 0.07 (0.03)    | 0.08 (0.03)   | 0.001   |
| septal e’, m/s                                | 0.05 (0.02)    | 0.06 (0.02)   | <0.001  |
| E/e’ (mean)                                   | 15.24 (7.01)   | 12.71 (5.87)  | <0.001  |
| Right ventricle diastolic diameter            | 31.35 (6.42)   | 33.71 (6.91)  | <0.001  |
| Tricuspid annular plane systolic excursion, mm| 17.09 (4.41)   | 18.04 (4.63)  | 0.005   |
| Tricuspid valve regurgitation pressure gradient, mm Hg | 29.17 (10.27) | 26.95 (8.22) | 0.002   |

Aortic valve regurgitation

- None                                      | 176 (38.3)     | 149 (40.5)    | 0.916   |
- Trace                                     | 115 (25.1)     | 84 (22.8)     |         |
- Mild                                      | 135 (29.4)     | 108 (29.3)    |         |
- Moderate                                  | 32 (7.0)       | 27 (7.3)      |         |
- Severe                                    | 1 (0.2)        | 0 (0.0)       |         |

Aortic valve stenosis

- None                                      | 405 (88.2)     | 334 (90.8)    | 0.149   |
- Mild                                      | 33 (7.2)       | 25 (6.8)      |         |
- Moderate                                  | 21 (4.6)       | 8 (2.2)       |         |
- Severe                                    | 0 (0.0)        | 1 (0.3)       |         |

Mitral valve regurgitation

- None                                      | 48 (10.5)      | 37 (10.1)     | 0.872   |
- Trace                                     | 149 (32.5)     | 123 (33.4)    |         |
- Mild                                      | 182 (39.7)     | 153 (41.6)    |         |
- Moderate                                  | 78 (17.0)      | 53 (14.4)     |         |
- Severe                                    | 2 (0.4)        | 2 (0.5)       |         |

Mitral valve stenosis

- None                                      | 446 (97.2)     | 364 (98.9)    | 0.175   |
- Mild                                      | 11 (2.4)       | 4 (1.1)       |         |
- Moderate                                  | 2 (0.4)        | 0 (0.0)       |         |

Tricuspid valve regurgitation

- None                                      | 33 (7.2)       | 29 (7.9)      | 0.340   |
Angiotensin Receptor Blockers Global Outcomes in HF with Preserved Ejection Fraction trial.30 Although our present study cannot provide a specific answer for the mechanism of HFpEF, our findings clearly suggest that future investigations of this condition should be sex specific.

In order to gain insight into the causes of diastolic dysfunction, we evaluated the association of various comorbidities with echocardiographic diastolic dysfunction. Systemic inflammation has been thought to be related to the development of diastolic dysfunction.6 However, C-reactive protein was not independently associated with echocardiographic diastolic dysfunction in our population. Numerous studies have correlated inflammatory markers with diastolic dysfunction and HFpEF in humans.31 Nevertheless, our present results show no such impact. Anemia and obesity were independently associated with development of diastolic dysfunction. Anemia may partially be related to iron deficiency. It affects the immune response, cardiomyocyte metabolism, and oxidative stress.32 Another possibility is that anemia may be just a surrogate marker of multimorbidity. Whether this association is the result of specific shared upstream causes of both anemia and cardiomyocyte dysfunction (eg, inflammation) or causal relationships between HF and anemia (eg, decreased iron absorption) is unclear. In obesity, adipose tissue may exacerbate metabolic inefficiency and contribute to systemic inflammation.33 Although C-reactive protein did not remain as an independent

| Variable                                      | Women         | Men          | P Value |
|-----------------------------------------------|---------------|--------------|---------|
| Trace                                         | 142 (30.9)    | 137 (37.2)   |         |
| Mild                                          | 178 (38.8)    | 130 (35.3)   |         |
| Moderate                                      | 92 (20.0)     | 61 (16.6)    |         |
| Severe                                        | 14 (3.1)      | 11 (3.0)     |         |
| Diastolic dysfunction according to the ASE/EACVI criteria (echocardiographic end point)†| 179 (52.8)    | 82 (32.0)    | <0.001  |

Data with listwise deletion are expressed as mean (SD) or number (percentage).

* A single patient with missing sex data was excluded from the entire analysis.

† Left atrial volume index and left ventricular ejection fraction was assessed with modified Simpson method.

Diastolic dysfunction was diagnosed according to the American Society of Echocardiography and European Association of Cardiovascular Imaging (ASE/EACVI) guidelines for diastolic function assessment.14 A total of 595 patients had enough echocardiographic data for the assessment of diastolic dysfunction based on the criteria.

Figure 1. Comorbidities related to diastolic dysfunction in the overall cohort.
Multivariable binary logistic regression analysis was performed in order to assess the impact of multiple comorbidities on the echocardiographic end point (diastolic dysfunction) in the overall cohort (N=595). Results are illustrated as a forest plot. Female sex, anemia, and obesity were significant factors associated with diastolic dysfunction. OR indicates odds ratio.
factor, this result does not reject the hypothesis that inflammation is a fundamental mechanism for the development of diastolic dysfunction. Unfortunately, the present study cannot provide enough data to answer this hypothesis. These topics need to be further investigated in basic science.

**Prognosis of HFpEF in Women and Men**

Crude rates of the clinical end point of all-cause death or heart failure readmission did not differ between women and men (Figure 2A). However, after adjustment of various confounders, female sex was independently associated with adverse clinical events in HFpEF (Figures 2B and 3). This may be a result of fewer baseline comorbidities in women than in men. Previous studies also reported that comorbidity burden in women is lower than that in men. The primary finding is, however, inconsistent with the previous data from a large-scale study (N=42,987) by Stolfo et al. In the Swedish Heart Failure Registry population, multivariate Cox and logistic regression models were fitted to investigate differences in prognosis, prognostic predictors, and treatments across men and women. Of 42,987 patients, 9,957 patients had HFpEF. Crude mortality/HF hospitalization rates were significantly higher in women than in men (hazard ratio [HR], 1.14; 95% CI, 1.07–1.21). After adjustments, however, the risk was significantly lower in women (HR, 0.93; 95% CI, 0.88–0.99). Differences not only in the basic comorbidities but also in the postdischarge medications such as angiotensin II receptor blockers and calcium channel blockers between the sexes may have affected the clinical outcomes. In the study from the Swedish Heart Failure Registry, these medications were adjusted,

Table 4. Incidence of the Clinical End Points

| Event                                | Women                  | Men                    | P Value |
|--------------------------------------|------------------------|------------------------|---------|
| All-cause death and heart failure readmission | 36.1/100 person-years | 30.5/100 person-years | 0.336   |
| All-cause death                      | 12.8/100 person-years | 12.8/100 person-years | 0.929   |
| Cardiac death                        | 6.1/100 person-years  | 5.1/100 person-years  | 0.544   |
| Noncardiac death                     | 6.7/100 person-years  | 7.4/100 person-years  | 0.601   |
| Death from unknown cause             | 0/100 person-years     | 0.3/100 person-years   | 0.368   |
| Heart failure readmission            | 24.1/100 person-years | 20.2/100 person-years | 0.426   |

**Figure 2. Clinical outcomes stratified by sex.**

A. The clinical endpoint of all-cause death or heart failure readmission was assessed in a time-to-first-event fashion with Kaplan-Meier analysis. In the crude comparison, no difference was found between women and men (log-rank P=0.191). B. Adjusted probability curves in women and men created with the multivariable Cox proportional hazards model included the following covariates: female sex, C-reactive protein, age, anemia (hemoglobin level <12 g/dL in women and <13 g/dL in men according to the World Health Organization definition), hypertension, diabetes mellitus, dyslipidemia, coronary artery disease, chronic kidney disease, atrial fibrillation, obesity (body mass index ≥25), and cholinesterase level. The cumulative probability curves show the model-predicted event rates for the “average” patient in women and men. HF indicates heart failure; and HR, hazard ratio.
whereas in our main analysis, we did not adjust the differences in these medications. However, our sensitivity analysis adjusting postdischarge medications provided consistent results (Figure S3). Racial difference would be one of the possible reasons for the opposite results between ours and the previous data. The difference in age (82±9 in the current cohort versus 79±10 in the Swedish Heart Failure Registry) and body mass index (22 versus 27) may also partially explain the opposite findings. This point remains to be further investigated in future studies.

**Clinical Implications**

Sex differences in HFpEF suggest the need for further research to better understand underlying pathophysiology, including contributions of sex hormones and sex hormone deficiency, and thereby identify novel preventive and disease-modifying treatments for HFpEF.

Anemia and obesity, besides female sex, were independently associated with diastolic dysfunction. Anemia or iron deficiency and weight control might be targets for preventing diastolic dysfunction. Besides female sex, coronary artery disease and chronic kidney disease were independently associated with worse clinical outcomes. Treatments for coronary artery disease and chronic kidney disease may be priorities in the treatments of HFpEF. Our results did not show significant interactions between sex and effects of any comorbidities (Figures S1 and S2). Therefore, aggressive therapeutic intervention for these comorbidities regardless of sex would be a reasonable option for the time being.

**Limitations**

Several limitations should be acknowledged. First, the present study is a multicenter prospective East-Asian HFpEF registry, which would limit the generalizability of the current findings to other races. The cutoff value for obesity (body mass index of 25 in the current analysis) would be different for other countries. Second, small sample size, especially of the subgroup analysis stratified by sex, might have resulted in type II error. Results should be interpreted with caution. Third, systemic inflammation was represented by C-reactive protein in the current study. However, other inflammatory markers (interleukin-6, tumor necrosis factor-α, etc) should be investigated in future studies. Fourth, diastolic dysfunction was assessed only in patients with enough echocardiographic data (68% of the entire cohort). This might have resulted in selection bias. Lastly, the study demonstrated that female sex was independently
associated with the presence of diastolic dysfunction. However, it is unclear whether the association of female sex with HFpEF is the result of innate biological differences (eg, sex hormones), the result of sex differences (environmental interactions that differ between sexes), or some other residual confounding (eg, women live longer than men). Future basic research would be mandatory to elucidate the specific mechanism of development of diastolic dysfunction in women.

CONCLUSIONS

In the PURSUIT-HFpEF prospective multicenter East-Asian HFpEF registry, women accounted for 55.2% of the overall cohort. Women had echocardiographic diastolic dysfunction more frequently than men. Female sex was independently associated with the presence of diastolic dysfunction and worse clinical outcomes in a cohort of elderly patients with HFpEF. Our results suggest that a sex-specific approach would be key to investigating the pathophysiology in HFpEF.

ARTICLE INFORMATION

Received August 25, 2020; accepted January 19, 2021.

Affiliations

From the Department of Cardiovascular Medicine (Y.S., S.H., D.N., H.M., K.O., T.D., A.S., H.K., B.O., T.S., Y.S.) and Department of Social and Environmental Medicine (T.K.), Osaka University Graduate School of Medicine, Osaka, Japan; Division of Biomedical Statistics, Department of Integrated Medicine, Graduate School of Medicine, Osaka University, Osaka, Japan (S.K.); Division of Cardiology, Osaka General Medical Center, Osaka, Japan (S.T., T.Y.); Division of Cardiology, Osaka Rosai Hospital, Osaka, Japan (M.Y.); Cardiovascular Division, Osaka Police Hospital, Osaka, Japan (T.H.); Division of Cardiology, Amagasaki Chuho Hospital, Hyogo, Japan (A.N., Y.Y.); Department of Medical Informatics, Osaka University Graduate School of Medicine, Suita, Japan (A.N.); and Division of Cardiology, Kawanishi City Hospital, Hyogo, Japan (Y.N.).

Acknowledgments

The authors thank Sugako Mitsuoka, Masako Terui, Nagisa Yoshioka, Satomi Kishimoto, Kyoko Tatsumi and Noriko Murakami for their excellent assistance in data collection, data management, and secretarial works.

Sources of Funding

This work was funded by Roche Diagnostics K.K. and Fuji Film Toyama Chemical Co. Ltd.

Disclosures

Y. Sotomi received personal fees from Daiichi-Sankyo, Bayer, Boehringer Ingelheim, and Bristol-Myers Squibb. S. Hikoso received grants from Roche Diagnostics, FUJIFILM Toyama Chemical, Actelion Pharmaceuticals; personal fees from Daiichi Sankyo, Astellas Pharma, Bayer, Pfizer Pharmaceuticals, Boehringer Ingelheim Japan, Kowa Company, and Ono Pharmaceutical. D. Nakatani received personal fees from Roche Diagnostics. H. Mizuno received personal fees from Daiichi Sankyo, Mitsubishi Tanabe Pharma Corporation, AstraZeneca K.K. and Actelion Pharmaceuticals, and received grants from Roche Diagnostic, FUJIFILM Toyama Chemical, Bristol-Myers Squibb, Co. Biosense Webster, Inc., Abbott Medical Japan, Otsuka Pharmaceutical, Daichi Sankyo Company, Mitsubishi Tanabe Pharma Corporation, Astellas Pharma, Kowa Company, Boehringer Ingelheim Japan, and Biotronik. The remaining authors have no disclosures to report.

Supplementary Material

Appendix S1
Table S1
Figures S1–S3

REFERENCES

1. McMurray JJV, Packer M, Desai AS, Gong J, Lefkopoulou MP, Rizkalla AR, Rouleau JL, Shc VC, Solomon SD, Swedberg K, et al. Angiotensin- nephrilisin inhibition versus enalapril in heart failure. N Engl J Med. 2014;371:993–1004. DOI: 10.1056/NEJMoa1409077.
2. Pieske B, Patel MJ, Westerhoud CM, Amstrom KI, Butler J, Ezekowitz J, Hernandez AF, Koglin J, Lam CSP, Ponikowski P, et al. Baseline features of the VICTORIA (vericiguat global study in subjects with heart failure with reduced ejection fraction) trial. Eur J Heart Fail. 2019;21:1596–1604. DOI: 10.1002/ejhf.1664.
3. Zannad F, Anker SD, Byra WM, Cleland JGF, Fu M, Gheorghiade M, Lam CSP, Mehran MR, Neaton JD, Nessel CC, et al. Rivaroxaban in patients with heart failure, sinus rhythm, and coronary disease. N Engl J Med. 2018;379:1332–1342. DOI: 10.1056/NEJMoa1808848.
4. Massie BM, Carson PE, McMurray JJ, Komajda M, McKelvie R, Zile MR, Anderson S, Donovan M, Iverson E, Staiger C, et al. Irbesartan in patients with heart failure and preserved ejection fraction. N Engl J Med. 2008;359:2456–2467. DOI: 10.1056/NEJMoa0805450.
5. Pitt B, Pfeifer MA, Assmann SF, Boineau R, Anand IS, Clogg B, Clausell N, Desai AS, Diaz R, Fleg JL, et al. Spironolactone for heart failure with preserved ejection fraction. N Engl J Med. 2014;370:1383–1392. DOI: 10.1056/NEJMoa1313731.
6. Beale AL, Meyer P, Marwick TH, Lam CSP, Kaye DM. Sex differences in cardiovascular pathophysiology: why women are overrepresented in heart failure with preserved ejection fraction. Circulation. 2018;138:198–205. DOI: 10.1161/CIRCULATIONAHA.118.034271.
7. Levy D, Larson MG, Vasan RS, Kannel WB, Ho KK. The progression from hypertension to congestive heart failure. JAMA. 1996;275:1557–1562. DOI: 10.1001/jama.1996.03530440037034.
8. Kannel WB, Hjortland M, D'Agostino R, Kannel J, Kannel B. The progression from hypertension to congestive heart failure: the Framingham Study. Am J Cardiol. 1974;34:29–34. DOI: 10.1016/0002-9149(74)90089-7.
9. O’Neal WT, Sandesara P, Hammadah M, Venkatesh S, Samman-Tahhan A, Kelli HM, Soliman EZ. Gender differences in the risk of adverse outcomes in patients with atrial fibrillation and heart failure with preserved ejection fraction. Am J Cardiol. 2017;119:1785–1790. DOI: 10.1016/j.amjcard.2017.02.045.
10. Klein SL, Flanagan KL. Sex differences in immune responses. Nat Rev Immunol. 2016;16:626–638. DOI: 10.1038/nri.2016.90.
11. 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. DOI: 10.1056/NEJM19712208280261.
12. Hoshida S, Watanabe T, Shinoda Y, Ikeoka K, Minamisaka T, Fukuoka H, Inui H, Ueno K, Suna S, Nakatani D, et al. Sex-related differences in left ventricular diastolic function and arterial elastance during admission in patients with heart failure with preserved ejection fraction: the Pursuit HFrEF study. Clin Cardiol. 2018;41:1529–1536. DOI: 10.1002/clc.23073.
13. Seo M, Yamada T, Tamaki S, Hikoso S, Yasumura Y, Higuchi Y, Nakagawa Y, Uematsu M, Abe H, Fuji H, et al. Prognostic significance of serum cholinesterase level in patients with acute decompensated heart failure with preserved ejection fraction: insights from the PURSUIT-HFpEF registry. J Am Heart Assoc. 2020;9:e014100. DOI: 10.1161/JAHA.119.014100.
14. Nagueh SF, Smith OA, Appleton CP, Byrd BF, Il, Dokainish H, Edvardsen T, Flachskampf FA, Gillebert TC, Klein AL, Lancellotti P, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society...
of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2016;29:277–314. DOI: 10.1016/j.echo.2016.01.011.

15. McLean E, Cogswell M, EglI, Wojdy1a D, de Benoist B. Worldwide prevalence of anaemia, who vitamin and mineral nutrition information system, 1993–2005. Public Health Nutr. 2009;12:444–454. DOI: 10.1017/S1368980009002401.

16. Fine JP, Gray RJ. A proportional hazards model for the subdivistion of a competing risk, J Am Stat Assoc. 1999;94:496–509. DOI: 10.1080/01621459.1999.10474144.

17. Juma S, Taabazuing MM, Montero-Odasso M. Clinical frailty scale in an acute medicine unit: a simple tool that predicts length of stay. Can Geriatr J. 2016;19:34–39. DOI: 10.5770/cogj.19.186.

18. Pieske B, Tschöpe C, de Boer RA, Fraser AG, Anker SD, Donal E, Ede1mann F, Fu M, Guazzi M, Lam CSP, et al. How to diagnose heart failure with preserved ejection fraction: the HFA-PEF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). Eur Heart J. 2019;40:3297–3317. DOI: 10.1093/eurheartj/ehz641.

19. Daimon M, Watanabe H, Abe Y, Hirata K, Hozumi T, Ishii K, Ito H, Iwakura K, Izumi C, Matsuzaki M, et al. Normal values of echocardiographic parameters in relation to age in a healthy Japanese population: the JAMP study. Circ. J. 2008;72:1859–1866. DOI: 10.1253/circj.CJ-08-0171.

20. Lau ES, Cunninghan T, Hardin KM, Liu E, Malhotra R, Nayor M, Lewis GD, Ho JE. Sex differences in cardiometabolic traits and determinants of exercise capacity in heart failure with preserved ejection fraction. JAMA Cardiol. 2020;530–37. DOI: 10.1001/jamaccardio.2019.4150.

21. Bea1e AL, Nanayakkara S, Segan L, Mariani JA, Maeder MT, van Empel V, Vizi D, Evans S, Lam CSP, Kaye DM. Sex differences in heart failure with preserved ejection fraction pathophysiology: a detailed invasive hemodynamic and echocardiographic analysis. JACC Heart Fail. 2019;7:239–249. DOI: 10.1016/j.jchf.2019.01.004.

22. Dhakal BP, Malhotra R, Murphy RM, Pappagianopoulos PP, Baggish AL, Weiner RB, Houstis NE, Eisman AS, Hough SS, Lewis GD. Mechanisms of exercise intolerance in heart failure with preserved ejection fraction: the role of abnormal peripheral oxygen extraction. Circ Heart Fail. 2015;8:288–294. DOI: 10.1161/CIRCHEARTFAILURE.A.114.001825.

23. Petre R, Quale MP, Rossman El, Ratcliffe SJ, Bailey BA, Houser SR, Margules KB. Sex-based differences in myocardial contractile reserve. Am J Physiol Regul Integr Comp Physiol. 2007;292:R810–R816. DOI: 10.1152/ajpregu.00377.2006.

24. Vääräniemi K, Koskela J, Tahvanainen A, Tikkakoski A, Wilenius M, Kähönen M, Kõõbi T, Niemelä O, Mustonen J, Pörsti I. Lower glomerular filtration rate is associated with higher systemic vascular resistance in patients without prevalent kidney disease. J Clin Hypertens (Greenwich). 2014;16:722–728. DOI: 10.1111/jch.12405.

25. Parks RJ, Ray G, Bienvenu LA, Rose RA, Howlett SE. Sex differences in SR Ca(2+) release in murine ventricular myocytes are regulated by the cAMP/PKA pathway. J Mol Cell Cardiol. 2014;75:162–173. DOI: 10.1016/j.yjmcc.2014.07.006.

26. Peterson LR, Soto PF, Herrero P, Mohammed BS, Avidan MS, Schechtman KB, Dence G, Gropler RJ. Impact of gender on the myocardial metabolic response to obesity. JACC Cardiovasc Imaging. 2008;1:442–433. DOI: 10.1016/j.jcmg.2008.05.004.

27. Zhao Z, Wang H, Jessup JA, Lindsey SH, Chappell MC, Groban L. Role of estrogen in diastolic dysfunction. Am J Physiol Heart Circ Physiol. 2014;306:H628–H640. DOI: 10.1152/ajpheart.00859.2013.

28. Kravtsov GM, Kam KW, Liu J, Wu S, Wong TM. Altered Ca(2+) handling by ryanodine receptor and Na(+)-Ca(2+) exchange in the heart from ovariectomized rats: role of protein kinase A. Am J Physiol Cell Physiol. 2007;292:C1625–C1635. https://doi.org/10.1152/ajpcell.00368.2006.

29. Chung E, Yeung F, Leinwand LA. Akt and MAPK signaling mediate pregnancy-induced cardiac adaptation. J Appl Physiol (1985). 2012;112:1564–1575. DOI: 10.1152/japplphysiol.00027.2012.

30. Solomon SD, McMurray JJV, Anand IS, Ge J, Lam CSP, Maggioni AP, Martinez F, Packer M, Pfeffer MA, Pieske B, et al. Angiotensin-neprilysin inhibition in heart failure with preserved ejection fraction. N Engl J Med. 2019;381:1609–1620. DOI: 10.1056/NEJMoa1908655.

31. Aslam F, Bandeali SJ, Khan NA, Alam M. Diastolic dysfunction in rheumatoid arthritis: a meta-analysis and systematic review. Arthritis Care Res (Hoboken). 2013;65:534–543. DOI: 10.1002acr.21861.

32. Macdougall IC, Canadu B, de Francisco AL, Filippatos G, Ponikowski P, Silverberg D, van Veldhuisen DJ, Anker SD. Beyond the cardiorenal anaemia syndrome: recognizing the role of iron deficiency. Eur J Heart Fail. 2012;14:882–886. DOI: 10.1038/ejhfhs056.

33. Kim HL, Kim MA, Oh S, Kim M, Park SM, Yoon HJ, Shin MS, Hong KS, Shin GJ, Shin WI. Sex difference in the association between metabolic syndrome and left ventricular diastolic dysfunction. Metab Syndr Relat Disord. 2016;14:507–512. DOI: 10.1089/met.2016.0078.

34. Hongiberg MC, Lau ES, Jones AD, Coles A, Redfield MM, Lewis GD, Givertz MM. Sex differences in exercise capacity and quality of life in heart failure with preserved ejection fraction: a secondary analysis of the RELAX and NEAT-HFpEF trials. J Card Fail. 2020;26:276–280. DOI: 10.1016/j.cardfail.2020.01.001.

35. Stolfo D, Ulij A, Vedin O, Stromberg A, Fexen UL, Rosano GMC, Sinagra G, Dahlstrom U, Savarese G. Sex-based differences in heart failure across the ejection fraction spectrum: phenotyping, and diagnostic and therapeutic implications. JACC Heart Fail. 2019;7:505–515. DOI: https://doi.org/10.1016/j.jchf.2019.03.011.
SUPPLEMENTAL MATERIAL
Appendix

The OCVC-Heart Failure Investigators
Chair: Yasushi Sakata, Department of Cardiovascular Medicine, Osaka University Graduate School of Medicine, 2-2 Yamada-oka, Suita 565-0871, Japan
Secretariat: Shungo Hikoso (Chief), Daisaku Nakatani, Hiroya Mizuno, Shinichiro Suna, Katsuki Okada, Tomoharu Dohi, Yohei Sotomi, Takayuki Kojima, Akihiro Sunaga, Hirota Kida, Bolrathanak Oeun, and Taiki Sato; Department of Cardiovascular Medicine, Osaka University Graduate School of Medicine, Suita, Japan.

Investigators:
Shunsuke Tamaki, Tetsuya Watanabe, and Takahisa Yamada, Osaka General Medical Center, Osaka, Japan; Takaharu Hayashi and Yoshiharu Higuchi, Osaka Police Hospital, Osaka, Japan; Masaharu Masuda, Mitsutoshi Asai, and Toshiaki Mano, Kansai Rosai Hospital, Amagasaki, Japan; Hisakazu Fuji, Kobe Ekisaikai Hospital, Kobe, Japan; Daisaku Masuda, Yoshihiro Takeda, Yoshiyuki Nagai, and Shizuya Yamashita, Rinku General Medical Center, Izumisano, Japan; Masami Sairyo, Yusuke Nakagawa and Shuichi Nozaki, Kawanishi City Hospital, Kawanishi, Japan; Haruhiko Abe, Yasunori Ueda, Masaaki Uematsu, and Yukihiro Koretsune, National Hospital Organization Osaka National Hospital, Osaka, Japan; Kunihiko Nagai, Ikeda Municipal Hospital, Ikeda, Japan; Masamichi Yano, Masami Nishino, and Jun Tanouchi, Osaka Rosai Hospital, Sakai, Japan; Yoh Arita and Shinji Hasegawa, Japan Community Health Care Organization Osaka Hospital, Osaka, Japan; Takamaru Ishizu, Minoru Ichikawa and Yuzuru Takano, Higashiosaka City Medical Center, Higashiosaka, Japan; Eisai Rin, Kawachi General Hospital, Higashiosaka, Japan; Yukinori Shinoda and Shiro Hoshida, Yao Municipal Hospital, Yao, Japan; Masahiro Izumi, Kinki Central Hospital, Itami, Japan; Hiroyoshi Yamamoto and Hiroyasu Kato, Japan Community Health Care Organization, Osaka Minato Central Hospital, Osaka, Japan; Kazuhiro Nakatani and Yuji Yasuga, Sumitomo Hospital, Osaka, Japan; Mayu Nishio and Keiji Hirooka, Saiseikai Senri Hospital, Suita, Japan; Takahiro Yoshimura and Yoshinori Yasuoka, National Hospital Organization Osaka Minami Medical Center, Kawachinagano, Japan; Akihiro Tani, Kano General Hospital, Osaka, Japan; Yasushi Okumoto and Hideharu Akagi, Kinan Hospital, Tanabe, Japan; Yasunaka Makino, Hyogo Prefectural Nishinomiya Hospital, Nishinomiya, Japan; Toshinari Onishi and Katsuomi Iwakura, Sakurabashi Watanabe Hospital, Osaka, Japan; Nagahiro Nishikawa and Yoshiyuki Kijima, Japan Community Health Care Organization, Hoshigaoka Medical Center, Hirakata, Japan; Takashi Kitao and Hideyuki Kanai, Minoh City Hospital, Minoh, Japan; Wataru
Shioyama and Masashi Fujita, Osaka International Cancer Institute, Osaka, Japan; Koichiro Harada, Suita Municipal Hospital, Suita, Japan; Masahiro Kumada and Osamu Nakagawa, Toyonaka Municipal Hospital, Toyonaka, Japan; Ryo Araki and Takayuki Yamada, Otemae Hospital, Osaka, Japan; Akito Nakagawa and Yoshio Yasumura, Amagasaki Chuo Hospital, Amagasaki, Japan; and Taiki Sato, Akihiro Sunaga, Bolrathanak Oeun, Hirota Kida, Takayuki Kojima, Yohei Sotomi, Tomoharu Dohi, Kei Nakamoto, Katsuki Okada, Fusako Sera, Shinichiro Suna, Hidetaka Kioka, Tomohito Ohtani, Toshihiro Takeda, Daisaku Nakatani, Hiroya Mizuno, Shungo Hikoso, Yasushi Matsumura and Yasushi Sakata, Osaka University Graduate School of Medicine, Suita, Japan.
Table S1. Association of the comorbidities and clinical endpoints

|                                | A composite of all-cause death and HF readmission* | All-cause death* | HF readmission† |
|--------------------------------|---------------------------------------------------|-----------------|-----------------|
|                                | Hazard ratio [95%CI]  | P value       | Hazard ratio [95%CI]  | P value       | Subdistribution hazard ratio [95%CI]  | P value       |
| Female sex                     | 1.538 [1.146, 2.064]  | 0.004         | 1.141 [0.733, 1.778]  | 0.560         | 1.553 [1.091, 2.211]  | 0.015         |
| C-reactive protein             | 1.071 [0.976, 1.175]  | 0.150         | 1.150 [1.047, 1.263]  | 0.004         | 0.829 [0.716, 0.960]  | 0.012         |
| Age                            | 1.030 [1.010, 1.050]  | 0.003         | 1.083 [1.042, 1.125]  | <0.001        | 1.008 [0.987, 1.031]  | 0.448         |
| Anemia                         | 0.916 [0.649, 1.292]  | 0.620         | 0.856 [0.481, 1.525]  | 0.600         | 1.045 [0.693, 1.576]  | 0.833         |
| Hypertension                   | 1.003 [0.690, 1.459]  | 0.990         | 0.776 [0.429, 1.402]  | 0.400         | 1.195 [0.715, 1.995]  | 0.497         |
| Diabetes mellitus              | 1.083 [0.793, 1.480]  | 0.620         | 1.055 [0.641, 1.737]  | 0.830         | 1.004 [0.701, 1.437]  | 0.983         |
| Dyslipidemia                   | 0.946 [0.697, 1.284]  | 0.720         | 0.943 [0.571, 1.556]  | 0.820         | 1.123 [0.781, 1.613]  | 0.532         |
| Coronary artery disease        | 1.518 [1.063, 2.167]  | 0.022         | 1.615 [0.973, 2.680]  | 0.064         | 1.392 [0.921, 2.104]  | 0.117         |
| Chronic kidney disease         | 1.745 [1.318, 2.311]  | <0.001        | 1.436 [0.939, 2.198]  | 0.095         | 2.062 [1.463, 2.907]  | <0.001        |
| Atrial fibrillation            | 1.206 [0.901, 1.614]  | 0.210         | 0.827 [0.527, 1.297]  | 0.410         | 1.418 [1.009, 1.994]  | 0.045         |
| Obesity                        | 1.161 [0.787, 1.712]  | 0.450         | 1.152 [0.646, 2.056]  | 0.630         | 1.008 [0.652, 1.556]  | 0.973         |
| Cholinesterase                 | 0.995 [0.992, 0.997]  | <0.001        | 0.991 [0.986, 0.996]  | 0.001         | 0.996 [0.993, 0.999]  | 0.007         |
Cox proportional hazard model was utilized to assess the impacts of the covariates on a composite of all-cause death and HF readmission, and all-cause death. †The Fine and Gray model was used for assessing subdistribution hazards for HF readmission considering all-cause death as a competing risk. Abbreviations: HF, heart failure, CI, confidence interval.
Figure S1. Comorbidities related to diastolic dysfunction in women and men

Multivariable binary logistic regression analysis was performed in order to assess the impact of multiple comorbidities on the echocardiographic endpoint (diastolic dysfunction) in women (Red) and men (Blue) separately. Results are illustrated as forest plot. In women, anemia was a unique and significant associated factor, whereas in men, there was no significantly associated factors with diastolic dysfunction. *P value for interaction between women and men.
Multivariable Cox proportional hazard model was constructed in order to assess the impact of multiple comorbidities on the post-discharge clinical endpoint in women (Red) and men (Blue) separately. Results are illustrated as forest plot. Chronic kidney disease and cholinesterase were significantly associated with the clinical endpoint both in women and men. Coronary artery disease was a significant predictor only in women, albeit no significant interaction. *P value for interaction between women and men.
Figure S3. Prognostic factors for the clinical endpoint in the overall cohort

Multivariable Cox proportional hazard model was constructed in order to assess the impact of multiple comorbidities on the post-discharge clinical endpoint in overall cohort with adjustment for post-discharge medications. Results are illustrated as forest plot. Medications which prescription rates were different between women and men were included as covariates (Table 2). The result was consistent with the main analysis.