Is There a Sex Difference in Japanese Patients With Heart Failure?

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Hear failure (HF) is a leading cause of cardiovascular mortality and morbidity both in Japan and the Western world.¹ In the United States, HF incidence has largely remained stable over the past several decades, with >650,000 new HF cases diagnosed annually, approximately 5.1 million persons with clinically manifest HF, and the prevalence of HF continuing to rise.² In 2008, the Ministry of Health, Labor and Welfare, Japan, estimated that there were 47,500 patients with HF and 27,900 patients hospitalized for this disease per day in this country.³ The incidence of HF increases with age, rising from approximately 20 per 1000 individuals aged 65–69 years to >80 per 1000 individuals among those ≥85 years old. In 2011, the number of deaths from HF was 69,368 (26,011 males, 43,357 females), and death rate (per 100,000 population) was 55.0 (42.3 in males, 67.0 in females).⁴

Article p428

HF affects men at a younger age than women. Women more frequently have diastolic HF, associated with the major risk factors of diabetes and hypertension, and men more frequently have systolic HF because of ischemic heart disease.¹ Meta-analyses from large multicenter trials confirm that women are less likely to receive guideline-related HF treatment, but nevertheless do better than their male counterparts.⁵ Martínez-Sellés et al performed the meta-analysis of sex differences in HF using the Meta-Analysis Global Group In Chronic Heart Failure (MAGGIC), and revealed that survival is better for women with HF compared with men, irrespective of ejection fraction (EF). Furthermore, this survival benefit is more marked

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in non-ischemic HF.⁶ Data from 31 studies (41,949 patients; 28,052 men, 13,897 women) from the MAGGIC showed that women were older (70.5 ± 12.1 vs. 65.6 ± 11.6 years), more likely to have a history of hypertension (49.9% vs. 40.0%), and less likely to have a history of ischemic heart disease (46.3% vs. 58.7%) and reduced EF (62.6% vs. 81.6%) compared with men. During a 3-year follow-up, 3,521 (25%) women and 7,232 (26%) men died, which was comparable. After the adjustment for age, male sex was an independent predictor of mortality (Figure), and the better prognosis associated with female sex was more marked in patients with HF of non-ischemic etiology, compared with ischemic etiology.⁶

HF and preserved EF (HFpEF) constitutes 30–50% of HF patients, and affects women more often than men. Deswal et al evaluated the sex difference in mortality and morbidity for HFpEF (EF >50%) using the ancillary arm of the Digitalis Investigation Group (DIG) trial. They concluded that, although the clinical manifestations of HF appear to be more severe in women with HFpEF, after adjustment for baseline clinical differences, HF hospitalizations are not increased and survival expectancy is better for women than men.⁷

In this issue of the Journal, Sakata et al⁸ used the CHF Registry in Tohoku area of Japan, named CHART-2 Study and show that female chronic HF (CHF) patients had better survival than males after adjustment for baseline differences, although the crude mortality rate was comparable between the sexes, possibly reflecting relatively severer clinical manifestation in females. They examined 4,736 consecutive CHF patients in stage C/D (mean age 69 years), revealing that, compared with male patients, female patients were 3.8 years older and had lower prevalence of ischemic heart disease, diabetes, smoking, myocardial infarction (MI) and cancer. At baseline, females had more preserved left ventricular function but had higher NYHA functional class and increased brain natriuretic peptide levels. In females, aspirin, β -blockers and statins were less frequently used and diuretics were more frequently used. Crude mortality rate was comparable between the sexes during the median 3.1-year follow-up (52.4/1,000 and 47.3/1,000 person-year for females and males, respectively, $P=0.225$). Multivariate Cox regression analysis revealed that females had a reduced risk of mortality (adjusted hazard ratio 0.791, 95% confidence interval 0.640–0.979, $P=0.031$). These results appear almost comparable with those in previous reports from Western countries, except the prevalence of hypertension was similar between the sexes in the present cohort, whereas in the previous reports, it was frequently observed in female HF patients.

To clarify the potential pathophysiological mechanisms underlying sex differences in heart failure, Meyer et al assessed sex-specific variation in clinical characteristics and biomarker levels in 567 patients (mean age 71 ± 11 years, 38% female). Levels of biomarkers related to inflammation (C-reactive protein, pentraxin 3, growth differentiation factor 15 (GDF-15), and interleukin-6) and extracellular matrix remodeling (syndecan-1 and periostin) were significantly lower in women compared with men. They conclude that female HF patients have a distinct clinical presentation and better outcomes compared with male patients. In addition, the lower mortality was independent of differences in clinical characteristics, but differential sex associations between several biomarkers and mortality might partly explain the survival difference.⁹

Hara et al¹⁰ investigated the association between serum n-3 polyunsaturated fatty acids (n-3 PUFA) levels and HF events in 712 survivors of acute MI (AMI) using The Osaka Acute Coronary Insufficiency Study (OACIS), which is a prospective and observational study of AMI from the Osaka region of Japan

(ID: UMIN000004575). They clarified that low levels of circulating n-3 PUFA are associated with decreased HF-free survival in post-AMI patients, and the effect of low serum eicosapentaenoic acid level on HF hospitalization was prominent in male patients, suggesting a sex difference in HF after AMI.

There are a number of alternative potential explanations for the better outcomes in women with HF. The female heart appears to respond to injury differently from the male heart. For example, women have been reported to have less ventricular remodeling, preservation of right ventricular function, and protection against ventricular arrhythmias, neurohormonal activation, genetic mutations, myocyte necrosis, and apoptosis.¹¹ Under stress, male hearts develop pathological hypertrophy with dilatation and poor systolic function more easily than female hearts. Women with aortic stenosis have concentric hypertrophy with better systolic function, less upregulation of extracellular matrix genes and better reversibility after unloading. Stressed female hearts maintain energy metabolism better than male hearts and are better protected against calcium overload. Estrogens and androgens and their receptors are present in the myocardium and lead to coordinated regulation of functionally relevant pathways.¹

In conclusion, female CHF patients seems to have a better survival than males after adjustment for baseline differences, although the crude mortality rate is comparable between the sexes, possibly reflecting relatively severer clinical manifestations in females. By understanding that women are less likely to receive guideline-related HF treatment, but nevertheless do better than their male counterparts, guideline-related HF treatments may be promoted for female HF patients. Further investigation of sex differences in HF is warranted, leading to evidence-based medicine for HF in light of sex differences.

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