*Circ J* 2008; **72:** 2009 – 2014

# Emerging Problems of Heart Failure Practice in Japanese Women

## —— Lessons From the CHART Study ——

Nobuyuki Shiba, MD*,**; Kotaro Nochioka, MD**; Haruka Kohno, RN**; Mika Matsuki, RN*,**; Jun Takahashi, MD**; Tomohiro Tada, MD**; Yutaka Kagaya, MD**; Hiroaki Shimokawa, MD*,**

**Background** The prognosis of patients with chronic heart failure (CHF) is poor in both men and women. However, the characteristics of, and effective treatment strategy for, female CHF patients still remain unclear. This study was designed to evaluate the prognosis and characteristics of female patients in a CHF cohort termed the Chronic Heart Failure Analysis and Registry in the Tohoku District.

**Methods and Results** Of 1,278 patients registered in the cohort, the study population comprised 1,166 symptomatic CHF patients with sufficient data. As compared with male patients, female patients were more likely to be older, have preserved systolic function and non-ischemic etiology of CHF, and underuse standard CHF medications. Although a previous study showed that sex-difference was not a significant prognostic factor in CHF patients, the unadjusted survival analysis revealed an increased event rate in female patients in the present study. Multivariate analysis revealed that older age, diabetes, ventricular tachycardia and anemia were significant prognostic risks in both men and women with CHF.

**Conclusions** Female sex had a significant link with elderly CHF patients. Given the explosive increase in elderly patients in Westernized countries, further studies are needed to elucidate the evidence for treatment of female CHF patients. (*Circ J* 2008; **72:** 2009 – 2014)

**Key Words:** Elderly; Non-ischemic cardiac disease; Preserved systolic function; Sex difference

Chronic heart failure (CHF) is a leading cause of mortality in most developed countries[1] The prognosis of CHF patients is still poor despite the recent progress in treatment from both the pharmacological and non-pharmacological aspect. Furthermore, ongoing rapid aging of populations in westernized countries will increase the number of CHF patients. The Japanese population has also been aging rapidly over the past few decades. The percentage of the population aged 65 years or older was 19.9% in 2005 and is expected to reach almost 30% by 2030[2] Japanese physicians urgently need an effective treatment strategy to improve the prognosis of elderly CHF patients and effective measures to prevent the development of congestive heart failure in these patients. Other developed countries, including the United States, will experience the same problem of aging in the near future.

Guidelines for CHF treatment have been developed based on accumulating scientific evidence obtained in randomized controlled trials with thousands of patients, but the entry criteria usually exclude minorities such as females or elderly patients[3] Most female CHF patients are elderly and many of those are categorized as CHF with preserved systolic function, for which there is currently no ideal treatment. These patients have many comorbidities and unsolved treatment problems, and CHF in female patients is an emerging serious problem that we have to manage urgently. In our previous reports we have already noted that the sex difference was not significantly associated with the mortality of patients with CHF[4,5] but there is still insufficient investigation of female CHF patients in Japan. Thus, the present study was designed to evaluate the current characteristics and prognosis of Japanese female patients with CHF in a CHF cohort, termed the Chronic Heart Failure Registry and Analysis in the Tohoku District (CHART) Study.[4,5]

## Methods

*The CHART Study and the Study Population*

The CHART Study is a prospective cohort of CHF patients that was started in February 2000 in cooperation with 26 affiliated hospitals in the Tohoku region, located in the northeastern area in Japan.[4,5] Patients were registered in the cohort when at least 1 of the following 3 criteria was fulfilled: (1) certain organic heart diseases in which the echocardiographic left ventricular ejection fraction (LVEF) was 50% or less, (2) organic heart disease in which the echocardiographic left ventricular (LV) end-diastolic dimension was 55 mm or more, or (3) organic heart disease and a documented history of clinical congestive heart failure defined by the Framingham criteria.[6] We performed annual follow-

*(Received December 4, 2007; revised manuscript received June 26, 2008; accepted July 24, 2008; released online October 24, 2008)*

*Departments of *Evidence-based Cardiovascular Medicine, **Cardiovascular Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan*

Mailing address: Nobuyuki Shiba, MD, Department of Evidence-based Cardiovascular Medicine and Department of Cardiovascular Medicine, Tohoku University Graduate School of Medicine, 1-1 Seiryo-machi, Aoba-ku, Sendai 980-8574, Japan. E-mail: nshiba@cardio.med.tohoku.ac.jp

All rights are reserved to the Japanese Circulation Society. For permissions, please e-mail: cj@j-circ.or.jp

**Table 1 Baseline Characteristics of Patients**

| | Male | Female | p value |
|---|---|---|---|
| *n* | 749 | 417 | |
| Age (years) | 66.3±13.7 | 72.2±12.0 | <0.001 |
| ≥75 years (%) | 28.1 | 46.6 | <0.001 |
| Follow-up period (years) | 3.3±1.6 | 3.1±1.7 | NS |
| NYHA class | 2.0±0.6 | 2.1±0.6 | <0.05 |
| BMI (kg/m$^2$) | 23.3±3.9 | 22.3±3.9 | <0.05 |
| BMI <18.5 kg/m$^2$ (%) | 6.6 | 15.1 | <0.01 |
| Blood pressure (mmHg) | | | |
| Systolic | 126.1±19.2 | 126.9±18.8 | NS |
| Diastolic | 72.3±10.8 | 70.2±11.2 | <0.05 |
| Heart rate (beats/min) | 74.5±14.1 | 75.4±14.9 | NS |
| LV end-diastolic dimension (mm) | 58.1±9.2 | 52.8±10.0 | <0.01 |
| LVEF (%) | 47.2±14.9 | 52.2±17.0 | <0.001 |
| ≥50% (%) | 39.3 | 53.1 | <0.05 |
| Etiology of CHF (%) | | | <0.001 |
| Ischemic cardiomyopathy | 28.0 | 17.0 | |
| Valvular heart disease | 22.0 | 34.1 | |
| LV hypertrophy | 13.4 | 16.5 | |
| Nonischemic cardiomyopathy | 31.5 | 25.4 | |
| Medical treatment (%) | | | |
| ACEI/ARB | 74.7 | 61.7 | <0.001 |
| β-blocker | 32.1 | 20.2 | <0.001 |
| Diuretics | 78.7 | 82.5 | NS |
| Digitalis | 47.3 | 50.1 | NS |
| Calcium antagonist | 30.4 | 29.8 | NS |
| Nitrate | 17.0 | 15.3 | NS |
| Antiarrhythmic | 18.3 | 17.3 | NS |
| Medical history | | | |
| Hypertension (%) | 38.9 | 41.0 | NS |
| Diabetes (%) | 18.7 | 19.4 | NS |
| Dyslipidemia (%) | 16.3 | 14.9 | NS |
| Atrial fibrillation (%) | 40.3 | 37.2 | NS |
| Ventricular tachycardia (%) | 18.6 | 13.9 | 0.05 |
| Admission for congestive heart failure (%) | 74.8 | 80.3 | <0.05 |
| Hemoglobin (g/dl) | 13.6±2.2 | 12.0±1.9 | <0.001 |
| Anemia (%) | 35.5 | 48.1 | <0.01 |
| Serum creatinine (mg/dl) | 1.1±0.8 | 1.0±0.8 | <0.05 |
| GFR (ml·min$^{-1}$·1.73 m$^{-2}$) | 60.0±35.2 | 60.4±33.4 | NS |
| B-type natriuretic peptide (pg/ml) | 244±332 | 313±360 | <0.05 |

*NYHA, New York Heart Association; BMI, body mass index; LV, left ventricular; LVEF, LV ejection fraction; CHF, chronic heart failure; ACEI, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker; GFR, glomerular filtration rate calculated by the Cockcroft-Gault equation.*

up surveys. Most patients usually visited the outpatient clinic of the 26 hospitals. We also conducted a telephone survey to minimize the drop out rate in cases of patients who changed their addresses. The 1-, 2-, and 3-year follow-up rates were 97.4%, 93.0%, and 87.4%, respectively[4] The endpoint of this study was the all-cause mortality and hospital admission for a cardiovascular cause was also recorded. The major outcome and other details of the CHART Study have previously been reported[4,5] Of 1,278 CHF patients who were registered in the CHART Study, the study population consisted of 1,166 symptomatic CHF patients with sufficient data.

*Data Analysis*

Comparisons of the baseline characteristics of male and female patients were performed using unpaired t-test or chi-square test. Numerical data are presented as the mean value ± standard deviation (SD). Cumulative survival curves were constructed by the Kaplan-Meier method and the difference between the curves was evaluated for significance using the log-rank test. Multivariate Cox regression analysis was used to estimate the factors that were significantly associated with the prognosis of the study population. The endpoint of the analysis was a composite event of admission because of congestive heart failure and all-cause mortality. The selection of covariates was performed using the backward stepwise method. The covariates evaluated in the model were age ≥75 years, anemia as defined by the WHO criteria, atrial fibrillation, diabetes, dyslipidemia, LVEF <50%, history of congestive heart failure, hypertension, ischemic etiology of CHF, serum creatinine level, the use of angiotensin-converting-enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARB), the use of β-blockers, and ventricular tachycardia. The association between disuse of CHF medication and patients' background factors was evaluated using multivariate logistic regression analysis. The covariates included in the model were age, anemia, atrial fibrillation, body mass index, diabetes, diastolic blood pressure, dyslipidemia, ejection fraction (EF), female sex, history of admission because of congestive heart failure, hypertension, ischemic etiology of CHF, New York Heart Association functional class, serum creatinine level, systolic blood pressure, and ventricular tachycardia. The selection of covariates was performed using the backward stepwise method.

All statistical analyses were performed using SPSS 15.0J

for Windows (SPSS, Chicago, IL, USA) and statistical significance was defined as a p-value less than 0.05.

## Results

*Baseline Characteristics and Characteristics of Female CHF Patients*

Mean follow-up period was 3.2±1.6 years and female patients accounted for 35.8% of the study population. Baseline characteristics of the CHF patients are shown in Table 1. The mean age of the female patients at the entry was significantly older than that of the male patients (72.2±12.0 vs 66.3±13.7 years). The prevalence of patients aged 75 years or older was 46.6% in the females and 28.1% in the males ($p<0.001$). Fig 1 shows the frequency of CHF patients by age and sex. Patients aged 79 years or younger were more frequently male; however, patients aged 80 years or older were relatively more often female. Female patients had significantly more different etiologies of CHF compared with male patients (Table 1). Valvular heart disease and LV hypertrophy were more frequently observed in female patients, whereas ischemic cardiomyopathy was a significantly less common etiology of CHF. More than half of the female patients had LVEF ≥50% and the mean LVEF was significantly higher in female patients than in male patients (Table 1: 52.2±17.0 vs 47.2±14.9%, $p<0.001$). Medication for CHF in the study population is shown in Table 1. The overall usage rates of ACEI, ARB, and β-blockers were surprisingly low at the entry of patients. Furthermore, sex-related differences in the prescribed CHF medications were noted for ACEI/ARB, and β-blockers.

*Prognosis of Female CHF Patients*

Unadjusted survival analyses using the Kaplan-Meier method were performed to evaluate the prognosis of female CHF patients using 2 endpoints: (1) composite event of all-cause mortality plus admission because of congestive heart failure and (2) composite event of cardiac-cause mortality plus admission because of congestive heart failure. These analyses clearly showed significantly increased crude event rates in female CHF patients during the follow-up period (Fig 2).

*Prognostic Risks in Female and Male CHF Patients*

Separate multivariate Cox regression analyses were also performed for the female (Table 2) and male (Table 3) patients to seek the factors associated with the composite event of admission because of congestive heart failure and all-cause mortality. Older age, diabetes, ventricular tachycardia, and anemia were significantly associated with the composite endpoint in both male and female patients. Reduced LVEF was a significant prognostic predictor in male patients; however, the significant association between LVEF and the composite endpoint was lost in female patients (Table 2).

*Factors Associated With Disuse of the Authorized CHF Treatment*

We constructed multivariate logistic regression analyses to examine which factors were related to disuse of standard CHF medical treatments such as ACEI/ARB and β-blockers. Initial analysis was performed using the overall study population and then we also separately analyzed the relationship between such disuse of medication and background characteristics in female and male patients. When using the overall

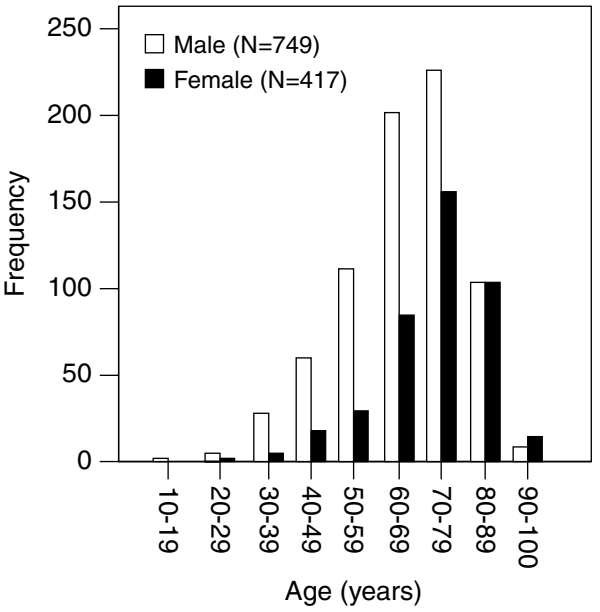


Fig 1. Number of patients with chronic heart failure by age and sex.

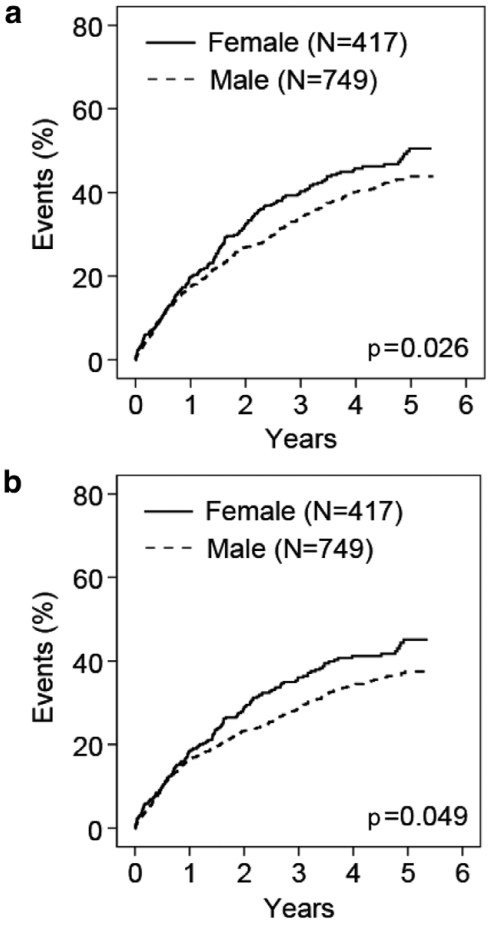


Fig 2. Unadjusted survival analyses of patients with chronic heart failure by sex. Endpoint: (a) composite event of all-cause mortality plus admission because of congestive heart failure, and (b) composite event of cardiac-cause mortality plus admission because of congestive heart failure.

**Table 2 Results of Multivariate Cox Regression Analysis: Factors Associated With Composite Endpoint of Admission for Congestive Heart Failure and All-Cause Mortality in 379 Female Patients**

| Covariate | Hazard ratio (95%CI) | p value |
|---|---|---|
| Age ≥75 years | 2.012 (1.461–2.771) | <0.001 |
| Diabetes | 1.638 (1.141–2.352) | 0.007 |
| Ventricular tachycardia | 1.522 (1.017–2.276) | 0.041 |
| Anemia | 1.399 (1.019–1.921) | 0.038 |

*CI, confidence interval.*

**Table 3 Results of Multivariate Cox Regression Analysis: Factors Associated With Composite Endpoint of Admission for Congestive Heart Failure and All-Cause Mortality in 668 Male Patients**

| Covariate | Hazard ratio (95%CI) | p value |
|---|---|---|
| Age ≥75 years | 2.264 (1.761–2.911) | <0.001 |
| Anemia | 1.855 (1.454–2.366) | <0.001 |
| Ventricular tachycardia | 1.536 (1.173–2.011) | 0.002 |
| LVEF <50% | 1.391 (1.077–1.798) | 0.012 |
| Diabetes | 1.357 (1.003–1.837) | 0.048 |

*Abbreviations see in Tables 1,2.*

**Table 4 Results of Multivariate Logistic Regression Analysis: Factors Associated With Disuse of CHF Medication**

| Medication | Covariate | Overall | | Female | | Male | |
|---|---|---|---|---|---|---|---|
| | | OR (95%CI) | p value | OR (95%CI) | p value | OR (95%CI) | p value |
| ACEI/ARB | Serum creatinine (mg/dl) | 1.336 (1.046–1.707) | 0.02 | 2.009 (1.071–3.769) | 0.03 | | |
| | Age (years) | 1.030 (1.013–1.047) | <0.001 | | | 1.036 (1.014–1.058) | 0.001 |
| | Hypertension | 0.496 (0.326–0.754) | 0.01 | 0.289 (0.135–0.618) | 0.001 | | |
| | LVEF (%) | | | 1.026 (1.005–1.048) | 0.02 | | |
| β-blocker | Age (years) | 1.041 (1.025–1.057) | <0.001 | 1.081 (1.046–1.116) | <0.001 | 1.030 (1.012–1.049) | 0.001 |
| | Ischemic etiology | | | 0.312 (0.121–0.805) | 0.02 | | |

*OR, odds ratio. Other abbreviations see in Tables 1,2.*

patient group, there was a significant association between the disuse of ACEI/ARB and renal insufficiency, elderly patients, and absence of hypertension (Table 4). Similarly, the disuse of β-blockers was significantly associated with elderly patients. Importantly, these analyses in the overall study population did not show a significant relationship between sex and disuse of standard CHF treatment. When only female patients were included in the analysis, renal insufficiency, absence of hypertension, and higher LVEF were associated with disuse of ACEI/ARB, and elderly patients and non-ischemic etiology were associated with disuse of β-blockers. When only male patients were included, the significant association between disuse of standard CHF medications and elderly patients was also observed, but such an association was lost in female patients regarding the use of ACEI/ARB (Table 4).

## Discussion

We clarified the characteristics of female CHF patients in our CHART cohort study. The major findings of the present study are as follows: (a) elderly patients, CHF with preserved systolic function, and non-ischemic etiology of CHF were frequently observed among the female patients, (b) the penetration rate of standard CHF treatment, such as ACEI/ARB and β-blockers, was relatively low in female patients, (c) although the sex difference was not a significant prognostic factor as presented in our previous study[4,5] the crude incidence rates of cardiovascular events were apparently higher in female patients after study entry, and (d) most of the characteristics exclusively observed in female patients may originate in the dominance of female patients in the elderly. These findings suggest an emerging problem of female CHF patients because the population in most developed countries is rapidly aging, with a resultant increase in the number of CHF patients.

### *Sex Difference and the Prognosis of CHF Patients*

Cardiovascular disease is the second leading cause of death in Japan. Many retrospective studies suggest that there are some clinically relevant differences between female and male patients in terms of prevalence, appearance, management and prognosis of the disease. For instance, women with atrial fibrillation have a greater risk of stroke than men with atrial fibrillation and women with diabetes have a significantly higher mortality from cardiovascular disease than men with diabetes[7,8] However, little is known of the reasons why cardiovascular disease affects female and male individuals differently.

The impact of sex differences on the prognosis of CHF patients is still controversial. Several observational studies and subanalyses of randomized controlled trials have reported that female patients have a better prognosis than male patients[9–16] The most recent report using the population of the CHARM Program showed that fewer women (30.4%) than men (33.3%) experienced cardiovascular death or heart failure hospitalization during the study period and that this prognostic advantage in females was maintained after adjustment for other background variables including age[17] In contrast to those findings, there are several reports that describe a comparable prognosis between male and female CHF patients[18–20] Furthermore, the SOLVD study revealed that male patients have a significantly better prognosis than female patients[21] Although our previous study failed to show that the sex-difference was a significant predictor of all-cause mortality[4,5] in the present study the unadjusted survival analyses constructed by Kaplan-Meier method showed that the crude event rates of the combined outcomes in female patients were apparently higher compared with male patients in a real clinical setting (Fig 2). The reason for these inconsistent results remains unknown; however, different background factors of the study populations may have influenced the results, because the sex is not a factor that can be randomized and the adjustment by multivariate analysis may not be perfect to eliminate the influence of confounding factors such as the etiology of heart failure and the age of patients. We speculate that the high proportion of elderly population in female patients in the present study is the main reason for the apparently poor prognosis in female CHF patients.

*Prognostic Risks in CHF Patients*

There have been many investigations of the prognostic predictors in patients with CHF, including our previous reports.[4,5] The present study results suggest that reduced LVEF may not be associated with the prognosis of female CHF patients. The real mechanism of such sex-specific difference is unknown; however, the higher incidence of patients with preserved LVEF among females may be a reason. Bhatia et al have reported that CHF patients with preserved EF are more likely to be older and female, and the adjusted 1-year mortality was similar between patients with LVEF <50% and those with LVEF ≥50%.[22] Owan et al also reported that survival did not improve over time for CHF patients with preserved EF, despite recent progress in CHF treatment.[23]

*Characteristics of Female CHF Patients*

Previous studies have demonstrated that female CHF patients are characterized by the following: (1) many of them are elderly, (2) LV systolic function is preserved in many patients, and (3) non-ischemic etiology of CHF is frequent![1–21] The present findings are consistent with those results. We also found that cachexia was frequent among the female patients, and the usage rates of standard CHF medications were lower. Most of the profiles observed in the female CHF patients were considered to be characteristics commonly found in elderly CHF patients.

*CHF Treatment in Female Patients*

Female CHF patients in the present study showed the lower usage rates of standard CHF treatments such as ACEI/ARB or β-blocker (Table 1). Previous reports showed that the association between sex and reduced prescription rates of evidence-based cardiovascular medications was inconsistent, as with heart failure; however, there was a strong decline in ACEI and β-blocker prescription with increasing age in most studies.[24–27] Masoudi et al reported that underuse of ACEI was commonly observed in elderly patients with CHF and they also revealed that patient, physician, and hospital factors were not strongly associated with underuse of ACEI/ARB, except for serum creatinine level.[28]

Several investigators have reported possible reasons for the underuse of standard treatment in CHF patients. Komajda et al showed that the low prescription rates of ACEI and β-blockers could be explained by the several factors: (1) underestimation of the poor prognosis of CHF patients, (2) underestimation of the benefit of such CHF treatment, (3) concerns about the potential adverse reactions, (4) elderly population, who are commonly CHF patients, tend to have many comorbidities such as asthma, pulmonary disease, diabetes, and stroke, (5) the etiology of the CHF might influence the prescription rate, (6) the medical specialty, such as cardiology or general practice, may influence the prescription rate, and (7) the high proportion of CHF patients with preserved LVEF, often because of hypertension, may be treated by calcium-channel blockers rather than the recommended CHF drugs.[29] The underuse of such CHF treatment was significantly associated with age in our analysis using the overall population (Table 4). The analysis using only female patients revealed that disuse of ACEI/ARB was significantly associated with renal dysfunction and preserved LVEF, but was not associated with elderly patients. The reason of this inconsistency remains unknown, but we speculated the following: (1) physicians were reluctant to prescribe ACEI/ARB in female CHF patients with renal dysfunction or preserved LVEF regardless of whether they were elderly or not, (2) because both renal dysfunction and preserved LVEF were frequently observed in elderly patients, these factors might have acted as confounding variables in our multivariate model.

*Aging Society and Female CHF Patients*

For the past 3 decades, Japanese people have been enjoying the longest life expectancy, 79.0 years in males and 85.8 years in females.[30] The most important contributory factor in the longevity of Japanese people is the reduced death rate in the elderly population,[31] which suggests an explosive increase in the number of elderly CHF patients in the near future in Japan. The most evident characteristic of the female CHF patients in the present study was older age, which might cause many of the other characteristics of female CHF patients. Female and elderly would be the common profile of future CHF patients, in whom we still need scientific evidence for the effective treatment of CHF and the prevention of congestive heart failure.

*Study Limitations*

In the multivariate Cox regression model used in the present study, 38 female patients and 81 male patients were excluded because of missing baseline data, which might have influenced the correct analysis of the difference between female and male CHF patients. The percentage of female patients who had coronary angiography before the entry might be different from that of male patients. Because our CHF cohort has no baseline data regarding coronary angiography, our diagnosis of ischemic heart disease may be not perfect in a small number of patients. This possible misdiagnosis of ischemic heart disease might influence the findings. Our CHF cohort did not include data regarding exercise tolerance in patients with CHF, which is considered to be an important prognostic predictor in these patients. Furthermore, the results cannot be extrapolated to the general population or patients with noncardiovascular diseases because the study population was a subpopulation of a cohort of CHF patients.

## Conclusion

Most developed countries are currently rapidly aging with a resultant explosive increase in the number of CHF patients, many of whom are elderly and female, which is a group that has not been enrolled in randomized controlled trials. We urgently need scientific evidence in order to improve the prognosis and quality of life for these patients.

## References


1. 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. *J Am Coll Cardiol* 2001; **38:** 2101–2113.
2. Status of Population Aging. The Status of Aging and Implementation of Measures for Aging Society in FY 2005. Annual Report on the Aging Society: 2006. Available at: http://www8.cao.go.jp/kourei/english/annualreport/2006/06wp-e.html (accessed 11 February 2008).
3. Heiat A, Gross CP, Krumholz HM. Representation of the elderly, women, and minorities in heart failure clinical trials. *Arch Intern Med* 2002; **162:** 1682–1688.
4. Shiba N, Watanabe J, Shinozaki T, Koseki Y, Sakuma M, Kagaya Y, et al. Analysis of chronic heart failure registry in the Tohoku district: Third year follow-up. *Circ J* 2004; **68:** 427–434.
5. Shiba N, Watanabe J, Shinozaki T, Koseki Y, Sakuma M, Kagaya Y, et al. Poor prognosis of Japanese patients with chronic heart failure following myocardial infarction: Comparison with nonischemic car-

diomyopathy. *Circ J* 2005; **69:** 143–149.
6. 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.
7. Wolf PA, Mitchell JB, Baker CS, Kannel WB, D'Agostino RB. Impact of atrial fibrillation on mortality, stroke, and medical costs. *Arch Intern Med* 1998; **158:** 229–234.
8. Huxley R, Barzi F, Woodward M. Excess risk of fatal coronary heart disease associated with diabetes in men and women: Meta-analysis of 37 prospective cohort studies. *BMJ* 2006; **332:** 73–78.
9. Schocken DD, Arrieta MI, Leaverton PE, Ross EA. Prevalence and mortality rate of congestive heart failure in the United States. *J Am Coll Cardiol* 1992; **20:** 301–306.
10. Ho KK, Anderson KM, Kannel WB, Grossman W, Levy D. Survival after the onset of congestive heart failure in Framingham Heart Study subjects. *Circulation* 1993; **88:** 107–115.
11. Adams KF Jr, Dunlap SH, Sueta CA, Clarke SW, Patterson JH, Blauwet MB, et al. Relation between gender, etiology and survival in patients with symptomatic heart failure. *J Am Coll Cardiol* 1996; **28:** 1781–1788.
12. Adams KF Jr, Sueta CA, Gheorghiade M, O'Connor CM, Schwartz TA, Koch GG, et al. Gender difference in survival in advanced heart failure: Insights from the FIRST study. *Circulation* 1999; **99:** 1816–1821.
13. Simon T, Mary-Krause M, Funck-Brentano C, Jaillon P. Sex differences in the prognosis of congestive heart failure: Results from the Cardiac Insufficiency Bisoprolol Study (CIBIS II). *Circulation* 2001; **103:** 375–380.
14. Ghali JK, Pina IL, Gottlieb SS, Deedwania PC, Wikstrand JC; MERIT-HF Study Group. Metoprolol CR/XL in female patients with heart failure: Analysis of the experience in Metoprolol Extended-Release Randomized Intervention Trial in Heart Failure (MERIT-HF). *Circulation* 2002; **105:** 1585–1591.
15. Ghali JK, Krause-Steinrauf HJ, Adams KF, Khan SS, Rosenburg YD, Yancy CW, et al. Gender differences in advanced heart failure: Insights from the BEST study. *J Am Coll Cardiol* 2003; **42:** 2128–2134.
16. Majahalme SK, Baruch L, Aknay N, Goedel-Meinen L, Hofmann M, Hester A, et al. Comparison of treatment benefit and outcome in women versus men with chronic heart failure (from the Valsartan Heart Failure Trial). *Am J Cardiol* 2005; **95:** 529–532.
17. O'Meara E, Clayton T, McEntegart MB, McMurray JJV, Pina IL, Granger CB, et al. Sex difference in clinical characteristics and prognosis in a broad spectrum of patients with heart failure: Results of the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) Program. *Circulation* 2007; **115:** 3111–3120.
18. Cowie MR, Wood DA, Coats AJ, Thompson SG, Suresh V, Poole-Wilson PA, et al. Survival of patients with a new diagnosis of heart failure: A population based study. *Heart* 2000; **83:** 505–510.
19. Opasich C, Tavazzi L, Lucci D, Gorini M, Albanese MC, Cacciatore G, et al. Comparison of one-year outcome in women versus men with chronic congestive heart failure. *Am J Cardiol* 2000; **86:** 353–357.
20. Galvao M, Kalman J, DeMarco T, Fonarow GC, Galvin C, Ghali JK, et al. Gender differences in in-hospital management and outcomes in patients with decompensated heart failure: Analysis from the Acute Decompensated Heart Failure National Registry (ADHERE). *J Card Fail* 2006; **12:** 100–107.
21. Bourassa MG, Gurne O, Bangdiwala SI, Ghali JK, Young JB, Rousseau M, et al. Natural history and patterns of current practice in heart failure: The Studies of Left Ventricular Dysfunction (SOLVD) Investigators. *J Am Coll Cardiol* 1993; **22:** 14A–19A.
22. Bhatia RS, Tu JV, Lee DS, Austin PC, Fang J, Haouzi A, et al. Outcome of heart failure with preserved ejection fraction in a population-based study. *N Engl J Med* 2006; **355:** 260–269.
23. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. *N Engl J Med* 2006; **355:** 251–259.
24. Hood S, Taylor S, Roeves A, Crook AM, Tlusty P, Cohen J, et al. Are there age and sex differences in the investigation and treatment of heart failure? A population-based study. *Br J Gen Pract* 2000; **50:** 559–563.
25. Muntwyler J, Cohen-Solal A, Freemantle N, Eastaugh J, Cleland JG, Follath F. Relation of sex, age and concomitant diseases to drug prescription for heart failure in primary card in Europe. *Eur J Heart Fail* 2004; **6:** 663–668.
26. Shah MR, Granger CB, Bart BA, McMurray JCV, Petrie MC, Michelson EL, et al. Sex-related differences in the use and adverse effects of angiotensin-converting enzyme inhibitors in heart failure: The study of Patients Intolerant of Converting Enzyme Inhibitors Registry. *Am J Med* 2000; **109:** 489–492.
27. Mejhert M, Holmgren J, Wandell P, Persson H, Edner M. Diagnostic tests, treatment and follow-up in heart failure patients: Is there a gender bias in the coherence to guidelines? *Eur J Heart Fail* 1999; **1:** 407–410.
28. Masoudi FA, Rathore SS, Wang Y, Havranek EP, Curtis JP, Foody JM, et al. National patterns of use and effectiveness of angiotensin-converting enzyme inhibitors in older patients with heart failure and left ventricular systolic dysfunction. *Circulation* 2004; **110:** 724–731.
29. Komajda M, Follath F, Swedberg K, Cleland J, Aguilar JC, Cohen-Solal A, et al. The EuroHeart Failure Survey programme: A survey on the quality of care among patients with heart failure in Europe. Part 2: Treatment. *Eur Heart J* 2002; **24:** 464–474.
30. Health and Welfare Statistics Association. Overview 1. Life expectancies at specified ages. *In*: Abridged Life Tables For Japan 2006. Statistics and Information Department, Minister's Secretariat. Ministry of Health, Labour and Welfare (In Japanese. English translation is available at http://www.mhlw.go.jp/english/database/db-hw/lifetb06/1.html).
31. Annual Reports on Health and Welfare 1998–1999 Social Security and National Life. Chapter 3. The Level of Standard that Japan's Social Security System Has Achieved. Section 1. High Standard of Health and Medical Services. Available at: http://www.mhlw.go.jp/english/wp/wp-hw/vol1/p1c3s1.html (accessed 12 November 2007).