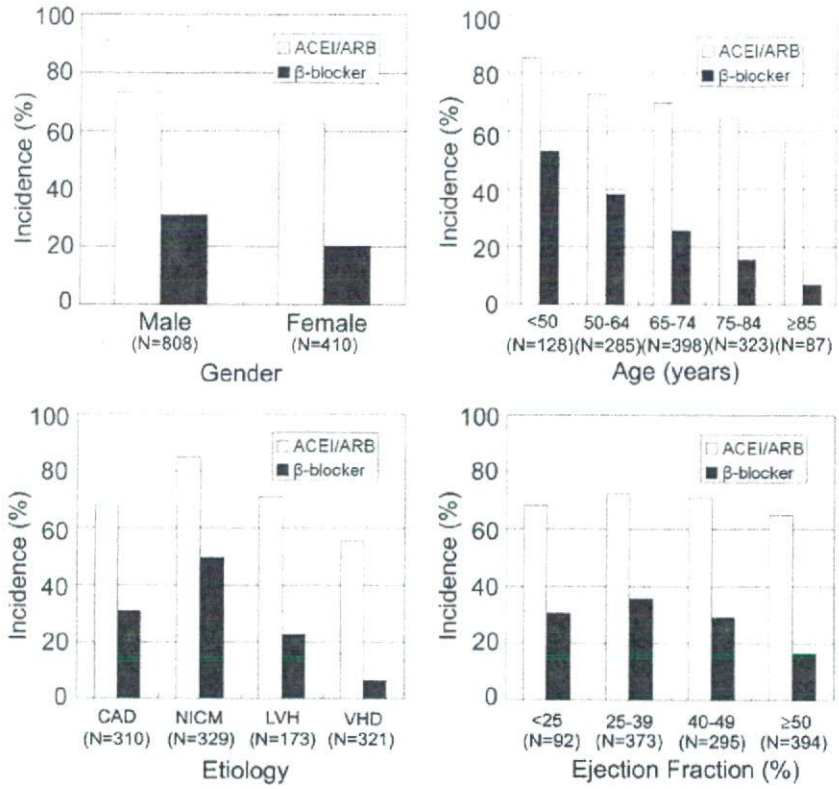


Figure 4 Prevalence of the use of renin-angiotensin inhibitors and β-blockers in the CHART-1 study. Copyright © 2007. Reproduced with permission from Shiba N, Takahashi J, Matsuki M. 2007. The CHART Study (Japanese). *Naika*, 99:410–14.

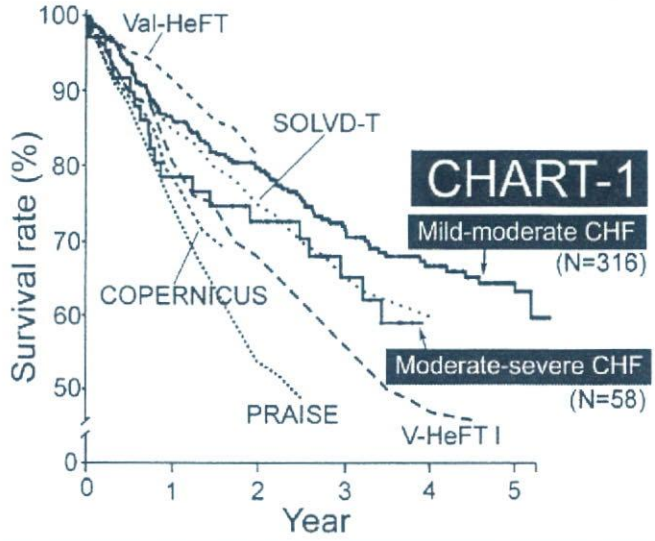
Abbreviations: ACEI, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker; CAD, coronary artery disease; NICM, non-ischemic cardiomyopathy; LVH, left ventricular hypertrophy; VHD, valvular heart disease.

II–IV and LVEF ≤40%) or moderate-severe CHF (NYHA III–IV and LVEF ≤35%) was 13% and 21%, respectively. Importantly, as is evident in Figure 5, the prognosis of Japanese patients with CHF was equally poor compared with Western CHF patients. Since the Japanese society is aging rapidly, a sharp increase in the number of CHF patients will be inevitable in the near future in Japan, as CHF is a disease of the elderly. Figure 6 shows the event rate in CHF patients based on age at the entry, demonstrating that elderly Japanese patients with CHF had an increased incidence of cardiac death and a combination of cardiac death and admission due to congestive CHF. This is because elderly CHF patients have a higher rate of combined risk factors, such as anemia, chronic kidney disease, hypertension, and atrial fibrillation. Appropriate prevention strategies against the development and progression of CHF should be undertaken in Japan.

Major CHF treatment trials in Japan

There are 2 published randomized treatment trials for CHF patients in Japan (Table 3). The Multicenter Carvedilol Heart Failure Dose Assessment (MUCHA) trial enrolled 174 patients with mild to moderate CHF to seek for the efficacy and optimum dose of carvedilol, with 3 treatment arms, including placebo, 5 and 20 mg of the β-blocker in daily dose (Hori et al 2004). During the 24–48 weeks of the treatment period, carvedilol achieved dose-related improvement of the rate of death or cardiovascular hospitalization to 25%, 9%, and 5% in the placebo, 5 mg, and 20 mg group, respectively ($p = 0.002$). The Assessment of Response to Candesartan in Heart Failure in Japan (ARCH-J) study investigated the efficacy of candesartan (8 mg once daily) in comparison with the placebo in 305 patients with symptomatic CHF (Matsumori et al 2003). During the 6-month follow-up period, fatal cardiovascular events occurred in 2 patients in each treatment group and the incidence of progression of CHF was 7% and 22% in the candesartan and the placebo group, respectively ($p = 0.0004$).

We have recently initiated a large outcome study with olmesartan in CHF patients, termed The Supplemental Benefit of Angiotensin II Receptor Blocker in Hypertensive



	Mild-moderate CHF	Moderate-severe CHF
N	316	58
NYHA	II-IV	III-IV
Ejection Fraction (Mean)	≤40% (31.1±6.6%)	≤35% (25.8±5.8%)
Age	66.3±13.3 years	67.2±12.9 years
Male	69.4%	64.4%
Coronary Artery Disease	35.3%	32.2%

Figure 5 Comparison of the prognosis of patients with CHF between Western clinical trials and the CHART-1 study. Copyright © 2007. Reproduced with permission from Shiba N, Takahashi J, Matsuki M. 2007. The CHART Study (Japanese). *Naika*, 99:410–14.
Abbreviations: HYHA, New York Heart Association.

Patients with Stable Heart Failure Using Olmesartan (SUPPORT trial), which is currently the largest outcome study in Japan (Table 3). The purpose of our SUPPORT trial is to examine whether an ARB, olmesartan, in addition to conventional treatment, reduces the mortality and morbidity of hypertensive patients with stable CHF. The primary endpoint is a combined event of all-cause death, nonfatal acute myocardial infarction, nonfatal stroke, and hospital admission due to congestive heart failure. We also aim to evaluate the beneficial effect of olmesartan on the

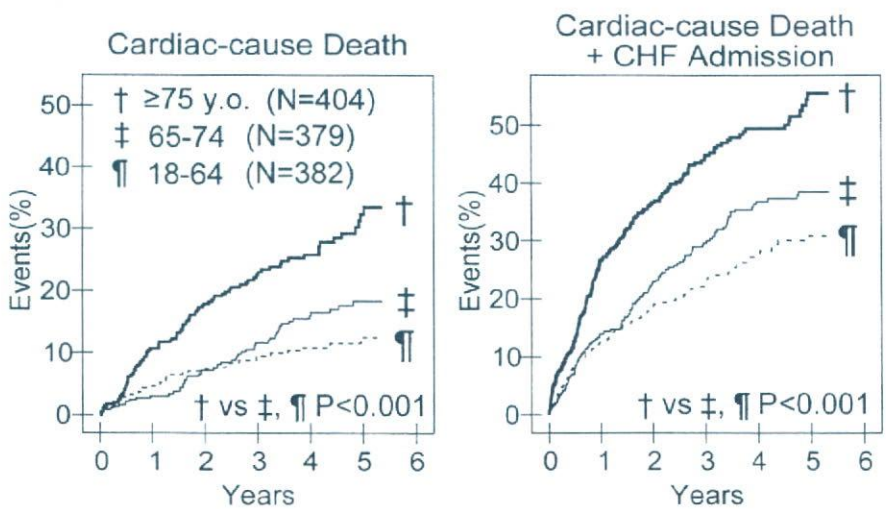


Figure 6 Prognosis of elderly patients with CHF in the CHART-1 study. Copyright © 2007. Reproduced with permission from Shiba N, Takahashi J, Matsuki M. 2007. The CHART Study (Japanese). *Naika*, 99:410–14.
Abbreviations: CHF, congestive heart failure.

progression of metabolic syndrome. The entry of patients was started in November 2007, and the results of the study will be obtained by the end of 2011.

There are 5 other small outcome trials that are currently in progress in Japan (Table 3). The Assessment of Beta-Blocker Treatment in Japanese Patients with Chronic Heart Failure (J-CHF) and the Japanese Diastolic Heart Failure Study (J-DHF) are investigating the effects of carvedilol in patients with systolic CHF and those with diastolic CHF, respectively. Another objective of J-CHF is to determine the optimum dose of carvedilol and to elucidate the differences in clinical characteristics between responders and nonresponders to the β-blocker. The Pitavastatin Heart Failure Study (PEARL study) is designed to evaluate the efficacy of pitavastatin for CHF with mild hypercholesterolemia. The Japanese Multicenter Evaluation of Long- versus short-acting Diuretics in Congestive Heart Failure (J-MELODIC) is designed to compare the effects of furosemide and azosemide in patients with CHF and to test the hypothesis that long-acting diuretics are superior to short-acting ones in those patients. The Japanese Heart Failure Outpatients Disease Management and Cardiac Evaluation Study (J-HOMECARE) was designed to evaluate the benefit of disease management program for prognosis, psychological status and quality of life of patients with CHF.

There are 2 large trials that have investigated the role of valsartan in Japanese patients with cardiovascular disease including CHF (Table 4). The Japanese Investigation of Kinetic Evaluation in Hypertensive Event and Remodeling Treatment (JIKEI-HEART) Study was designed to investigate whether concomitant treatment with valsartan in addition to conventional treatment improves the prognosis of Japanese patients with hypertension, ischemic heart disease, or congestive heart failure. The results of this study have recently been published (Mochizuki et al 2007). After a median follow-up period of 3.1 years, the incidences of stroke, transient ischemic attack, angina pectoris, and CHF were significantly lower in patients treated with valsartan compared with those with the conventional treatment. However, the benefit of the add-on valsartan treatment in a sub-population with CHF, which accounted for 11% of the total population, has not been published yet. The Add-on Effects of Valsartan on Morbi-Mortality (KYOTO-HEART) study was designed to assess the add-on effect of valsartan on the conventional treatment in terms of the morbidity and mortality in Japanese hypertensive patients with high risks of cardiovascular diseases including CHF (Table 4).

Many of the randomized clinical trials performed in Japan utilize the prospective randomized open blinded endpoint (PROBE) design, as an alternative to the randomized double-blind placebo-controlled design (Tables 3 and 4). This is mainly because the PROBE study tends to be more cost effective and its open-labeled medication may minimize ethical considerations (Hansson et al 1992).

Racial difference in morbidity and mortality due to cardiovascular diseases

Several researchers have suggested that cardiovascular risk factors have different prognostic impact among different populations. The Seven Countries Study Research Group showed a substantial heterogeneity among populations in terms of the death rate due to coronary artery disease, even at a similar level of blood pressure (Van den Hoogen et al 2000). The proportion of deaths attributable to cardiovascular disease has also been reported to vary among different cohorts even at the similar serum cholesterol level. The long-term follow-up for 25 years for 12,763 men in 16 cohorts in Europe, the United States, and Japan showed that the risk factors of cardiovascular disease, such as insufficient physical activity and high serum cholesterol level, were not significantly associated with all-cause death in several countries including Japan (Menotti et al 2001). Since these differences cannot be explained by other baseline characteristics, smoking habits, or genetic difference, environmental and/or behavioral factors may play an important role in the development of cardiovascular diseases. The Ni-Hon-San Study, which compared cardiovascular disease rates and risk factors in Japanese men living in Japan, Hawaii, and California, showed that the mortality rate due to coronary artery disease was lowest in Japanese men living in Japan, whereas it was highest in those living in California (Benfante 1992). Racial differences may also influence the effect of medical treatment for CHF. Several studies demonstrated that genetic polymorphisms and/or a difference in β1-receptor sensitivity, which are frequently observed in the Japanese population, might change the pharmacokinetics or the clinical effect of medical drugs, such as ACEI and β-blockers (Kubota et al 2000; Xie et al 2001; Ranade et al 2002).

Future direction for the management of CHF in Japan

CHF is a slowly progressive disease from stage A to stage D unless appropriately treated as described in the ACC/AHA guidelines (Hunt et al 2001). The strategy to manage CHF has been changing recently from treatment to prevention

Table 3 Multicenter randomized clinlical trials for patients with chronic heart failure in Japan

Trial [Reference]	Design	Age, years (Mean)	Comparison	Total enrollment	HF stage NYHA	Study start Expected completion	Mean follow-up	Primary outcome *Published main outcome	Status
MUCHA Trial [Hori 2004]	RDBPC	20–79 (60)	Carvedilol 5 mg Carvedilol 20 mg Placebo	174	C-D II-III		24–48 weeks	Dose-related improvement of HF with carvedilol*	Published
ARCH-J [Matsumori 2003]	RDBPC	≥20 (64)	Candesartan Placebo	305	C-D II-III		6 months	Slowing progression of HF with candesartan*	Published
J-CHF	PROBE	20–79	Carvedilol; 2.5 mg, 5 mg, or 20 mg	480 (exp.)	C-D II-III	Jul 2003 Dec 2009		Cardiovascular mortality Hospitalization for HF	Recruiting
J-DHF	PROBE	≥20	Carvedilol Control	800 (exp.)	C-D	May 2004 Mar 2011		Cardiovascular mortality Hospitalization for HF	Recruiting
SUPPORT Trial	PROBE	20–79	Olmesartan Standard therapy	1000 (exp.)	C-D II-IV	Nov 2006 Sep 2011		Combination of mortality/AMI/Stroke/admission due to HF	Recruiting
PEARL Study	RO	20–79	Pitavastatin Control	500 (exp.)	C-D II-III	Jul 2006 Jul 2010		Cardiac mortality Hospitalization for HF	Recruiting
J-MELODIC	PROBE	≥20	Furosemide Azosemide	300 (exp.)	C-D II-III	Jun 2006 Mar 2010		Cardiovascular mortality Hospitalization for HF	Recruiting
J-HOMECARE	RO	N/A	Education/counseling Control	300 (exp.)	C-D	Dec 2006 Dec 2008		Mortality Readmission for HF	Recruiting

Data are retrieved from published papers or the UMIN Clinical Trials Registry (http://www.umin.ac.jp/ctr/index-j.htm)/ClinicalTrials.gov (http://clinicaltrials.gov/).
Abbreviations: RDBPC, randomized double-blind placebo-controlled design; NYHA, New York Heart Association; HF, heart failure; PROBE, prospective randomized open blinded end-point design; exp., expected; AMI, acute myocardial infarction, RO; randomized open-label design.

Table 4 Multicenter randomized clinlical trials for patients with cardiovascular risks including CHF in Japan

Trial [Reference]	Design	Study population	Age, years (Mean)	Comparison	Total enrollment	Study start Expected completion	Duration	Primary outcome *Published main outcome	Status
JIKEI-Heart Study [Mochizuki 2007]	PROBE	Hypertension coronary disease heart failure	20–79 (65)	Valsartan Standard therapy	3081		3.1 years	Prevention of cardiovascular events with additional valsartan*	Published
KYOTO-HEART Study	PROBE	Hypertension with one or more risk factors including heart failure	20–79	Valsartan Standard therapy	3000 (exp.)	Jan 2004 Oct 2007		Combination of stroke/AMI/CHF etc.	Recruiting

Data are retrieved from published papers or the UMIN Clinical Trials Registry (http://www.umin.ac.jp/ctr/index-j.htm) / ClinicalTrials.gov (http://clinicaltrials.gov/).
Abbreviations: PROBE, prospective randomized open blinded end-point design; exp., expected; AMI, acute myocardial infarction; CHF, congestive heart failure.

(Bansal et al 2006). Japanese CHF patients have several different profiles compared with Western CHF patients as follows; (*a*) the prevalence of CHF of ischemic origin is lower, (*b*) the percentage of elderly population is remarkably high, and (*c*) the penetration rate of evidence-based medicine, such as ACEI/ARB or β-blockers, is not sufficiently high yet. The current situation of the management of CHF in Japan is probably caused by the fact that the number of randomized treatment trials for Japanese patients is not enough yet. Given the expected future increase in Japanese patients with CHF, effective prevention strategy is necessary. Our on-going CHART-2 and SUPPORT studies will enable us to obtain effective strategies to improve the management of CHF in Japan.

Conclusions

The prevalence of CHF will rapidly increase in the next decades in many industrialized countries, including Japan. Large cohort studies with CHF patients are useful for risk stratification and determination of preventive measures for the disorder. Large-scale, randomized treatment trials also are needed, especially in Japan, in order to obtain further evidence to improve the management of patients with CHF.

Acknowledgments

Active investigators of the CHART studies were described in the paper previously published (Shiba et al 2004) and at the website of the Tohoku Heart Failure Association (see http://tohoku.cardiovascular-medicine.jp). The CHART-1 study was supported by the research grants from the Ministry of Health, Labor and Welfare and Gonryo Medical Foundation. We are grateful for the assistance of research nurses who are working at the Tohoku Heart Failure Association; Mika Matsuki, Shizuka Osaki, Kiriko Yukishita, Yuuko Kidoguchi, Miho Hotta, Haruka Kohno, and Keiko Nishiura.

References

Bansal D, Chahoud G, Smith ES, et al. 2006. Prevention of heart failure. *Curr Opin Cardiol*, 21:510–16.

Benfante R. 1992. Studies of cardiovascular disease and cause-specific mortality trends in Japanese-American men living in Hawaii and risk factor comparisons with other Japanese populations in the Pacific region: a review. *Hum Biol*, 64:791–805.

Bettencourt P, Ferreira A, Dias P, et al. 2000. Predictors of prognosis in patients with stable mild to moderate heart failure. *J Card Fail*, 6:306–13.

Deedwania PC. 2003. The key to unraveling the mystery of mortality in heart failure: An integrated approach. *Circulation*, 107:1719–21.

Exercise and Physical Activity Reference for Health Promotion 2006. Office for Lifestyle-related Diseases Control, General Affairs Division, Health Service Bureau, Ministry of Health, Labour Welfare [online]. Accessed on June 10, 2007. URL: http://www.nih.go.jp/eiken/english/research/program_exercise_epar2006.html.

Ezekowitz JA, McAlister FA, Armstrong PW, et al. 2003. Anemia is common in heart failure and is associated with poor outcomes: insights from a cohort of 12 065 patients with new-onset heart failure. *Circulation*, 107:223–5.

Hansson L, Hedner T, Dahlof B. 1992. Prospective randomized open blinded end-point (PROBE) study. A novel design for intervention trials. *Blood Press*, 1:113–19.

Hori M, Sasayama S, Kitabatake A, et al. 2004. Low-dose carvedilol improves left ventricular function and reduces cardiovascular hospitalization in Japanese patients with chronic heart failure: the Multicenter Carvedilol Heart Failure Dose Assessment (MUCHA) trial. *Am Heart J*, 147:324–30.

Hunt SA, Baker DW, Chin MH, et al. 2001. ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: Executive summary. *J Am Coll Cardiol*, 38:2101–13.

Ito M. 2004. Health Insurance Systems in Japan: a Neurosurgeon's View. *Neurol Med Chir* (Tokyo), 44:617–28.

Kubota T, Yamamura Y, Ohkawa N, et al. 2000. Frequencies of CYP2D6 mutant alleles in a normal Japanese population and metabolic activity of dextromethorphan O-demethylation in different CYP2D6 genotypes. *Br J Clin Pharmacol*, 50:31–4.

Life Expectancies at Specified Ages. Abridged Life Tables For Japan 2006, Ministry of Health, Labour and Welfare [online]. Accessed on June 10, 2007. URL: http://www.mhlw.go.jp/english/database/db-hw/lifetb06/1.html.

Masoudi FA, Havranek EP, Wolfe P, et al. 2003. Most hospitalized older persons do not meet the enrollment criteria for clinical trials in heart failure. *Am Heart J*, 146:250–7.

Matsumori A, ARCH-J study investigators. 2003. Efficacy and safety of oral candesartan cilexetil in patients with congestive heart failure. *Eur J Heart Fail*, 5:669–77.

Menotti A, Blackburn H, Kromhout D, et al. 2001. Cardiovascular Risk Factors as Determinants of 25-year All-cause Mortality in the Seven Countries Study. *Eur J Epidemiol*, 17:337–46.

Mochizuki S, Dahlöf B, Shimizu M, et al. 2007. Valsartan in a Japanese population with hypertension and other cardiovascular disease (Jikei Heart Study): a randomised, open-label, blinded endpoint morbidity-mortality study. *Lancet*, 369:1431–9.

O'Meara E, Clayton T, McEntegart MB, et al. 2006. Clinical correlates and consequences of anemia in a broad spectrum of patients with heart failure: results of the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) Program. *Circulation*, 113:986–94.

Ranade K, Jorgenson E, Sheu WHH, et al. 2002. A polymorphism in the beta-1 adrenergic receptor is associated with resting heart rate. *Am J Hum Genet*, 70:935–42.

Rector TS, Cohn JN. 1994. Prognosis in congestive heart failure. *Annu Rev Med*, 45:341–50.

Shiba N, Watanabe J, Shinozaki T, et al. 2004. Analysis of chronic heart failure registry in the Tohoku district: third year follow-up. *Circ J*, 68:427–34.

Shiba N, Watanabe J, Shinozaki T, et al. 2005. Poor prognosis of Japanese patients with chronic heart failure following myocardial infarction – comparison with nonischemic cardiomyopathy. *Circ J*, 69:143–9.

Shiba N, Takahashi J, Matsuki M. 2007. The CHART Study (Japanese). *Naika*, 99:410–14.

Summary of Vital Statistics. 2005. Summary of Vital Statistics. Ministry of Health, Labour and Welfare [online]. Accessed on July 6, 2007. URL: http://www.mhlw.go.jp/english/database/db-hw/populate/index.html.

Tada T, Shiba N, Watanabe J, et al. 2007. Prognostic value of anemia in predicting sudden death of patients with diastolic heart failure. *Int J Cardiol*, In Press.

The Status of Aging and Implementation of Measures for Aging Society in FY 2005. Annual Report on the Aging Society 2007, Cabinet Office [online]. Accessed on June 10, 2007. URL: http://www.cao.go.jp/index-e.html.

Tsutsui H, Tsuchihashi-Makaya M, Kinugawa S, et al. 2006. Clinical characteristics and outcome of hospitalized patients with heart failure in Japan. –Rationale and design of Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD)-. *Circ J*, 70:1617–23.

Tsutsui H, Tsuchihashi-Makaya M, Kinugawa S, et al. 2007. Characteristics and outcomes of patients with heart failure in general practices and hospitals. –Japanese Cardiac Registry of Heart Failure in General Practice (JCARE-GENERAL). *Circ J*, 71:449–54.

Van den Hoogen P, Feskens EJM, Nagelkerke NJD, et al. 2000. The Relation between Blood Pressure and Mortality due to Coronary Heart Disease among Men in Different Parts of The World. *N Engl J Med*, 342:1–8.

Watanabe J, Shiba N, Shinozaki T, et al. 2005. Prognostic value of plasma brain natriuretic peptide combined with left ventricular dimensions in predicting sudden death of patients with chronic heart failure. *J Card Fail*, 11:50–5.

Watanabe J, Shinozaki T, Shiba N, et al. 2006. Accumulation of risk markers predicts the incidence of sudden death in patients with chronic heart failure. *Eur J Heart Fail*, 8:237–42.

Xie HG, Kim RB, Wood AJJ, et al. 2001. Molecular basis of ethnic differences in drug disposition and response. *Annu Rev Pharmacol Toxicol*, 41:815–50.

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Emerging Problems of Heart Failure Practice in Japanese Women

—— Lessons From the CHART Study ——

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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-

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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 ($ml \cdot min^{-1} \cdot 1.73\,m^{-2}$)	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

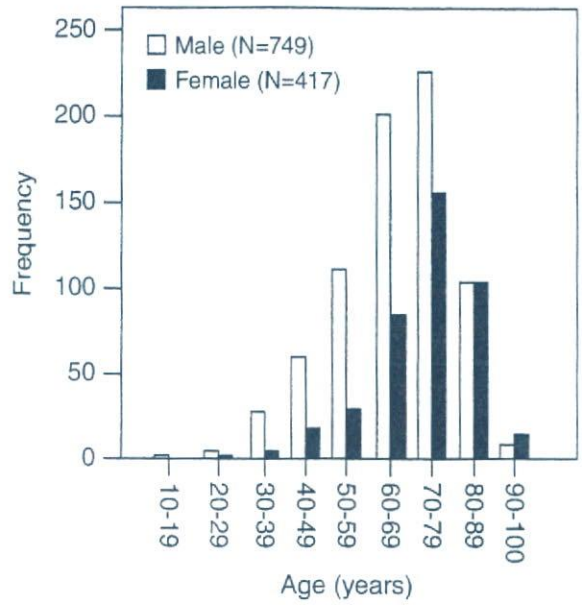

Fig 1. Number of patients with chronic heart failure by age and sex.

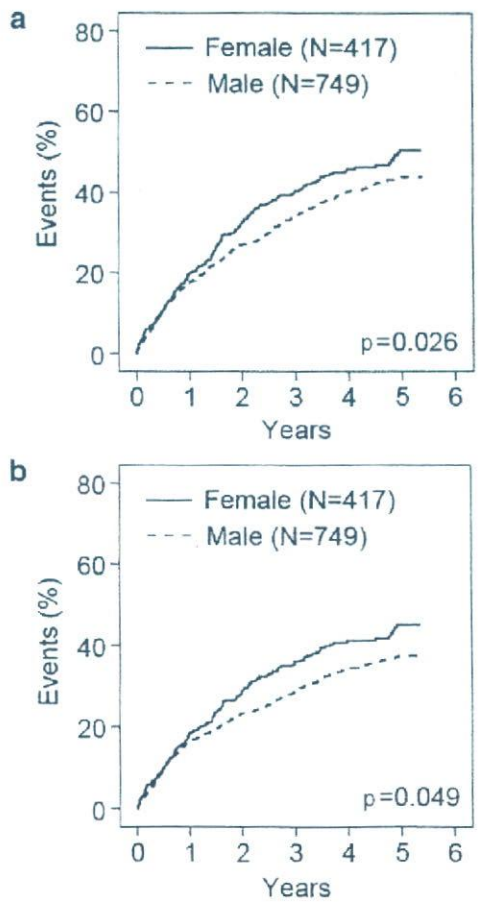

Fig 2. Unadjusted survival analyses of patients with chronic heart failure by sex. Endpoint: (a) composite event of all-cause mortality plus admission because of congestive heart failure, and (b) composite event of cardiac-cause mortality plus admission because of congestive heart failure.

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[11–21] 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).

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Prognostic Importance of Chronic Kidney Disease in Japanese Patients With Chronic Heart Failure

—— Implications of the CHART Study ——

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Background Renal insufficiency is common in patients with chronic heart failure (CHF), so to improve the prognosis of patients with cardiovascular risks clinical guidelines recommend estimating the glomerular filtration rate (GFR), which detects chronic kidney disease more accurately than does the serum creatinine level alone. However, the clinical usefulness of the estimated GFR (eGFR) in Japanese CHF patients is still unclear.

Methods and Results Of 1,278 patients registered in a Japanese CHF registry, termed the Chronic Heart Failure Analysis and Registry in the Tohoku District study, the study population included 920 symptomatic patients with sufficient data. Baseline eGFR ($ml \cdot min^{-1} \cdot 1.73\,m^{-2}$) was calculated using the Cockcroft-Gault equation. Patients were divided into three groups based on eGFR: ≥60, 30–59, and <30 $ml \cdot min^{-1} \cdot 1.73\,m^{-2}$. Kaplan-Meier analysis revealed that the incidence of the combined event of all-cause death and admission because of CHF was significantly higher in patients with reduced eGFR and such patients were older and more frequently had an ischemic etiology of CHF, a higher prevalence of diabetes, lower hemoglobin level, and higher B-type natriuretic peptide level. Multivariate Cox regression analysis showed that reduced eGFR was significantly associated with the combined endpoint.

Conclusions GFR should be evaluated in all Japanese patients with CHF to improve risk stratification and treatment. (*Circ J* 2008; **72:** 173–178)

Key Words: Estimated glomerular filtration rate; Heart failure; Prognosis; Renal insufficiency; Risk stratification

Chronic heart failure (CHF) is the most frequent cause of mortality in many developed countries and the prevalence of patients with CHF will explosively increase in Japan, because of the rapid aging of the Japanese population.[1] Investigation of the risk factors for mortality and risk stratification of CHF patients is the first-line strategy to improve the prognosis and quality of life (QOL) of these patients.[2,3] Many Western investigators have reported that renal insufficiency is common in CHF patients and severe chronic kidney disease (CKD) is associated with mortality.[4,5] The serum creatinine level has been the commonly used marker for evaluating renal function in the clinical setting; however, this examination may not be sufficient for accurate diagnosis of CKD. The guidelines from the United States National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) recommend estimating the glomerular filtration rate (GFR) in all patients with risk factors for cardiovascular diseases to identify CKD earlier in order to slow disease progression. The estimated GFR (eGFR), calculated from the serum creatinine level using a prediction equation, detects CKD more accurately than does the serum creatinine level alone[6] and it is also used in disease staging. The purpose of the present study was to elucidate the prognostic importance of CKD evaluated by eGFR in Japanese patients with CHF using a heart failure cohort from the Chronic Heart Failure Analysis and Registry in the Tohoku District (CHART) study.

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Methods

Study Population

The rationale and details of the CHART study have been described previously.[2] Eligible subjects were stable patients with at least one of the following clinical findings: (1) certain organic heart disease and a documented history of clinical CHF defined by the Framingham criteria;[7] (2) organic heart disease and an echocardiographic ejection fraction (EF) ≤50%; or (3) organic heart disease and an echocardiographic left ventricular end-diastolic dimension ≥55 mm. We started the entry of patients on February 2000 and follow-up surveillance was performed annually. Of 1,278 patients who were included in the CHART registry, the present study population comprised 920 patients with sufficient data who had at least New York Heart Association (NYHA) class II symptoms. Patients on chronic hemodialysis at study entry were excluded.

Renal Function

We calculated the baseline eGFR using the Cockcroft-Gault (CG) equation (ml/min)[8] and the abbreviated Modification of Diet in Renal Disease (MDRD) Study equation ($ml \cdot min^{-1} \cdot 1.73\,m^{-2}$)[9] (Table 1). We adjusted the eGFR for body surface area (BSA: m^2) by multiplying by 1.73/BSA

Table 1 Formulas for Estimating Glomerular Filtration Rate

Cockcroft-Gault equation[8]
C_{Cr} (ml/min) = ((140−age)×weight)/(72×S_{Cr})×(0.85, if female)
CG-eGFR (ml·min^{-1}·1.73 m^{-2}) = C_{Cr}×(1.73/BSA)
BSA (m^2) = (body weight)$^{0.425}$×(height)$^{0.725}$×0.007184
Abbreviated MDRD Study equation[9]
MDRD-eGFR (ml·min^{-1}·1.73 m^{-2}) = 186×(S_{Cr})$^{-1.154}$×(age)$^{-0.203}$×(0.742, if female)×(1.210, if black)

Age is in years and weight is in kilograms for each equation.
CG, Cockcroft-Gault equation; C_{Cr}, creatinine clearance; S_{Cr}, serum creatinine concentration (mg/dl); eGFR, estimated glomerular filtration rate; BSA, body surface area; MDRD, Modification of Diet in Renal Disease.

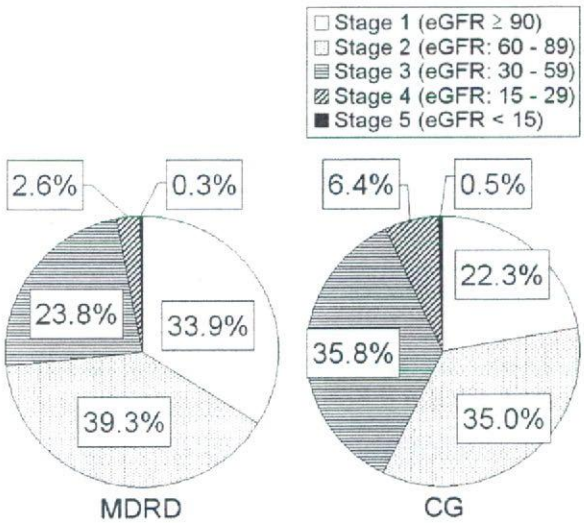

Fig 1. Distribution of the study population by stage of chronic kidney disease based on two equations for estimating of glomerular filtration rate. eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease Study equation; CG, Cockcroft-Gault equation.

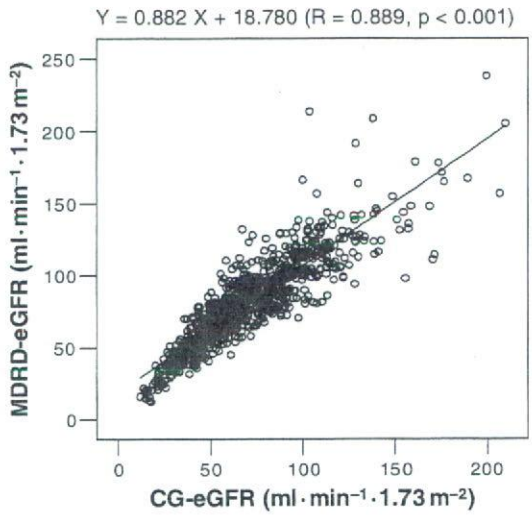

Fig 2. Correlation between estimated glomerular filtration rates using the MDRD or CG equation. GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease Study equation; CG, Cockcroft-Gault equation; eGFR, estimated glomerular filtration rate.

when using the CG equation. The eGFR was categorized into five stages as recommended by the KDOQI guidelines[6]

Statistical Analysis

The study population was divided into three groups based on the stage of CKD: (1) patients with normal or mildly reduced GFR (eGFR ≥60 ml·min^{-1}·1.73 m^{-2}), (2) those with moderately reduced GFR (eGFR: 30–59 ml·min^{-1}·1.73 m^{-2}), and (3) those with severely reduced GFR (eGFR <30 ml·min^{-1}·1.73 m^{-2}). The baseline characteristics of the patients in the three strata were compared by chi-square test for dichotomous variables and ANOVA tests for continuous variables. Data are expressed as means±standard deviations (SD). Least-squares linear regression analysis and a correlation coefficient were used to describe the relationship between the eGFRs calculated by the MDRD and CG equations. A Bland-Altman plot was also used to assess the agreement between both eGFRs.[10] Survival curves of patients with CKD were constructed using the Kaplan-Meier method and were compared with the log-rank test. Multivariate Cox proportional hazards analyses were also performed to determine the association of eGFR with a combination of all-cause mortality plus admission because of CHF, using the following covariates: age, gender, etiology of CHF, serum hemoglobin level, left ventricular EF, body mass index (BMI), NYHA functional class, medications for CHF, and comorbidities such as diabetes, dyslipidemia, or ventricular tachycardia. Prior to the multivariate analysis, the associations among all covariates were evaluated using the Spearman's rank correlation test. Statistical significance was defined as $p<0.05$. The Bland-Altman plot was constructed using MedCalc ver. 9.3.0 (available at: http://www.medcalc.be) and all other statistical analyses were performed using SPSS 15.0J for Windows (Chicago, IL, USA).

Results

The eGFR in Patients With CHF

The mean age of the study population was 68.3±13.6 years and males accounted for 65.1% of patients. The mean follow-up period was 3.45±1.75 years. The prevalence of patients with renal insufficiency, which was categorized based on the stages defined by the KDOQI guidelines using two equations, is shown in Fig 1. Patients with CKD, which was defined as eGFR <60 ml·min^{-1}·1.73 m^{-2}, accounted for 26.7% and 42.7% of the study population when using the MDRD equation and CG equation, respectively. Fig 2 shows the relationship between two eGFRs calculated using each equation. There was a significantly good correlation between them ($R=0.889$, $p<0.001$); however, the eGFR calculated using the MDRD equation tended to be greater than that calculated by the CG equation, especially in patients with reduced eGFR. The Bland-Altman plot

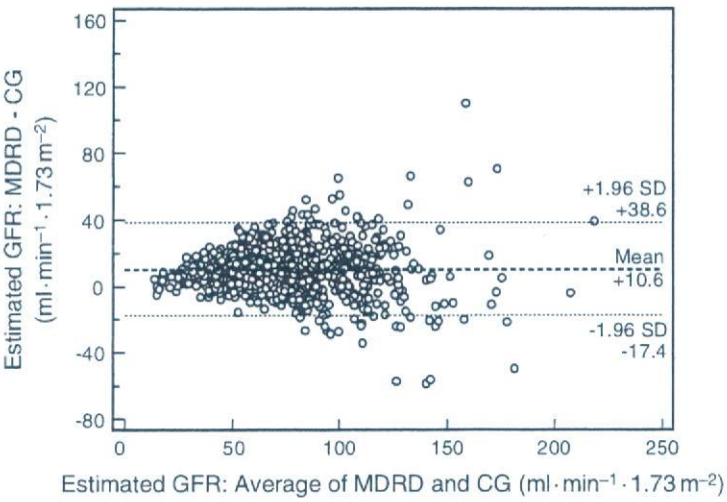

Fig 3. Bland-Altman plot of the two estimated glomerular filtration rates. MDRD, Modification of Diet in Renal Disease Study equation; CG, Cockcroft-Gault equation.

Table 2 Baseline Characteristics of the Study Population by Stage of Chronic Kidney Disease Evaluated by the CG-eGFR

	eGFR (ml·min⁻¹·1.73 m⁻²)			*p value*
	≥60	*30–59*	*<30*	
N	*527*	*329*	*64*	
Follow-up (years)	*3.7±1.7*	*3.2±1.8*	*2.7±1.7*	
Age (years)	*62.0±13.1*	*76.2±8.5*	*80.4±9.5*	*<0.001*
Male	*69.4%*	*60.5%*	*53.1%*	*0.03*
Body mass index	*23.9±3.7*	*22.1±3.5*	*21.2±2.8*	*<0.001*
NYHA III/IV	*14.60%*	*24.30%*	*39.10%*	*<0.001*
Kidney function				
eGFR (ml·min⁻¹·1.73 m⁻²)	*88.8±24.9*	*46.5±8.4*	*24.2±4.9*	
Serum creatinine (mg/dl)	*0.8±0.2*	*1.1±0.3*	*2.0±0.8*	*<0.001*
Ischemic etiology of CHF	*23.9%*	*36.5%*	*35.9%*	*<0.001*
Medical history				
HF admission	*30.0%*	*28.9%*	*26.6%*	*NS*
Hypertension	*45.5%*	*48.3%*	*64.1%*	*0.02*
Diabetes	*17.1%*	*21.9%*	*28.1%*	*<0.05*
Dyslipidemia	*18.2%*	*10.9%*	*17.2%*	*0.02*
Atrial fibrillation	*39.3%*	*47.1%*	*45.3%*	*0.07*
Ventricular tachycardia	*21.3%*	*21.6%*	*15.6%*	*NS*
Medications				
Diuretics	*77.0%*	*82.8%*	*87.3%*	*NS*
β-blocker	*34.3%*	*23.4%*	*20.3%*	*0.01*
ACEI/ARB	*74.4%*	*69.6%*	*54.7%*	*0.003*
Echocardiography				
LVDd (mm)	*57.2±9.6*	*54.1±10.1*	*53.2±8.4*	*<0.001*
LVEF (%)	*50.5±15.6*	*52.8±16.9*	*55.1±14.3*	*0.03*
Other factors				
BNP (pg/ml)	*196.1±297.4*	*329.6±347.5*	*432.4±394.8*	*<0.001*
Hemoglobin (g/dl)	*13.7±1.9*	*12.4±2.1*	*10.6±1.9*	*<0.001*
Anemia	*25.5%*	*52.6%*	*88.9%*	*<0.001*

NYHA, New York Heart Association; CHF, chronic heart failure; HF, heart failure; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; LV, left ventricular; Dd, end-diastolic dimension; EF, ejection fraction; BNP, B-type natriuretic peptide. Other abbreviations see in Table 1.

showed that the scatter of the differences between the two eGFRs increased as the eGFR increased and, importantly, the mean difference was 10.6 ml·min^{-1}·1.73 m^{-2} (Fig 3).

Baseline Characteristics and Survival Analysis

Baseline characteristics of the patients stratified by eGFR calculated by the CG equation are summarized in Table 2. Reduced kidney function was associated with a variety of cardiovascular risks. Patients with lower eGFR were older and had lower BMI, more severe symptoms of CHF, higher level of B-type natriuretic peptide, lower level of hemoglobin, and a higher prevalence of hypertension and diabetes. Those patients were less likely to be taking β-blockers, angiotensin-converting-enzyme inhibitors, or angiotensin II receptor blockers. The Kaplan-Meier analyses included the following two endpoints: (1) combined event of all-cause death and admission because of congestive heart failure and (2) admission because of congestive heart failure (Fig 4). The event-free rates of patients with more severe CKD were significantly lower than those of patients with less severe CKD when eGFR was evaluated using the CG equation (Fig 4). The 1- and 3-year rates of the combined event of all-cause death and admission because of congestive heart failure in patients with eGFR <30 ml·min^{-1}·

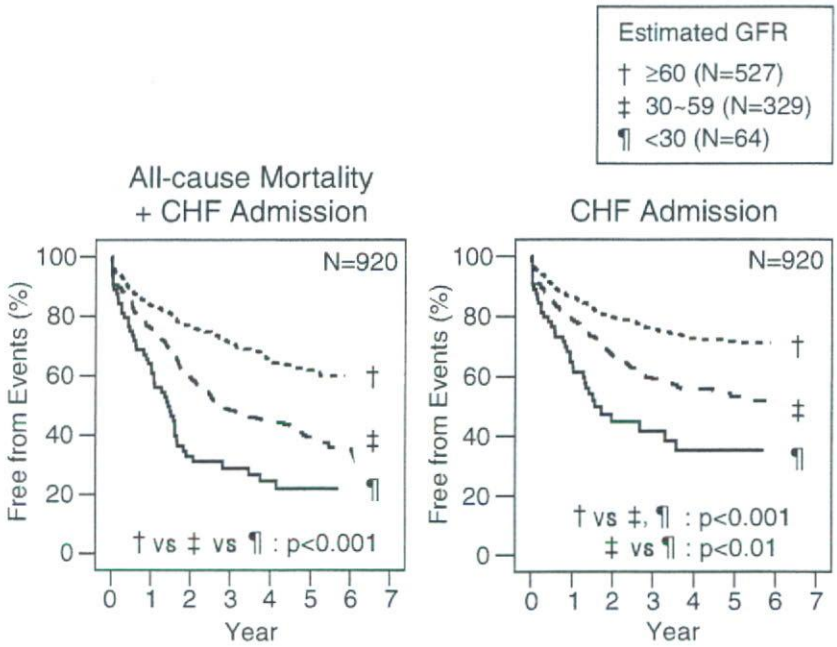

Fig 4. Kaplan-Meier curves of freedom from the two endpoints. (Left) Combined event of all-cause mortality and admission because of congestive heart failure. (Right) Admission because of congestive heart failure. CHF, congestive heart failure; GFR, glomerular filtration rate.

Table 3 Results of Multivariate Cox Analysis Using Two Methods of Calculating eGFR

Factors	*CG*				*MDRD*			
	N	*HR*	*95%CI*	*p value*	*N*	*HR*	*95%CI*	*p value*
Age (years)		*1.02*	*1.00–1.03*	*0.003*		*1.02*	*1.01–1.03*	*<0.001*
NYHA		*1.47*	*1.22–1.77*	*<0.001*		*1.45*	*1.20–1.74*	*<0.001*
Diabetes		*1.48*	*1.18–1.87*	*<0.001*		*1.47*	*1.12–1.85*	*0.001*
VT		*1.51*	*1.20–1.89*	*<0.001*		*1.50*	*1.20–1.89*	*<0.001*
Hemoglobin (g/dl)		*0.89*	*0.85–0.94*	*<0.001*		*0.89*	*0.85–0.94*	*<0.001*
EF (%)		*0.99*	*0.98–0.99*	*0.004*		*0.99*	*0.98–0.99*	*0.003*
eGFR (ml·min^{-1}·1.73 m^{-2})				*0.04*				*0.045*
≥60	*527*	*1.00*	–	–	*674*	*1.00*	–	–
30–59	*329*	*1.31*	*1.03–1.68*	*0.03*	*219*	*1.32*	*1.04–1.68*	*0.02*
<30	*64*	*1.56*	*1.05–2.32*	*0.03*	*27*	*1.51*	*0.91–2.50*	*0.12*

HR, heart rate; CI, confidence interval; VT, ventricular tachycardia. Other abbreviations see in Tables 1,2.

1.73 m^{-2} were 35.9% and 71.1%, respectively. The respective rates of admission because of congestive heart failure in those patients were 35.1% and 58.3%, respectively.

Multivariate Cox Regression Analysis

Results of the multivariate Cox regression analysis are shown in Table 3. The Spearman's rank correlation test did not show good or significant correlations between the severity of CKD and the covariates other than age, which was included in the equation of calculating GFR (Table 1). The eGFR was calculated using the CG and MDRD equations and a lower eGFR was significantly associated with the development of the combined event of all-cause death plus admission because of congestive heart failure, as were age, NYHA class, diabetes, ventricular tachycardia, lower hemoglobin level and lower left ventricular EF. When eGFR was calculated by the CG equation, hazard ratios of patients with moderate CKD (eGFR: 30–59 ml·min^{-1}·1.73 m^{-2}) and severe CKD (eGFR <30 ml·min^{-1}·1.73 m^{-2}) were 1.31 (95% confidence interval (CI) 1.03 to 1.68, p=0.03) and 1.56 (95% CI 1.05 to 2.32, p=0.03), respectively. However, when the eGFR was calculated using the MDRD equation, the significant relationship between reduced GFR and the combined endpoint was observed only in patients with moderate CKD, which showed a hazard ratio of 1.32 (95% CI 1.04 to 1.68, p=0.02) (Table 3).

Discussion

The major findings of the present study are as follows: (1) patients with CKD defined as eGFR <60 ml·min^{-1}·1.73 m^{-2} accounted for 26.7–42.7% of Japanese patients with symptomatic CHF; (2) GFR estimated using the abbreviated MDRD equation tended to be greater than that estimated by the CG equation; (3) patients with more severe CKD had more cardiovascular risks than those with less severe CKD and these patients also had a significantly increased risk of the combined event of the all-cause mortality and admission because of congestive heart failure. Therefore, risk stratification using eGFR is a first-line strategy to improve the survival and QOL of Japanese patients with symptomatic CHF.

Estimation of GFR

Significant kidney dysfunction may be present despite a normal serum creatinine level. The KDOQI guidelines define the stages of CKD based on an eGFR that is calculated

using the serum creatinine level. The two most commonly used formulas for GFR estimation are the abbreviated MDRD and CG equations (Table 1). We found a strong relationship between the two eGFRs (Fig 2), although the Bland-Altman plot did not reveal sufficient agreement between them (Fig 3). Furthermore, there was a considerable difference in the mean values of the two eGFRs, which might influence the diagnosis of CKD. Validation studies performed in middle-aged patients with CKD have shown that the MDRD equation is more accurate than the CG equation, which calculates creatinine clearance. However, we speculated that the CG equation might be more appropriate for our purposes because it can estimate GFR better than the MDRD equation in older patients[11] and the mean age of the population in the present study was 68.3 years, which was much older than that of the participants in the MDRD Study, whose mean age was 50.6 years.[9] Equations to estimate eGFR might need modification using Japanese coefficients. Imai et al reported that 0.881×MDRD might be a better estimation than the original MDRD equation; however, they also concluded that a new equation was needed for more accurate estimation of GFR in Japanese patients with CKD stage 3 or 4.[12]

Renal Dysfunction and Prognosis

Several investigators have explored the influence of renal impairment on the prognosis of patients with CHF. Multivariate analyses using populations of randomized treatment trials or population-based studies performed in Western countries showed that CKD is significantly associated with a poor prognosis of patients with CHF.[4,5,13] In the present study, Kaplan-Meier analysis showed that patients with a lower eGFR had an increased rate of the combined event of all-cause death and admission because of CHF. Furthermore, multivariate Cox regression analysis clearly showed that more severe CKD independently predicted a poor prognosis after adjustment for other cardiovascular risk factors (Table 3). When using the MDRD equation to calculate eGFR, the association between severe CKD (eGFR $<30\,ml \cdot min^{-1} \cdot 1.73\,m^{-2}$) and the combined endpoint did not reach the significant level. We speculate that this may be because of the limited number of patients who were categorized as severe CKD using the MDRD equation (n=27, Table 3).

Anemia and CKD

In the present study, patients with CKD were associated with many risk factors for cardiovascular disease (Table 2). Several researchers have shown that anemia and CKD are interrelated in patients with CHF.[4,5] Anemia can be caused by kidney dysfunction[14] and is reported to be an independent predictor of the prognosis of these patients.[5] Multivariate analysis in the present study revealed that a low hemoglobin level was independently and significantly associated with the development of events, as was the severity of CKD (Table 3).

Other Prognostic Risks and eGFR

GFR is considered to decrease as age increases and the eGFR is calculated by an equation including age as shown in Table 1.[8,9] The present study also showed that patients with more severe CKD were significantly older (Table 2). However, multivariate analysis including age as a covariate revealed that eGFR was one of the significant predictors for the prognosis in patients with CHF.

The present study also showed that other four covariates (ie, higher NYHA class, diabetes, ventricular tachycardia, and low EF) were significantly and independently associated with the prognosis of these patients, and those factors may be also associated with renal dysfunction. CKD is considered to be linked to increased incidence of atrial and ventricular arrhythmias.[15] Several structural and physiologic substrates, such as electrolyte abnormalities, volume overload, and adverse pharmacologic interactions, based on CKD may be potential mechanisms of such a relationship. Higher NYHA and low EF are frequently observed in patients with advanced CHF and the reduced cardiac output in these patients activates sympathetic nerve activity and the renin-angiotensin system, which results in further progression of CKD in CHF patients.[16] Chronic diabetes frequently results in diabetic nephropathy and it is one of the most common causes of CKD and end-stage renal disease. However, in the present study the Spearman's rank correlation test showed that there was not a good and significant relationship between the severity of CKD and the four covariates. Several researchers, including us, have already reported that these factors are significantly and independently associated with the prognosis of patients with CHF.[2,3,5] and that they are still important prognostic factors for risk stratification as eGFR is.

Conclusions

CKD is also common in Japanese patients with CHF and its severity is inversely associated with survival and QOL, as several Western investigators have previously reported. GFR, which is easily calculated using a prediction equation, should be evaluated in all patients with CHF to improve risk stratification and treatment.

References

1. Cabinet Office. Annual report on the aging society: 2006. Available at: http://www8.cao.go.jp/kourei/whitepaper/index-w.html; accessed July 20, 2007.
2. 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 cardiomyopathy. *Circ J* 2005; **69:** 143–149.
3. 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.
4. Hillege HL, Nitsch D, Pfeffer MA, Sweberg K, McMurray JJV, Yusuf S, et al. Renal function as a predictor of outcome in a broad spectrum of patients with heart failure. *Circulation* 2006; **113:** 671–678.
5. Go AS, Yang J, Ackerson LM, Lepper K, Robbins S, Massie BM, et al. Hemoglobin level, chronic kidney disease, and the risks of death and hospitalization in adults with chronic heart failure: The ANemia in Chronic Heart failure: Outcomes and Resource utilization (ANCHOR) study. *Circulation* 2006; **113:** 2713–2723.
6. National Kidney Foundation. K/DOQI, clinical practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. *Am J Kidney Dis* 2002; **39:** S1–S266. Available at: http://www.kidney.org/professionals/KDOQI/guidelines_ckd/toc.htm; accessed July 20, 2007.
7. 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.
8. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976; **16:** 31–41.
9. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: A new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 1999; **130:** 461–470.
10. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986; **i:** 307–310.

11. Lamb EJ, Webb MC, Simpson DE, Coakley AJ, Newman DJ, O'Riordan SE. Estimation of glomerular filtration rate in older patients with chronic renal insufficiency: Is the Modification of Diet in Renal Disease Formula an Improvement? *J Am Geriatr Soc* 2003; **51:** 1012–1017.
12. Imai E, Horio M, Nitta K, Yamagata K, Iseki K, Hara S, et al. Estimation of glomerular filtration rate by the MDRD study equation modified for Japanese patients with chronic kidney disease. *Clin Exp Nephrol* 2007; **11:** 41–50.
13. Mcclellan WM, Flanders WD, Langston RD, Jurkovitz C, Presley R. Anemia and renal insufficiency are independent risk factors for death among patients with congestive heart failure admitted to community hospitals: A population-based study. *J Am Soc Nephrol* 2002; **13:** 1928–1936.
14. Ezekowitz JA, McAlister FA, Armstrong PW. Anemia is common in heart failure and is associated with poor outcomes: Insights from a cohort of 12065 patients with new-onset heart failure. *Circulation* 2003; **107:** 223–225.
15. Soman SS, Sandberg KR, Borzak S, Hudson MP, Yee J, McCullough PA. The independent association of renal dysfunction and arrhythmias in critically ill patients. *Chest* 2002; **122:** 669–677.
16. McCullough PM. Interface between renal disease and cardiovascular illness. *In*: Braunwald E, editor. Heart disease, 7th edn. Philadelphia: Saunders; 2005; 2161–2172.

Prognostic Effects of Benidipine in Patients With Vasospastic Angina: Comparison With Diltiazem and Amlodipine

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Abstract: We have previously reported the changing clinical characteristics of patients with vasospastic angina (VSA) before and after the introduction of new calcium channel blockers (benidipine and amlodipine) in 1990. In this subanalysis study, we compared the prognostic effects of 3 calcium channel blockers (benidipine, diltiazem, and amlodipine) on the incidence of cardiovascular events in patients with VSA in our cohort study, where 527 patients (318 men and 209 women) enrolled after 1990 (from January 1990 to December 2002) were followed-up for a mean period of 5.2 years. There was no significant difference in the clinical characteristics among the 3 calcium channel blocker groups. Multivariate analysis demonstrated that 4 factors, including smoking, hypertension, diabetes mellitus and reduced left ventricular ejection fraction, were significant risk factors for cardiovascular events. Among the 3 calcium channel blockers examined, benidipine (n = 148) tended to be associated with a lower incidence of total events, cardiovascular events, and cerebral infarction, compared with diltiazem (n = 313) and amlodipine (n = 111). Furthermore, benidipine significantly reduced the incidence of vascular infarction events, a possible indicator of atherosclerosis, as compared with diltiazem. These results suggest that benidipine may be more useful for the treatment of VSA as compared with diltiazem and amlodipine.

Key Words: coronary artery spasm, prognosis, calcium channel blockers, benidipine

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Coronary artery spasm plays an important role in a variety of ischemic heart diseases, not only in variant angina but also in unstable angina, myocardial infarction (MI), and sudden death.[1] Japanese patients with angina pectoris are known to have a high prevalence of coronary spasm compared with those in Western countries, suggesting that the treatment of the spasm with calcium channel blockers would improve their prognosis. Indeed, most patients with vasospastic angina (VSA) can be controlled with calcium channel blockers with a relatively good quality of life and prognosis.[1,2]

We have previously reported the initial results of our cohort study that enrolled 726 patients with VSA, in which we examined their changing clinical characteristics and long-term prognosis before and after the introduction of new calcium channel blockers (benidipine and amlodipine) in 1990.[3] Almost all the patients (96%) were treated with calcium channel blockers and the overall survival without cardiovascular events at 5 years was good (96%). The presence of significant coronary stenosis had a negative prognostic impact both before and after 1990, whereas diabetes mellitus, smoking, and a history of MI became more influential after 1990. We thus considered that the overall prognosis of patients with VSA would continue to be good in the era of new calcium channel blockers.[3] However, it remains to be examined whether there is any difference in the prognostic effects among the calcium channel blockers (benidipine, diltiazem, and amlodipine) that we used in the new era of calcium channel blockers after 1990. Indeed, it has been demonstrated that calcium channel blockers are not identical on the basis of quantitative studies on their pharmacological properties.[4] In the present subanalysis study, we thus addressed this important clinical issue in our cohort of patients with VSA.

METHODS

Patients

From January 1990 to December 2002, a total of 573 patients with VSA were admitted to our hospital and registered in our cohort.[3] They were followed-up at our hospital or related hospitals and 527 patients (318 men and 209 women) were successfully followed-up with a mean period of 5.2 (range 0.3–12.9) years (follow-up rate, 92%). The mean age of the patients was 62 years (range 31–92).

The diagnosis of VSA was made when at least one of the following criteria was met: 1) recurrent resting angina associated with ST-segment elevation of at least 2 mm in at least 2 electrocardiogram leads; and 2) epicardial coronary spasm demonstrated by coronary angiography during spontaneous

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angina or angina provoked by intracoronary administration of ergonovine maleate or acetylcholine, hyperventilation, or cold pressor test.[2,3] Coronary angiographic examination was performed in 476 patients (90%). Ninety-nine of the 476 patients (21%) had significant (≥75%) coronary artery stenosis after intracoronary, intravenous, or sublingual nitroglycerin or isosorbide dinitrate.

Treatment

Most of the VSA patients (n = 494, 94%) were treated with calcium channel blockers, including benidipine (n = 148; Kyowa Hakko Kogyo Co., Ltd, Tokyo, Japan),[5] diltiazem (n = 313; Tanabe Seiyaku Co, Ltd, Osaka, Japan),[6] and amlodipine (n = 111; Pfizer Japan Inc, Tokyo, Japan).[7] In the present analysis, the patients treated with nifedipine (n = 68) were excluded due to the relatively small number that was not enough for the present analysis. Other antianginal drugs used included nitrates (61%), β-blockers (17%), and nicorandil (15%). The compliance rate of each calcium channel blockers was good (>90%) and that the doses of each drug were within equivalent therapeutic ranges.[3,4]

Follow-up

Total events were defined as combined events of cardiac death, deaths from stroke and MI, and incidences of MI, heart failure, cerebral infarction, cerebral hemorrhage, and aortic aneurysm. Cardiovascular death included cardiac death and death from MI. Cardiovascular events included cardiovascular death and nonfatal MI. Moreover, vascular infarction events were defined as cardiovascular death, nonfatal MI, and cerebral infarction.

Statistical Analysis

The results are expressed as means ± SD. The adjusted χ^2 test or *t*-test was used to compare the clinical characteristics, the use of antianginal drugs, the frequency of anginal attacks, and the use of sublingual nitroglycerin. Wald test was used to analyze the incidence of total events, cardiovascular events, cerebral infarction, vascular infarction events, and the difference among the groups treated with each calcium channel blocker. The survival curves were plotted according to Kaplan-Meier estimator. The influence of the possible prognostic factors and the effect of treatment on the prognosis were first analyzed by univariate analysis followed by multivariate analysis. Statistical significance was set at $P < 0.05$.

RESULTS

Clinical Characteristics

Clinical characteristics of the patients with VSA treated with different calcium channel blockers are shown in Table 1. There was no significant difference in the clinical characteristics among the 3 calcium channel blocker groups.

Prognostic Effects of Clinical Characteristics

Univariate analysis showed that among the clinical characteristics of the patients with VSA, left ventricular ejection fraction (LVEF), smoking, hypertension, diabetes mellitus, previous MI, and family history of ischemic heart disease were important risk factors. Furthermore, multivariate analysis demonstrated that LVEF, smoking, hypertension, and diabetes mellitus were the significant prognostic factors (Fig. 1).

TABLE 1. Characteristics of Patients With Vasospastic Angina

	Benidipine (n = 148)	Diltiazem (n = 313)	Amlodipine (n = 111)
Age (years)	65.0 ± 9.5	61.1 ± 10.2	63.3 ± 9.1
Male/female	79/69	194/119	65/46
Angina attacks (attacks/month)	8.0 ± 17.2	10.9 ± 26.0	10.3 ± 22.0
Use of sublingual nitroglycerin (tablets/month)	3.5 ± 12.8	5.2 ± 15.4	4.8 ± 15.4
Number of diseased vessels	0.3 ± 0.6	0.2 ± 0.5	0.3 ± 0.6
Coronary artery disease	33 (22.3%)	55 (17.6%)	19 (17.1%)
LVEF (%)	70.4 ± 10.4	70.0 ± 9.7	68.1 ± 12.4
Smoking	46 (31.1%)	125 (41.2%)	36 (32.4%)
Hypertension	80 (54.1%)	129 (41.2%)	55 (49.5%)
Hyperlipidemia	65 (43.9%)	117 (37.4%)	50 (45.0%)
Diabetes mellitus	29 (19.6%)	51 (16.3%)	24 (21.6%)
Previous myocardial infraction	16 (10.8%)	58 (18.5%)	20 (18.0%)
Family history of ischemic heart disease	28 (18.9%)	55 (17.6%)	18 (16.2%)

Data are means ± SD or n (%).

Prognostic Effects of Medical Treatment

The impact of the treatment with calcium channel blockers on the incidence of cardiovascular events in patients with VSA is shown in Table 2. Among the events examined, the incidence of MI and heart failure was relatively higher, and the incidence of cerebral infarction was higher than that of cerebral hemorrhage. The incidence of cardiac death tended to be lower in the benidipine and amlodipine groups as compared with the diltiazem group, although there was no death due to heart failure or aortic aneurysm in the present study.

We examined the prognosis of each group by multivariate analysis, using the risk factors (smoking, hypertension, diabetes mellitus, and LVEF) that were related to the occurrence of cardiovascular events as independent variables. The odds ratio for the prognostic impact of each drug is shown in Figure 2. Benidipine tended to be associated with a better prognosis in general and significantly reduced the incidence of vascular infarction events. By contrast, diltiazem was associated with a worse prognosis in general, and significantly increased the incidence of total events, cerebral infarction and vascular infarction events. Amlodipine had no significant impact on the prognosis. Thus, new calcium channel blockers launched after 1990 (benidipine and amlodipine), especially benidipine, were associated with better prognosis.

Figure 3 shows the survival rate without cardiovascular events in patients with VSA treated with each calcium channel blocker. Benidipine tended to be associated with a better prognosis than amlodipine or diltiazem. Figure 4 shows the survival rate without cerebral infarction. The prognosis was better in patients treated with benidipine or amlodipine than in those treated with diltiazem. Figure 5 shows the survival rate without vascular infarction events. Among the 3 groups, the