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.

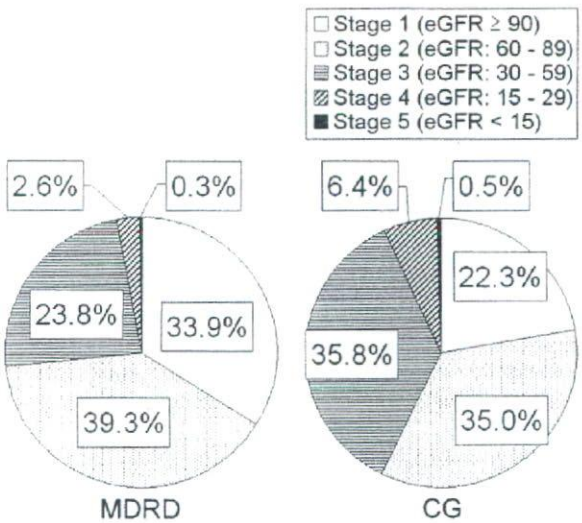

Fig 1. Distribution of the study population by stage of chronic kidney disease based on two equations for estimating of glomerular filtration rate. eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease Study equation; CG, Cockcroft-Gault equation.

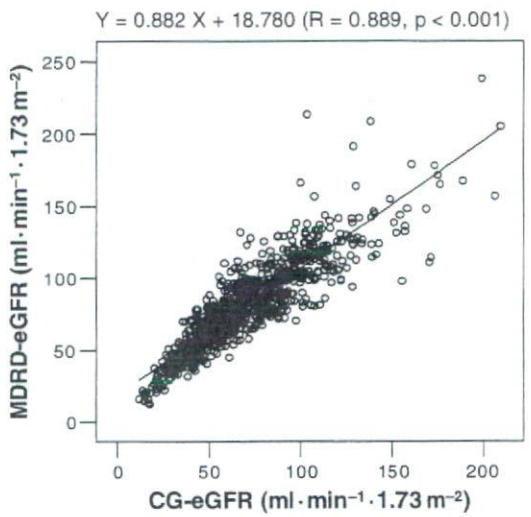

Fig 2. Correlation between estimated glomerular filtration rates using the MDRD or CG equation. GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease Study equation; CG, Cockcroft-Gault equation; eGFR, estimated glomerular filtration rate.

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

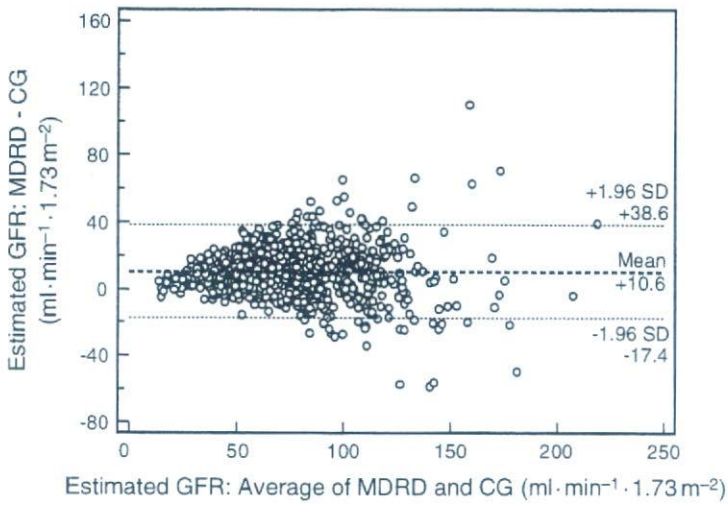

Fig 3. Bland-Altman plot of the two estimated glomerular filtration rates. MDRD, Modification of Diet in Renal Disease Study equation; CG, Cockcroft-Gault equation.

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}·

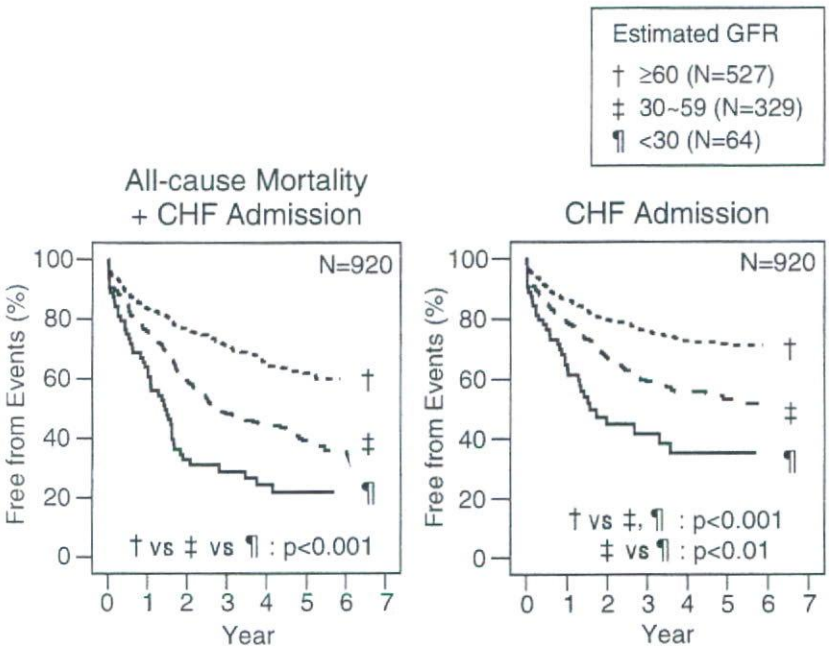

Fig 4. Kaplan-Meier curves of freedom from the two endpoints. (Left) Combined event of all-cause mortality and admission because of congestive heart failure. (Right) Admission because of congestive heart failure. CHF, congestive heart failure; GFR, glomerular filtration rate.

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·min^{-1}·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.

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Chronic heart failure in Japan: Implications of the CHART studies

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Abstract: The prognosis of patients with chronic heart failure (CHF) still remains poor, despite the recent advances in medical and surgical treatment. Furthermore, CHF is a major public health problem in most industrialized countries where the elderly population is rapidly increasing. Although the prevalence and mortality of CHF used to be relatively low in Japan, the disorder has been markedly increasing due to the rapid aging of the society and the Westernization of lifestyle that facilitates the development of coronary artery disease. The Chronic Heart Failure Analysis and Registry in the Tohoku District (CHART)-1 study was one of the largest cohorts in Japan. The study has clarified the characteristics and prognosis of Japanese patients with CHF, demonstrating that their prognosis was similarly poor compared with those in Western countries. However, we still need evidence for the prevention and treatment of CHF based on the large cohort studies or randomized treatment trials in the Japanese population. Since the strategy for CHF management is now changing from treatment to prevention, a larger-size prospective cohort, called the CHART-2 study, has been initiated to evaluate the risk factors of CHF in Japan. This review summarizes the current status of CHF studies in Japan and discusses their future perspectives.

Keywords: heart failure, aging, Japanese

Introduction

Chronic heart failure (CHF) is the leading cause of mortality in most developed countries (Hunt et al 2001). The prevalence and mortality rates of CHF used to be relatively lower in Japan compared with other Western countries. In Japan, approximately 1 to 2 million patients have CHF and nearly 170,000 patients die due to heart diseases each year (approximately 130 per 100,000 person-years) (Summary of Vital Statistics 2005). However, the prevalence and death rates of cardiovascular diseases and CHF have been rapidly increasing in Japan, due to the Westernization of lifestyle, including dietary habits, and the aging population (The Status of Aging 2007). The Chronic Heart Failure Analysis and Registry in the Tohoku District (CHART)-1 study was one of the largest cohort studies with Japanese CHF patients (N = 1,278), which was designed to evaluate the characteristics and prognosis of those patients. We have also started a new cohort study, named the CHART-2 study (N = 10,000, expected) aiming to elucidate the effective preventive measures for CHF. This review briefly summarizes the major socio-medical issues of Japanese patients with CHF, their clinical characteristics and prognosis found in our CHART-1 study, and the current status of CHF studies in Japan.

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Socio-medical status of Japanese patients with CHF

Rapid aging of Japanese population

Until the 1980s, Japan had a lower percentage of elderly citizens compared with any other developed countries. However Japan is now one of the countries in which the

population is aging rapidly. Figure 1 shows the time-course of aging and population projections between 1950 and 2055, which is assembled using the data reported by the Japanese Cabinet Office (The Status of Aging 2007). As of October 1, 2006, the total population of Japan was 127.8 million and the number of elderly aged 65 or older was 26.6 million, accounting for 21% of the total population. The elderly population is expected to continue to increase rapidly and the percentage of the elderly will reach 35.8 million (27%) in 2055 (The Status of Aging 2007). Life expectancy in Japan at birth has also drastically increased since World War II to 78.6 years for males and 85.5 years for females in 2005 (Life Expectancies at Specified Ages 2006). The Japanese Cabinet Office expects that it will reach 83.7 years for males and 90.3 years for female in 2055. Thus, in the near future, Japanese society will encounter more difficult medical problems due to rapid aging, which other developed countries have never before experienced.

Changing causes of death in Japan

Infectious diseases such as pneumonia, tuberculosis, and gastroenteritis were the leading causes of death in Japan until the mid 1900s. The major health problems in Japanese society have drastically changed since World War II. The morbidity and mortality rates of lifestyle-related diseases such as cancer, heart disease, stroke, and diabetes mellitus have dramatically increased. Approximately 60% of the mortality is now attributed to lifestyle-related diseases (cancer, 31%; ischemic heart disease 16%; cerebrovascular disease 13%; diabetes mellitus 1%; and hypertensive disease 0.6%) and the medical costs for these diseases amounts to 10.2 trillion yen (87.8 billion US dollars), accounting for approximately 30% of the total cost of the Japanese health insurance in 2003 (Exercise and Physical Activity Reference for Health Promotion 2006). Currently, heart disease is the second most frequent cause of death in Japan. Figure 1 shows the trend of the mortality due to heart diseases, which is constructed using the reports of death certificates in Japan (Summary of Vital Statistics 2005). There is a clear trend for the increase in death due to heart disease since 1950s (there was a temporary sharp decline in 1995 due to the tenth revision of the International Classification of Diseases regarding the description of diagnosis in death certificates).

Health insurance system and future economic burden in Japan

In Japan, all citizens are enrolled in the mandatory health insurance system based on employment and residential status. The average number of visits to a doctor per year is 16 in Japan, versus 5.8 visits in the United States (Itoh 2004). As elderly patients tend to visit doctors more frequently and to have more medication or high-cost medical care, medical

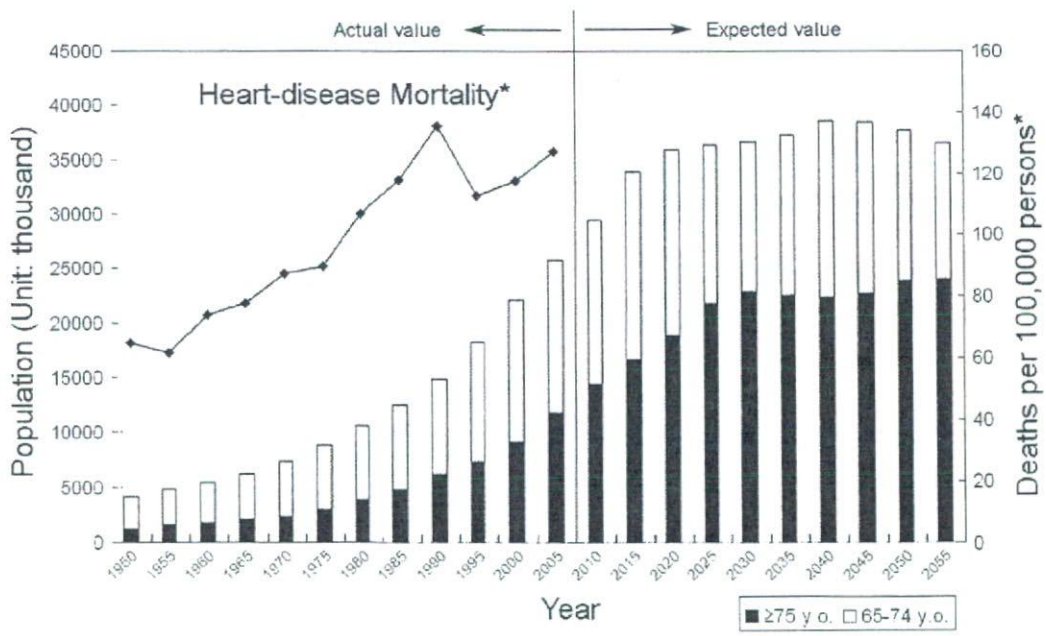


Figure 1 Time-course and future prediction of the increase in elderly population and heart-disease mortality in Japan. Data are based on the Status of Aging and Implementation of Measures for Aging Society in 2005, reported by the Japanese Cabinet.

expenditure for the elderly is already taking one-third of the national health expenditure, and is projected to reach a half of the expenditure by the year 2025 (Itoh 2004). Progressive aging of the society and the consequent increase in the number of patients with CHF will cause more financial burden within Japanese society, which could lower the quality of medical services in the future.

An overview of heart failure studies in Japan

In Japan, medical treatment for patients with CHF is mainly based on the evidence obtained from randomized trials in the United States and Europe. There have been no sufficient randomized treatment trials or prospective cohort studies in Japan to clarify the real characteristics of Japanese patients with CHF or to improve their prognosis and quality of life. The mandatory health insurance system, the shortage of the budget to fulfill mega-trials, and the absence of trained research nurse system may all be responsible for the current situation. This section describes several cohort studies with Japanese CHF patients, major outcomes of the CHART-1 study, and randomized treatment trials for CHF performed with Japanese patients, either those that have already been published or are currently in progress. Finally, racial differences will be discussed, because this issue may also influence the impact of risk factors and/or the effects of treatments for CHF.

Prospective cohort studies in Japan

There are few multi-institutional prospective cohort studies with CHF patients in Japan (Table 1). The Chronic Heart Failure Analysis and Registry in the Tohoku District (CHART)-1 study was the first cohort study in Japan, including more than 1,000 Japanese patients with stable CHF, who were registered at 26 hospitals in the Tohoku district with a population of approximately 9.8 million (Shiba et al 2004). The CHART-1 study was initiated in February 2000 and was completed in December 2005. The total number of CHF patients enrolled was 1,278 and the mean follow-up period was 3.5 years. Details of design and the main outcome will be presented at the following part in this article. The Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD) is a registry of hospitalized patients with worsening CHF at 164 hospitals throughout the country between January 2004 and June 2005 (Tsutsui et al 2006). Death and hospital admission of the patients were followed through 2006 with the mean follow-up period of at least 1 year. Results of this study will appear in the near future. The Japanese Cardiac Registry of

Table 1 Multicenter prospective cohort study for patients with chronic heart failure in Japan

Study [Reference]	Study population	Age, years (Mean)	Total enrollment	Heart failure stage/NYHA	Study start Expected completion	Mean follow-up	1-year mortality	Status
CHART-1 Study [Shiba 2004]	Chronic heart failure outpatients/ hospitalized pts.	≥18 (68)	1278	(B) C-D I-IV		3.5 years	7.3%	Published
JCARE-CARD [Tsutsui 2006]	Hospitalized patients with heart failure	≥15	2676	C-D		At least one year		Completed
JCARE-GENERAL [Tsutsui 2007]	Outpatients with heart failure	≥15 (74)	2685	C-D		One year	6.3%	Published
CHART-2 Study	Chronic heart failure High risk for heart failure outpatients/ hospitalized pts.	≥20	10000 (expected)	B-D I-IV	Oct 2006 Sep 2011			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: NYHA, New York Heart Association; pts, patients.

Heart Failure in General Practice (JCARE-GENERAL) is a registry of outpatients with CHF managed by cardiologists in hospitals and primary care physicians in general practice (Tsutsui et al 2007). Baseline data of totally 2,685 patients were collected during November 2004 and follow-up data were collected for 1 year after the enrolment. During the mean follow-up period of 427 days, the crude mortality rate was 6.7% in patients managed by cardiologists and 5.9% in those managed by general physicians. The Chronic Heart Failure Analysis and Registry in the Tohoku District (CHART)-2 study is currently the largest prospective and hospital-based cohort study with patients with CHF in Japan. This study was designed to investigate the characteristics and prognosis of a total of 10,000 patients with symptomatic CHF (Stage C/D in the ACC/AHA classification) and those with structural heart disease but without signs or symptoms of CHF (Stage-B in the AHA/ACC classification) (Hunt et al 2001). This study will elucidate the incidence and prognostic impact of metabolic syndrome in those patients, especially on the development of the first symptomatic CHF. The CHART-2 study was started in October 2006 and will be completed in September 2011.

The CHART-1 Study

Risk stratification is the first line strategy to improve the prognosis and quality of life of patients with CHF. A number of factors have been found to correlate with the mortality of patients with CHF (Rector et al 1994; Deedwania 2003; Bettencourt et al 2000). The CHART-1 study was started to register patients with stable CHF in February 2000 to clarify the characteristics and prognosis and to seek for prognostic factors in Japanese CHF patients (Shiba et al 2004, 2005). Patients were enrolled when at least one of the following criteria was met: (1) left ventricular ejection fraction (LVEF) <50%, (2) left ventricular end-diastolic dimension >55 mm, or (3) at least one episode of congestive heart failure. Patients less than 18 years old or those with clinically unstable conditions were excluded. Baseline data, including laboratory findings, results of echocardiography, and medical treatments for CHF, were recorded and annual surveillance was performed until the end of 2005.

Characteristics and prognosis of patients with CHF in Japan.

A total of 1,278 patients were enrolled in the CHART-1 cohort. The mean age of the study population was 68.3 years, and male accounted for 66% of the total study population. The prevalence of diabetes mellitus and hypertension was 19% and 47%, respectively. Other baseline characteristics of patients are shown in Table 2. Ischemic etiology accounted for only 25% and the percentage of patients older than 65 years was 66%. Patients with preserved systolic function (defined as LVEF >50%) accounted for 45% of the total population. During the mean follow-up period of 3.5 years, all-cause mortality rate at 1-, 2-, and 3-year was 7%, 16%, and 22%, respectively (Figure 2). Multivariate Cox analysis showed that several covariates, such as age, diabetes mellitus, ventricular tachycardia, serum level of B-type natriuretic peptide (BNP), rural residence, and NYHA functional class, were significantly associated with all-cause mortality (Shiba et al 2004). Figure 3 shows the Kaplan-Meier analyses of freedom from all-cause mortality in patients stratified by serum level of BNP or LVEF. Patients with higher BNP concentration had a significantly poorer prognosis (Watanabe et al 2005), however, the prognostic impact was not significantly different between patients with 200–500 pg/mL of BNP level and those with >500 pg/mL (Figure 3A). The all-cause mortality of patients with preserved systolic function (LVEF > 50%) was not significantly different than that of patients with

Table 2 Baseline characteristics of the Japanese patients in the CHART-1 study

No. of patients	1,278
Follow-up period (years)	3.5 ± 1.7
Age (years)	68.3 ± 13.4
≤39	3.7%
40–64	30.2%
65–74	32.8%
≥75	33.3%
Male (%)	66.0%
NYHA	
I	19.7%
II	63.0%
III	16.5%
IV	0.8%
Underlying disease	
Coronary artery disease	25.4%
Valvular heart disease	26.4%
Left ventricular hypertrophy	14.0%
Non-ischemic cardiomyopathy	28.6%
Other	5.6%
Left ventricular ejection fraction (%)	51.1 ± 15.9
<30%	11.7%
30–50%	43.7%
>50%	44.6%
Hypertension	47.4%
Diabetes	18.9%
Dyslipidemia	16.7%
Atrial fibrillation	41.8%
Ventricular tachycardia	20.1%
History of heart failure admission	23.4%

Abbreviations: NYHA, New York Heart Association.

moderately decreased LVEF (30%–50%). However the prognosis of those with severely low LVEF (<30%) was the lowest with frequent episodes of sudden cardiac death (Figure 3B). The 3-year incidence of sudden death was higher in patients with LVEF <30% than those with LVEF ≥30% (15% vs 4%, respectively, $p < 0.001$). Primary prevention of sudden cardiac death with an implantable cardioverter defibrillator in those patients should be recommended when they meet the criteria in the authorized guidelines (Watanabe et al 2006). Recently, anemia has been emphasized as an important prognostic predictor in patients with CHF (Ezekowitz et al 2003). Our data also showed that anemia was significantly associated with all-cause mortality, cardiac-cause mortality, and sudden death in patients with diastolic CHF (Tada et al 2007), as well as in those with systolic CHF, as reported by other researchers (O'Meara et al 2006).

Treatment of patients with CHF in Japan

Treatments with angiotensin converting enzyme inhibitors (ACEI), angiotensin II receptor blockers (ARB), or β-blockers are recommended to improve prognosis and quality of life for patients with CHF (Hunt et al 2001). However it has previously been reported that such evidence-based treatments might not be sufficiently used in patients who should have had benefits of such medications (Masoudi et al 2003). The overall usage rate of ACEI/ARB or β-blocker in patients enrolled in the CHART-1 study was 70% and 28%, respectively (Figure 4). The penetration rate of these medications was relatively lower in female patients, elderly patients, and those with valvular heart disease or preserved LVEF, and this trend was more evident for the treatment with β-blocker than ACEI/ARB (Figure 4). These results suggest that future clinical trials are still necessary for such minorities who have not usually been enrolled in major randomized treatment trials for CHF.

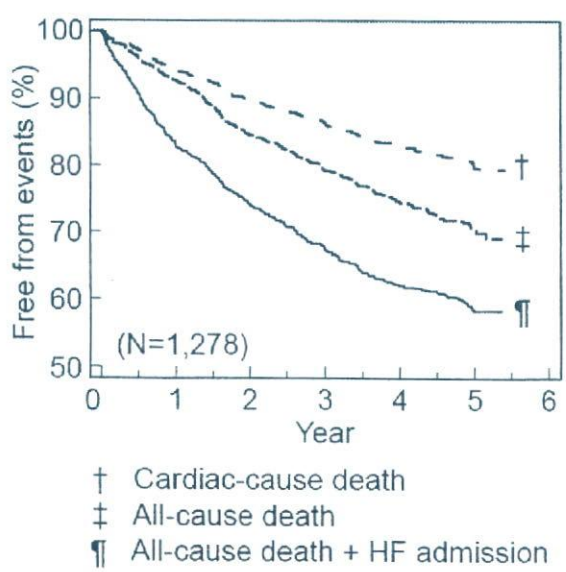


Figure 2 Prognosis of the Japanese patients with CHF in the CHART-1 study. Copyright © 2004. Reproduced with permission from Shiba N, Watanabe J, Shinozaki T, et al. 2004. Analysis of chronic heart failure registry in the Tohoku district: third year follow-up. *Circ J*. 68:427–34.
Abbreviations: HF, heart failure.

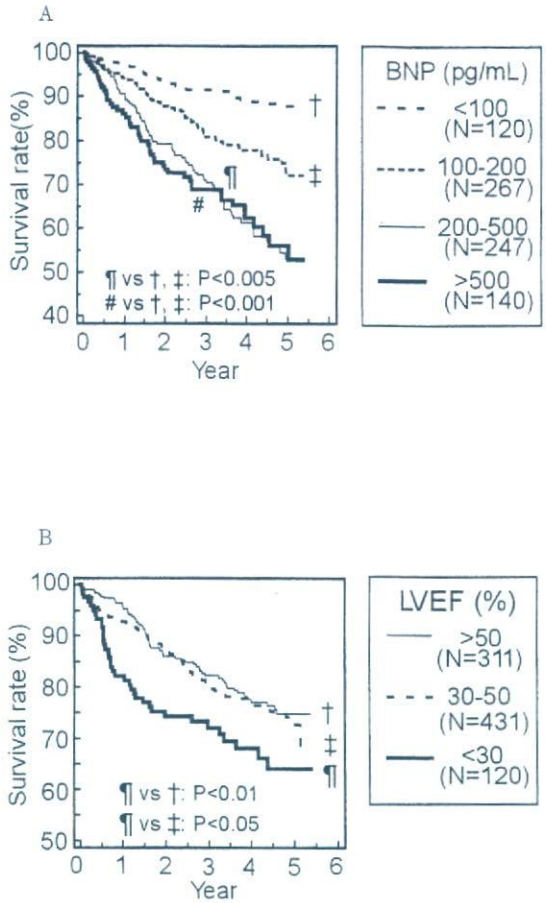


Figure 3 Kaplan-Meier curves of freedom from all-cause death stratified by (A) BNP and (B) LVEF in the CHART-1 study.
Abbreviations: BNP, B-type natriuretic peptide; LVEF, left ventricular ejection fraction.

Clinical outcomes of Japanese patients with CHF

Figure 5 showed survival curves of placebo groups in randomized treatment trials for CHF performed in Western countries, superimposed with the result obtained in our CHART-1 study with Japanese CHF patients. One-year all-cause mortality of patients with mild-moderate CHF (NYHA

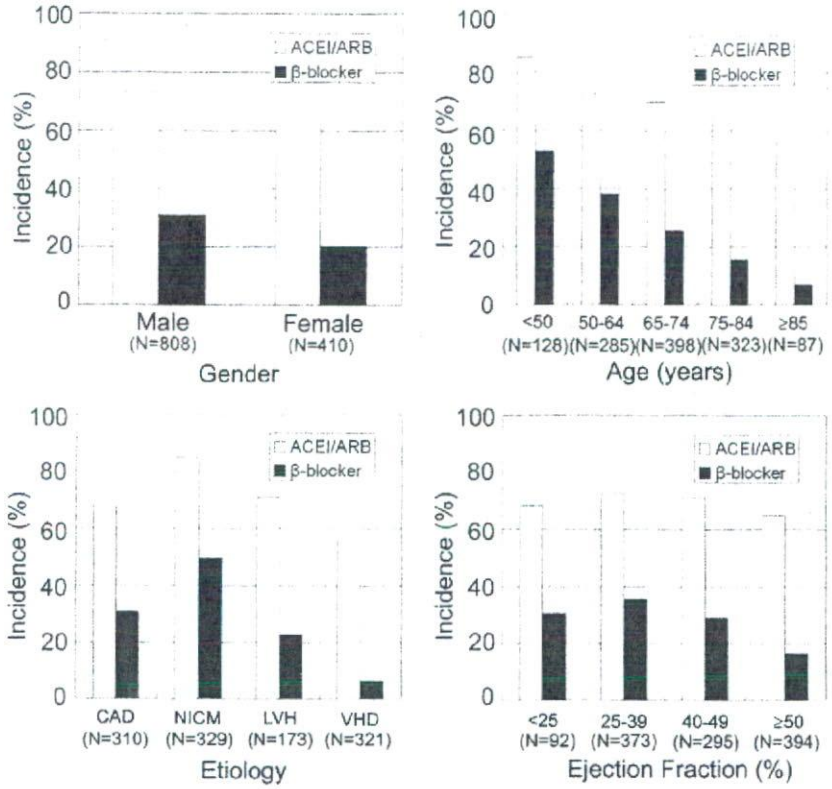


Figure 4 Prevalence of the use of renin-angiotensin inhibitors and β-blockers in the CHART-1 study. Copyright © 2007. Reproduced with permission from Shiba N, Takahashi J, Matsuki M. 2007. The CHART Study (Japanese). *Naika*, 99:410–14.

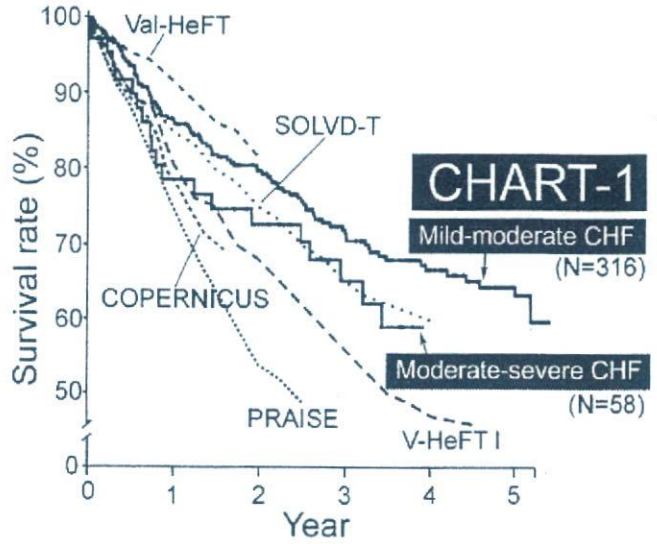
Abbreviations: ACEI, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker; CAD, coronary artery disease; NICM, non-ischemic cardiomyopathy; LVH, left ventricular hypertrophy; VHD, valvular heart disease.

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

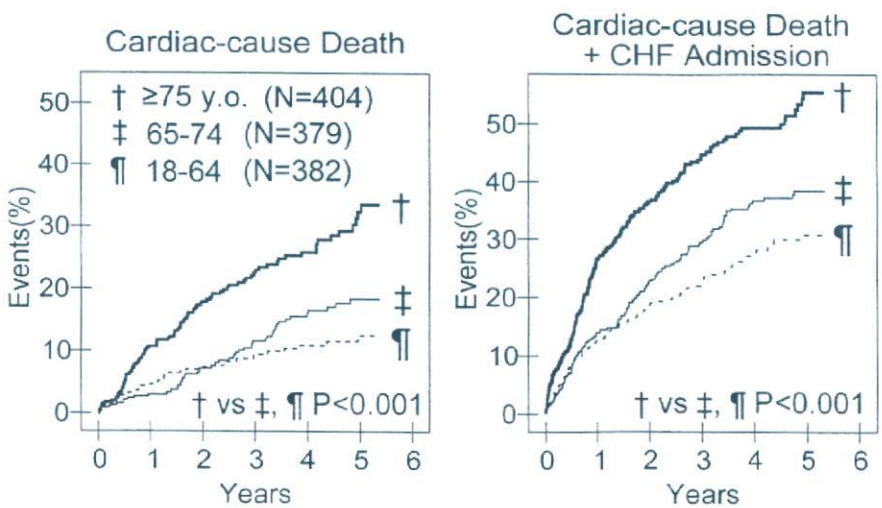


Figure 6 Prognosis of elderly patients with CHF in the CHART-1 study. Copyright © 2007. Reproduced with permission from Shiba N, Takahashi J, Matsuki M. 2007. The CHART Study (Japanese). *Naika*, 99:410–14.
Abbreviations: CHF, congestive heart failure.

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.

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医薬品副作用学

—薬剤の安全使用アップデート—

II. 副作用概論

薬効群別副作用

高脂血症治療薬

福本義弘　　下川宏明

薬効群別副作用

高脂血症治療薬

Lipid-lowering medications

福本義弘　　下川宏明

Key words：スタチン，腎機能低下，併用注意，筋肉痛，横紋筋融解症

はじめに

近年我が国では，食生活の欧米化とともに高脂血症や肥満が多く認められるようになった．それに加え，高血圧，糖尿病，喫煙，ストレスなどの多くの因子が関与し，冠動脈粥状硬化が進展，その粥状硬化プラークが破綻することにより冠動脈内が血栓により閉塞して，急性心筋梗塞を発症する症例が増えている．現在，虚血性心疾患による死亡率は増加傾向にあり，日本での死亡率は第2位である．したがって急性心筋梗塞の予防には，生活習慣を是正し，これら多数のリスクファクターを修正する必要がある．そのためにはまず食生活を改善し，適度な運動を継続する習慣をつけ，禁煙，塩分制限，飲酒制限に努め，ストレスに関するカウンセリングなどを行い，更に必要に応じ薬物療法を行うことになる．

本稿では，その一環としての高脂血症の治療方法およびその意義，高脂血症治療薬の副作用について概説する．

1. 生活習慣の是正

a. 食事療法

我が国では食生活の欧米化とともにコレステロール値の増加が認められているが，その一方，オリーブ油摂取習慣のある地中海沿岸諸国では，総コレステロール値が低く虚血性心疾患の発症頻度が低い．このことからオレイン酸のLDL低下作用が注目されている．また，青魚を多く食するエスキモーに虚血性心疾患の発症率が低いことから，青魚に多く含まれるEPA(eicosapentaenoic acid)やDHA(docosahexaenoic acid)などのω-3系多価不飽和脂肪酸も注目を浴びている．これら不飽和脂肪酸摂取は，リポ蛋白に対する直接効果以外に血栓症の抑制や免疫反応の低下などのメカニズムによって動脈硬化形成を抑制する可能性がある．ただし動脈硬化の進展予防のために魚，野菜を多く食事に取り入れることは好ましいが，特に補助食品を使用する必要はない．

すなわち野菜，海藻，魚介類などを多く摂取し，肉類は脂肪の少ない鶏肉(皮，卵を除く)や子牛などにし，卵やレバーなどコレステロールの多い食品や飽和脂肪酸の多い乳製品，牛肉などはなるべく避ける．ショ糖を多く含む菓子類や果糖の多い果物，アルコールの過剰摂取はトリグリセリド値を上昇させるので，これらを制限する．食物繊維は胆汁酸中のコレステロール再吸収を阻害する作用があり1日25-30g摂取するようにする．抗酸化作用のあるビタミンA，C，E摂取量の増加により心血管系のリスクが

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低下するとの疫学的成績があり，これらを多く含む野菜や薬物の摂取は望ましいし，紅茶や赤ワインには抗動脈硬化作用が示唆されているポリフェノール系抗酸化物の総称であるフラボノイドが含まれており，これらも好ましい．また肥満は虚血性心疾患の独立した危険因子であることがフラミンガム研究で示されており，食事療法，運動療法により是正する必要がある．

b. 運動療法

フラミンガム研究によると，身体活動が低い者ほど冠動脈疾患や血管疾患が増加することが示されている．心筋梗塞後は運動療法を中心にした心臓リハビリテーションにより活動能力の向上，心筋灌流の改善，治療コンプライアンスの向上，QOLの改善，心血管系死亡の減少，虚血症状の軽減，粥状硬化の安定化，その後の冠動脈イベントリスクの低下などの効果が期待できる．運動療法に用いられる処方は，トレッドミルテストなどより運動終了時に得られた最大心拍数の60–80％または最大酸素摂取量の40–85％に相当する歩行，ジョギング，水泳，サイクリングなど全身運動を20–30分，その前後で5–10分間のウォーミングアップとクーリングダウンを設け，週3–5回程度行うものが一般的に推奨されている[1]．このような運動療法により，運動耐容能の増加，安静時および一定運動負荷時における心筋酸素消費量の低下が得られる．運動療法は自律神経系に対しても効果的で，心筋梗塞後は交感神経が早期に回復し，副交感神経は3–5カ月にわたり，あるいは更に時間をかけて徐々に回復するようである．しかしながら，検査室における運動負荷試験と日常生活における運動では性質を異にし，日常生活で急に階段を上ったり，バスや電車に遅れまいと急に走り出したりすると，胸痛を訴えることがあることを考慮する必要がある．日常生活における各種運動時の患者自身による管理としては自己脈の計り方（10秒の6倍もしくは15秒の4倍）を指導し，最高心拍数をコントロールする．

c. 禁煙指導

我が国の喫煙人口は先進国の中では最も高い．次第に減少傾向にはあるものの，若年者と女性の喫煙率はむしろ増加している．喫煙が日本人の虚血性心疾患における危険因子であることは明らかであり，特に若年発症の虚血性心疾患患者の大部分は喫煙者である．急性心筋梗塞患者において，禁煙は必須であり，禁煙を実行すると，禁煙後1年で再梗塞率と死亡率はほぼ半減し，その後徐々に減少し数年で非喫煙者のレベルに達する．しかしながら3割～半数の急性心筋梗塞患者は禁煙後6–12カ月以内に喫煙を再開している．禁煙開始直後の患者ではニコチンガムまたはニコチンパッチにより，ニコチン禁断症状が緩和されることが示されている．この製剤の活性物質ニコチンには交感神経様作用があるため，心筋梗塞急性期での使用は推奨されないが，ガムやパッチに含有されるニコチン量はタバコよりも非常に低いため，急性離脱症状がみられる場合には，喫煙の再開よりもこれらの製剤の方がよいと思われる．また最近，受動喫煙の問題が注目されており，受動喫煙者は軽喫煙者に匹敵するレベルで頸動脈壁が肥厚し，内皮依存性血管拡張作用低下，運動耐容能低下，HDLコレステロール低下，LDLコレステロール上昇，血小板凝集能亢進などが生じる．梗塞後の受動喫煙については今後の研究が必要であるが，著者らは可能なかぎり受動喫煙を回避するよう指導している．

d. 飲　酒

日系米国人を調査したホノルル研究によると，飲酒は虚血性心疾患の発症を抑制し，フラミンガム研究においても，男性では飲酒により心筋梗塞，狭心症が減少，女性では狭心症が減少することが示された．適度な飲酒はHDLコレステロールを上昇させ，動脈硬化性病変を減少させるが，過剰になると肝でのVLDL合成が促進され，血中トリグリセリドが上昇し，HDLコレステロールが低下する．アルコールの過剰摂取は高トリグリセリド血症の主要な原因になっているので，こうした例では適量の飲酒に減らすよりもむしろ禁酒が望ましい．

著者らは日常診療において，まず上記のように生活習慣を是正するよう指導している．一部

表1 高脂血症治療薬の薬効別分類

LDLコレステロール低下	スタチン 陰イオン交換樹脂 フィブラート ニコチン酸誘導体 プロブコール
トリグリセリド低下	フィブラート ニコチン酸誘導体 イコサペント酸エチル
HDLコレステロール上昇	フィブラート ニコチン酸誘導体 スタチン

の患者では十分是正されるが，多くの場合不十分である．したがって薬物療法を行うことになる．

2. 高脂血症に対する薬物療法と注意点

a. コレステロール治療目標

生活指導，食事療法によってもLDLコレステロール125 mg/dl以上の患者には高コレステロール血症薬物療法を行う．これまでの欧米および日本で行われた大規模臨床試験の結果から，HMG-CoA還元酵素阻害薬(スタチン)投与により虚血性心疾患患者の死亡率低下が明らかとなっており，既に冠動脈疾患を発症している患者の高脂血症治療は，一次予防の患者より更に厳重に行う必要がある．日本動脈硬化学会動脈硬化性疾患診療ガイドラインでは，冠危険因子の有無により治療目標値は異なるが，冠動脈疾患を有する場合は，LDLコレステロール100 mg/dl未満(総コレステロール180 mg/dl未満)である．我が国で高コレステロール血症に投与できる薬物は，スタチン，プロブコールおよび陰イオン交換樹脂(レジン)，更にトリグリセリド低下効果を合わせもつ薬物として，フィブラート，ニコチン酸誘導体があげられる(**表1**)．最もコレステロール低下作用の強いスタチンでは，LDLコレステロール値20-50%の低下が期待でき，最も使用頻度の高い高脂血症治療薬である．

b. スタチン

コレステロール生合成経路において，スタチンはHMG-CoAからメバロン酸への過程を触媒する律速酵素であるHMG-CoA還元酵素を特異的・拮抗的に阻害することによりコレステロール合成を抑制する．これにより肝細胞内コレステロール含量を低下させ，LDL受容体活性が増強し，血中から肝細胞内へのLDLの取り込みが増加することで，血清中のLDLコレステロールが低下する．

水溶性スタチンであるプラバスタチン10 mgでLDLコレステロールが約22%低下し，脂溶性スタチンであるフルバスタチン30 mgでLDLコレステロールが約28%低下，シンバスタチン30 mgでLDLコレステロールが約30%低下，アトルバスタチン10 mgでLDLコレステロールが約40%低下する[2,3]．スタチンの副作用として，特に注意が必要なのが横紋筋融解症であり，高齢者および腎機能低下例における筋肉痛，CK上昇，血中・尿中ミオグロビンの上昇では薬剤を中止すべきである．特にフィブラート，ニコチン酸製剤，シクロスポリン，エリスロマイシンなどとの併用でその頻度が高まる．スタチンの禁忌として過敏症の既往歴，重篤な肝障害，妊娠が，原則禁忌として，腎機能低下時におけるフィブラートの併用があげられるが，必要であれば，患者にその旨を十分説明し，定期的な問診と採血(一般的には最初の3カ月は毎月，その後は3カ月ごと)を含めた注意深い観察が必要である(**表2**)．

c. プロブコール

コレステロールの胆汁中への異化排泄促進作用が主で，総コレステロールを低下させるが，HDLコレステロールも低下させることが多い．本薬剤には強い抗酸化作用があり，これに関連すると考えられる抗動脈硬化作用があるが，失神発作を伴う心室性不整脈が出現する可能性があるため注意が必要である．多源性心室性期外収縮の多発など重篤な心室性不整脈を有する患者や，テルフェナジンもしくはアステミゾール投与中だとQT延長，心室性不整脈を引き起こすため禁忌である(**表2**)．

d. 陰イオン交換樹脂(レジン)

腸管内で胆汁酸と結合してその糞中排泄量を