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Poor Prognosis of Japanese Patients With Chronic Heart Failure Following Myocardial Infarction

—— Comparison With Nonischemic Cardiomyopathy ——

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Background Myocardial infarction (MI) is one of the major etiologies of chronic heart failure (CHF) in Japan.
Methods and Results The prognoses of CHF patients after MI (n=283) were investigated by comparing them with those of CHF patients with nonischemic cardiomyopathy (NICM, n=310) from the CHF registry (CHART; n=1,154). The Kaplan-Meier (KM) analyses revealed that the 3-year all-cause mortality was significantly higher in the MI cohort compared with the NICM cohort (29.0% vs 12.4%, p<0.0005). Age/gender/treatment-adjusted KM analysis revealed significant differences only in the cohorts with preserved left ventricular ejection fraction (LVEF), defined as LVEF >45%, or in less symptomatic patients (New York Heart Association I or II). Multivariate Cox regression analysis showed that β-blocker (BB) was associated with a significant reduction in mortality from cardiac causes, and either angiotensin-converting enzyme inhibitor or angiotensin receptor blocker (ACEI/ARB) was significantly related to the improvement of survival in the MI cohort (adjusted hazard ratio: 0.222 and 0.497, p<0.05), even though these medicines were used significantly less often in the MI cohort.
Conclusions Underlying MI has a significant impact on the survival of Japanese CHF patients, especially those with preserved LVEF or with fewer symptoms. The appropriate expansion of ACEI/ARB or BB therapy might be necessary to improve their survival. (*Circ J* 2005; **69:** 143 – 149)

Key Words: Angiotensin-converting enzyme inhibitor; Beta-blocker; Chronic heart failure; Myocardial infarction; Nonischemic cardiomyopathy

Myocardial infarction (MI) is an important cardiovascular disease in terms of its severity and incidence. As in other industrialized countries, it is a major public health problem in Japan. Left ventricular (LV) remodeling after MI exacerbates LV dysfunction and causes chronic heart failure (CHF) that is generally progressive[1]. However, the real prognosis of Japanese patients with CHF caused by an underlying MI is still unknown. Many studies indicate that the prevention and improvement of LV remodeling by angiotensin-converting enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB) or β-blocker (BB) significantly improves the prognosis of CHF patients after MI[2–4]. The 3 objectives of the present study were: (1) to compare the prognoses of CHF patients following MI with those of CHF patients with nonischemic cardiomyopathy (NICM) using our CHF registry, (2) to clarify the prognoses of CHF patients with preserved systolic LV function or fewer CHF symptoms in the MI cohort, and (3) to determine the independent predictors of outcome, including ACEI/ARB or BB.

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Methods

Patient Population

In February 2000, we started a hospital-based CHF registry called the Chronic Heart Failure Registry and Analysis in the Tohoku District (CHART) in order to perform epidemiological analyses of Japanese patients with CHF. Member hospitals, associate physicians, and the design of the CHART registry have been described elsewhere[5,6]. Oral or written informed consent was obtained from each patient and the study protocol, which was approved by the human research committee of Tohoku University School of Medicine, conformed to the ethical guidelines of the 1975 Declaration of Helsinki. Patients were enrolled when at least one of the following criteria was met: (1) LV ejection fraction (LVEF) was less than 50%, (2) LV end-diastolic diameter (LVDD) was equal to or more than 55 mm, or (3) at least one episode of congestive heart failure. All recruited patients had a structural disorder of the heart and were treated with standard therapy for CHF, including diuretics, digitalis, ACEI, ARB, or BB to maintain their ability to perform the activities of daily life without severe symptoms. Although our CHF criteria were relatively broader than the 'traditional' CHF criteria, we recruited less symptomatic patients with preserved systolic LV function and therefore we might have included Stage B patients, based on the new CHF classification proposed by the 2001 ACC/AHA guidelines[1]. As of February 2003, 1,154 CHF patients were enrolled in the registry and the mean follow-up period was 1.9±0.9 (mean±SD) years. From that group, the study population comprised 283 CHF

Table 1 Baseline Characteristics of the Study Population

	MI		NICM		p value	
N	*283*		*310*			
Follow-up years	*1.8±1.0*		*1.9±0.9*		*NS*	
Patients' characteristics						
Age (years)	*69.5±10.6*		*60.7±14.5*		*<0.0001*	
>70 years (%)	*52.8*		*30.7*		*<0.0001*	
Male (%)	*75.7*		*70.3*		*NS*	
Symptoms						
NYHA	*2.0±0.7*		*2.0±0.6*		*NS*	
I or II (%)	*81.8*		*81.7*		*NS*	
Heart-disease risk factors						
BNP (pg/ml)	*325.4±377.3*		*224.9±387.9*		*0.01*	
>100 pg/ml (%)	*71.6*		*49.0*		*<0.001*	
LVDD (mm)	*57.4±9.1*		*60.5±9.0*		*<0.001*	
>60 mm (%)	*35.7*		*50.7*		*0.001*	
LVEF (%)	*43.0±12.9*		*41.1±12.6*		*NS*	
≤45% (%)	*56.5*		*63.7*		*NS*	
Medical history (%)	*All*	*EF >45%*	*All*	*EF >45%*		
Hospital admission for HF	*52.3*	*49.5*	*74.3*	*71.8*	*<0.001,*	*0.001*
Hypertension	*37.0*	*39.3*	*30.0*	*33.7*	*NS,*	*NS*
Diabetes	*32.1*	*31.1*	*14.5*	*14.6*	*<0.001,*	*0.007*
Hyperlipidemia	*35.7*	*29.8*	*13.8*	*15.5*	*<0.001,*	*0.020*
Atrial fibrillation	*19.6*	*29.9*	*28.3*	*31.4*	*0.016,*	*NS*
Ventricular tachycardia	*17.3*	*14.8*	*22.3*	*17.1*	*NS,*	*NS*
Medical treatment (%)						
BB	*25.7*	*26.4*	*47.4*	*45.0*	*<0.001,*	*0.006*
ACEI/ARB	*66.8*	*61.3*	*85.8*	*88.0*	*<0.001,*	*<0.001*

MI, CHF following myocardial infarction; NICM, CHF with nonischemic cardiomyopathy; NS, not significant; NYHA, New York Heart Association functional class; BNP, brain natriuretic peptide; LVDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; HF, heart failure; BB, β-blocker; ACEI, angiotensin-converting enzyme inhibitor; ARB, angio-tensin receptor blocker.

Table 2 Numbers of Patients Who Reached Endpoints

Endpoint	MI		NICM	
	n	*Years*	*n*	*Years*
Death of cardiac cause				
Sudden death	*24*	*1.14±0.80*	*14*	*0.89±0.63*
Death from heart failure	*12*	*1.04±1.01*	*10*	*1.12±0.91*
Death of non-cardiac cause	*24*	*1.20±0.77*	*6*	*1.21±0.65*
Hospital admission for cardiac causes	*53*	*0.97±0.90*	*55*	*1.01±0.83*

MI, CHF following myocardial infarction; NICM, CHF with nonischemic cardiomyopathy.

patients with MI and 310 CHF patients with NICM.

Diagnosis of MI and the NICM Cohort

The diagnosis of MI was made when both of the following criteria were met: (1) typical findings of MI on electrocardiography (ECG) and (2) wall motion abnormalities that corresponded to the ECG findings, revealed by B-mode echocardiography or contrast ventriculography. The diagnosis of NICM was made when a CHF patient who met the entry criteria of the CHART registry did not have significant valvular dysfunction, definite signs of coronary involvement revealed by angiography or ECG, any history of MI, any congenital cardiac abnormality, or LV hypertrophy.

Statistical Analysis

Baseline data were collected at the time of entry into the registry. Comparisons of numerical data between the 2 arms were by independent t-test and chi-square test for comparisons of categorical data. Endpoints were all-cause death, cardiac-cause death, and all cardiac events, which was a combined endpoint of cardiac-cause death and hospital admissions for cardiac causes. Comparison of survival between the 2 arms was by Kaplan-Meier method, and the 2 survival curves were compared by the log-rank test. Multivariate relationships between the baseline data and endpoints were analyzed by the Cox proportional hazard model. Covariables that were used in the multivariate analysis are shown in Appendix 1. Significant covariables were selected by the backward stepwise method. Statistical significance was defined as $p<0.05$. All statistical analyses were conducted using SPSS 11.0J (Chicago, IL, USA).

Results

Of the 1,154 CHF patients who were enrolled in CHART during the study period, 291 had MI as the etiology of CHF and 8 were excluded from the present study because baseline data were not complete. Similarly, there were 323 CHF patients with NICM in the registry and 13 of them were excluded for the same reason.

Baseline Comparison (Table 1)

In the present study, the patients with MI were significantly older than those with NICM. Furthermore, the MI

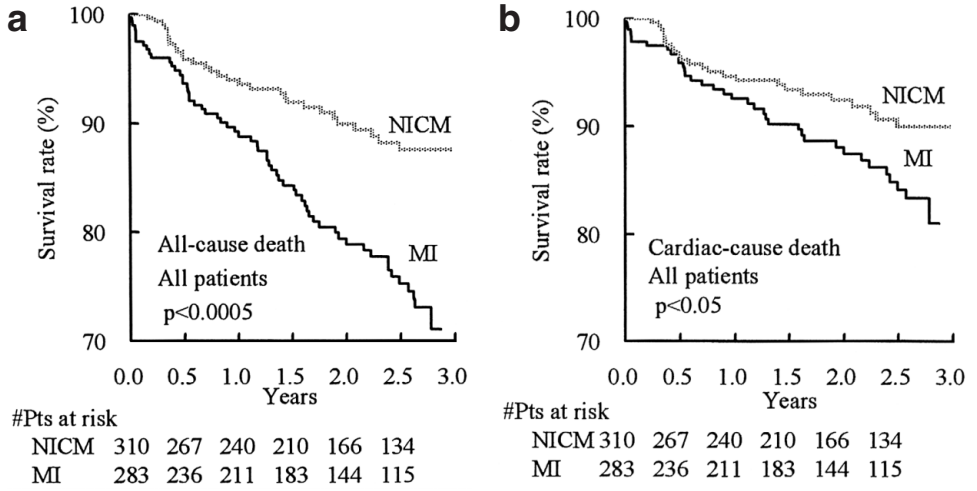

Fig 1. Kaplan-Meier curves of (a) all-cause and (b) cardiac-cause death in the nonischemic cardiomyopathy (NICM) or myocardial infarction (MI) cohorts.

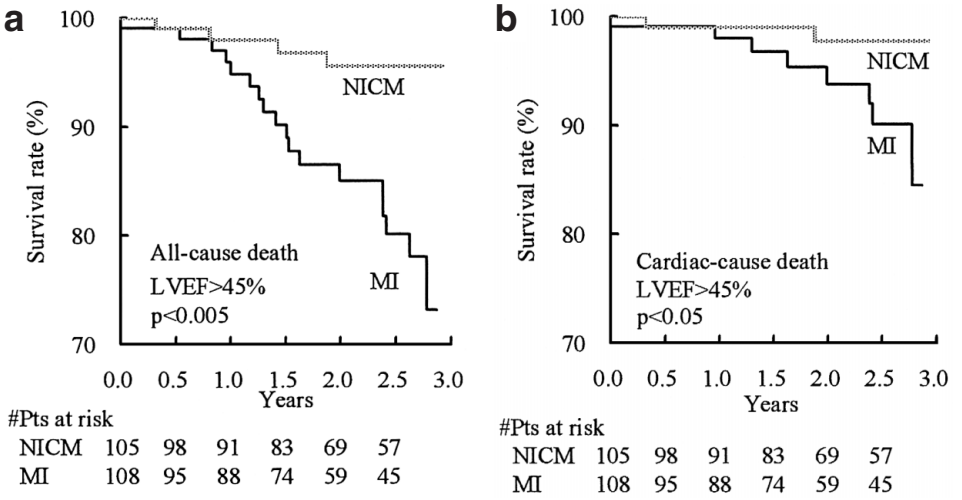

Fig 2. Kaplan-Meier curves of (a) all-cause and (b) cardiac-cause death of the nonischemic cardiomyopathy (NICM) or myocardial infarction (MI) patients with preserved left ventricular ejection fraction (LVEF).

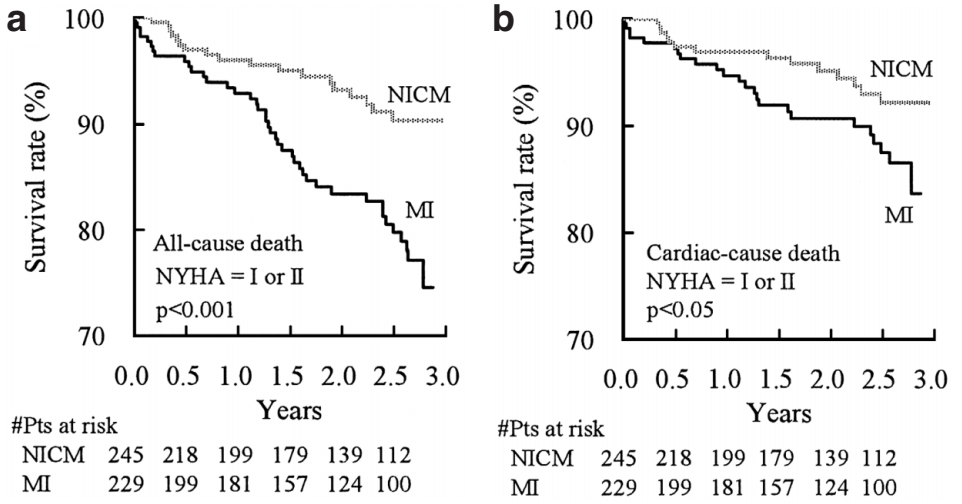

Fig 3. Kaplan-Meier curves of (a) all-cause and (b) cardiac-cause death of the nonischemic cardiomyopathy (NICM) or myocardial infarction (MI) patients with fewer symptoms.

Table 3 Hazard Ratios of MI as an Etiology of CHF Adjusted by Age, Gender, and Treatments

	n	*Endpoint*	*HR (MI vs NICM)*	*95% CI*	*p value*
LVEF >45%	*213*	*All-cause death*	*3.61*	*1.10–11.79*	*0.03*
		Cardiac-cause death	*7.07*	*1.07–46.66*	*0.04*
NYHA I or II	*474*	*All-cause death*	*2.33*	*1.25–4.36*	*0.008*
		Cardiac cause death	*2.01*	*0.96–4.18*	*0.06*

MI, myocardial infarction; CHF, chronic heart failure; HR, hazard ratio; NICM, nonischemic cardiomyopathy; CI, confidence interval; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association functional class.

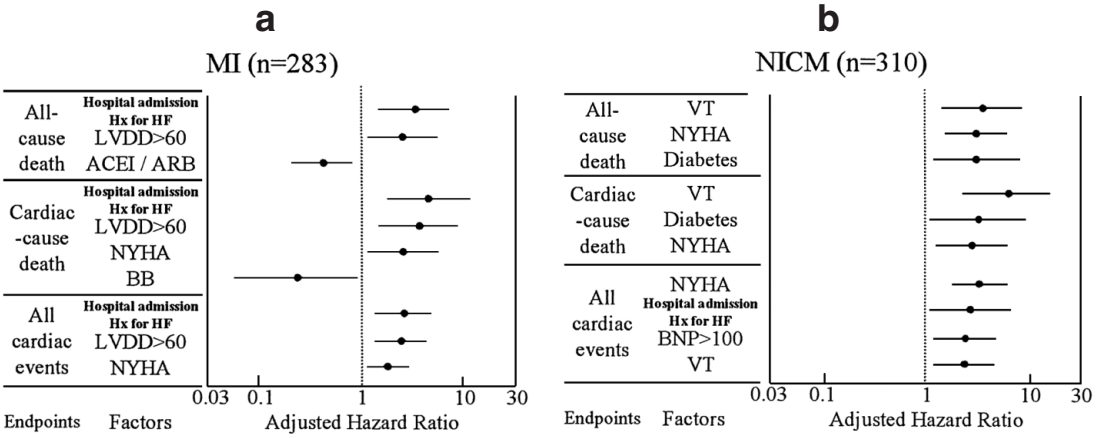

Fig 4. Results of multivariate Cox regression analysis of (a) the myocardial infarction (MI) cohort and (b) the nonischemic cardiomyopathy (NICM) cohort. Hx, history; HF, heart failure; LVDD, left ventricular end-diastolic diameter; NYHA, New York Heart Association functional class; BB, β-blocker; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; VT, ventricular tachycardia; BNP, brain natriuretic peptide.

cohort was significantly more often complicated by diabetes and hyperlipidemia compared with the NICM cohort. Echocardiographic findings revealed that the NICM cohort had a significantly larger LVDD, although there was no difference in LVEF between the 2 cohorts. The history of hospital admission because of congestive heart failure prior to enrollment was more frequently observed in the NICM cohort. The use of BB or ACEI/ARB was significantly less frequent in the MI arm.

Crude Comparison of Prognoses Between the MI and NICM Cohorts

Table 2 shows the numbers of patients who reached the endpoints during the study period. Fig 1 shows the Kaplan-Meier survival analysis of the 2 cohorts. The 3-year all-cause and cardiac-cause mortality rates were significantly higher in the MI cohort (29.0% vs 12.4%, $p<0.0005$ and 19.0% vs 10.0%, $p<0.05$) than in the NICM cohort.

Prognoses of CHF Patients With Preserved LVEF or With Fewer Symptoms

We also performed Kaplan-Meier analysis stratified according to LVEF or New York Heart Association (NYHA) functional class. As shown in Fig 2, the 3-year all-cause and cardiac-cause mortality rates of the MI cohort with preserved LVEF, defined as LVEF >45%, were significantly higher than those of the NICM cohort with preserved LVEF (26.8% vs 4.5%, $p<0.005$ and 15.5% vs 2.3%, $p<0.05$). The incidence of hospital admission because of congestive heart failure prior to the entry was higher in the NICM arm even when we selected patients with LVEF >45% (Table 1). The less symptomatic MI patients, whose NYHA class was I or II at registration, had significantly higher 3-year all-cause and cardiac-cause mortality rates (25.4% vs 9.7%, $p<0.001$ and 16.3% vs 7.7%, $p<0.05$) than the less symptomatic NICM patients (Fig 3). Table 3 shows the results of the Cox regression analysis adjusted by age, gender, and medical treatments including BB or ACEI/ARB. Myocardial infarction as an underlying etiology of CHF was significantly associated with the all-cause and cardiac-cause mortality rates in CHF patients with preserved LVEF in this model (adjusted hazard ratio (HR): 3.61 and 7.07, respectively). Similarly, MI was significantly associated with the all-cause mortality in CHF patients with NYHA I–II symptoms (adjusted HR: 2.33). However, if we included the whole study population, MI as an etiology of CHF was not a significant predictor for the all-cause or cardiac-cause mortality in this adjusted Cox regression model.

Multivariate Cox Regression Analysis

Fig 4 shows the HR and confidence intervals of factors significantly associated with the all-cause mortality, cardiac-cause mortality, and all cardiac events revealed by the Cox proportional hazard model. All covariables used in the model are listed in the Appendix 1 and NYHA class was used as a continuous variable in the analysis. Hospital admissions prior to study entry, increased severity of LV remodeling (shown as LVDD >60 mm), and more severe symptoms related to heart failure are considered to be important risk factors that may exacerbate the prognosis of CHF patients with MI (Fig 4a). In the NICM cohort, ventricular tachycardia (VT) and diabetes were significant predictors. However, LV remodeling was not a significant

factor in the model (Fig 4b).

Impact of Modern Medicine in CHF Patients With MI (Fig 4a)

The multivariate Cox proportional hazard model using all the MI cohort showed that the use of BB was associated with a significant reduction in the cardiac-cause mortality and that the use of ACEI/ARB was significantly related to the improvement of the survival in the MI cohort (adjusted HR: 0.222, p=0.048 and 0.497, p=0.046). Of note, the proportions of patients who were treated by ACEI/ARB or BB were as low as 66.8% and 25.7% in the MI cohort (Table 1).

Discussion

Mortality of Japanese CHF Patients After MI

The present study shows that the 3-year mortality of Japanese CHF patients with an underlying MI is approximately 30%. The Framingham study revealed that the 2-year survival rates of patients who had ischemia as an etiology of heart failure and survived 90 or more days after the onset of heart failure were 64% in men and 75% in women[7] Massie et al reviewed several Western treatment megatrials performed between 1987 and 1995 and showed that ischemic heart disease as an etiology of CHF accounted for 54–74% of the study populations of these trials[8] They also showed that the 3-year mortality rates were approximately 30% in CHF patients treated by ACEI and 40% in CHF patients without ACEI. The mortality rate of patients enrolled in our hospital-based CHF registry appears to be lower than these Western community-based study and treatment trials. However, the MI cohort in the present study included patients whose LVEF was more than 45% (43.5% of all the MI cohort) and less symptomatic patients whose NYHA class was I–II (81.8% of the all MI cohort). We speculate that the mortality of Japanese CHF patients with an underlying MI is comparable with some of the placebo arms in Western treatment trials, although further investigation is necessary.

Prognostic Difference Between the NICM and MI Cohorts

Several studies have shown that CHF caused by NICM has a better prognosis than CHF resulting from MI. Stevenson et al reported that coronary artery disease was an independent predictor for the mortality of patients awaiting heart transplantation[9] Several large treatment trials for CHF also showed that the mortality of the placebo arm was lower in patients with nonischemic CHF than in those with ischemic CHF[10,11] In contrast to the data from clinical trials, the Framingham study suggested that men who develop heart failure as a result of ischemic heart disease survived longer than those with other etiologies[12] Matsumori et al reported that the 1-year all-cause mortality of patients with dilated cardiomyopathy in Japan was 5.6%[13] The present study showed a similar all-cause mortality rate in the NICM cohort of 6.0% at 1 year and 12.4% at 3 years after study entry.

The Kaplan-Meier analysis in the present study revealed that the all-cause mortality and the cardiac-cause mortality were both significantly lower in the NICM arm, although the baseline characteristics were not similar between the 2 arms, as shown in Table 1. Furthermore, the adjusted Cox regression analysis revealed that MI as an etiology of CHF was a significant risk for all-cause/cardiac-cause mortality in the CHF patients with preserved LVEF or fewer symptoms (Table 3). However, this significant impact of ischemic etiology was not observed in the Cox regression models using the total study population including CHF patients with severely impaired LVEF or more severe symptoms.

Diastolic Heart Failure and Prognosis

Chronic heart failure with preserved LVEF is also known as 'diastolic heart failure' (DHF);[14,15] and its prognosis and clinical profile are still controversial. Initially, the prognosis of patients with DHF was considered to be better than that of patients with reduced LVEF;[16] however, more recent studies have suggested that the outcomes may not be different![17] The present study revealed that the prognosis of patients with DHF might differ between patients following MI and those with NICM. However, a precise diagnosis of 'DHF' may not be possible because our database does not include data regarding LV relaxation, filling, diastolic distensibility, or diastolic stiffness. Further investigation is necessary to clarify this matter.

Severe LV Systolic Dysfunction and Prognosis

Many investigators have reported that severe LV systolic dysfunction had a negative impact on the survival of patients with MI![18,19] LVEF was not a significant independent predictor for mortality in the multivariate analysis of the present study. Luchi et al noted that there was a significant relation between mortality and LVEF for medically treated patients, but not for surgically treated patients[20] We speculate that revascularization therapies, including coronary bypass surgery and percutaneous coronary intervention, may have altered the impact of LVEF on the survival of the study population.

Brain Natriuretic Peptide and Prognosis

The plasma concentration of brain natriuretic peptide (BNP) is an important predictor of the prognosis in patients with CHF[21] BNP may also predict mortality from arrhythmic instability as well as that from pump failure[22] The relationship between the plasma BNP concentration and the etiology of CHF is still unknown. The present study showed that the BNP concentration was higher in the MI cohort than in the NICM cohort (Table 1), although there was no significant difference in LVEF between the 2 cohorts and LVDD was significantly larger in the NICM cohort. The real reasons for the higher BNP concentration in the MI cohort are unknown. The higher LV filling pressure in CHF patients with an underlying MI may cause a higher BNP concentration, which predicts poorer prognosis in the MI arm. Furthermore, the mean age of the MI cohort was higher than that of the NICM cohort, which might have caused the elevation of BNP[23]

Multivariate Cox regression model did not show that the plasma BNP concentration was an independent predictor in the MI cohort, even though it was significantly associated with all cardiac events in the NICM cohort (Fig 4). However, the univariate Cox analysis showed that the BNP concentration was significantly associated with the all-cause mortality, cardiac-cause mortality, and all cardiac events in the MI cohort (data not shown). Our previous report using the total population of the CHART registry (n=1,154) showed that the plasma BNP concentration was an independent predictor of all-cause mortality[6] It is possible that the plasma BNP concentration would have

appeared as an independent predictor of prognosis if we had collected a much larger MI cohort sample.

Sudden Death and the MI Cohort

The incidence of sudden death was higher in the MI cohort (Table 2) and VT was an independent predictor of prognosis in the NICM cohort, but not in the MI cohort (Fig 4). Ventricular tachycardia was one of the covariables in the final model selected by the backward stepwise method and its significance levels were 0.071 (HR: 2.009 [0.941–4.287(95% confidence interval)]) in the model when the all-cause mortality was the outcome variable and 0.053 (HR: 2.591 [0.988–6.797]) when the cardiac-cause mortality was the outcome variable. We speculate that VT might have been significant if the study population were much larger.

Potential Causes of the Differences in Prognosis Between the 2 Arms

Follath et al noted that the prognostic difference between ischemic and nonischemic heart failure might result from the manner of diagnosis and patient selection[24] Because several cardiologists were making the diagnosis of NICM or MI in real clinical settings, the true etiology of CHF may not be known with certainty in the present study. Other researchers have reported different effects of drug therapy on morbidity and mortality in ischemic and nonischemic cardiomyopathies;[25–27] which may be one of the reasons for the difference in the prognosis between the 2 arms.

Effect of Modern Medicine

Several treatment mega-trials have reported the significant impact of ACEI/ARB and BB on the prognosis of CHF patients.[28–31] The study population of these trials included various proportions of patients with CHF of an ischemic origin, which fell in the range of 48–71%. Ishikawa et al reported that the use of BB might prevent cardiac events in Japanese patients following MI.[32] We also found that both ACEI/ARB and BB were significantly associated with a better prognosis in CHF patients whose etiology was MI in the real clinical setting. However, the application of these drugs was still low in the present study, as shown in Table 1. We could expect a further improvement in survival if the use of such drugs is appropriately promoted.

Study Limitations

Study Design Our CHF registry, CHART, is hospital-based and many associate cardiologists enrol patients in the registry during their daily medical work. The present study might have erred in its estimation of the real CHF population in Japan, albeit the diagnoses of CHF and its etiology were conducted more correctly than in a community-based study. The study population included asymptomatic patients who were classified as Stage B heart failure, which was introduced by the 2001 ACC/AHA guidelines for CHF. Therefore, we might not be able to compare our result with the mortality of CHF patients diagnosed on the basis of traditional criteria of heart failure.

Impact of Revascularization Following Acute MI Recent advances in reperfusion therapy after acute MI have reduced the risk of LV remodeling and dysfunction, both of which may result in the development of CHF. An improvement in LV function may occur in both the early and chronic stages after acute MI and may be influenced by pharmacological or mechanical therapies.[18,19,33] CHART does not include information regarding reperfusion therapies or additional percutaneous/surgical interventions. Although we could not evaluate the impact of such revascularization strategies, the present study mainly discusses the prognoses of patients who were already diagnosed as having CHF resulting from MI.

Conclusion

An underlying MI poses a significant risk for survival of Japanese CHF patients, especially those with preserved LVEF or with fewer symptoms. The benefits of modern treatments for CHF patients following MI were verified in the 'real world' of the clinical situation. The penetration of the new drugs appeared to be poor in Japan, particularly BB. Increased use of BB and ACEI/ARB will further improve the prognosis of CHF patients after MI.

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Appendix 1

Independent covariables used in the multivariate Cox proportional hazard model: gender, a history of hospital admission because of congestive heart failure with hemodynamic decompensation prior to study entry, hypertension, diabetes, ventricular tachycardia, the plasma concentration of BNP >100 pg/ml, NYHA functional class, use of BB or ACEI/ARB, atrial fibrillation, age >60 years old, LVDD >60 mm, LVEF ≤45%.