Circulation Journal
Official Journal of the Japanese Circulation Society
http://www.j-circ.or.jp

ORIGINAL ARTICLE
Myocardial Disease

Improved Long-Term Prognosis of Dilated Cardiomyopathy With Implementation of Evidenced-Based Medication

– Report From the CHART Studies –

Ryoichi Ushigome, MD; Yasuhiko Sakata, MD, PhD; Kotaro Nochioka, MD, PhD; Satoshi Miyata, PhD; Masanobu Miura, MD, PhD; Soichiro Tadaki, MD; Takeshi Yamauchi, MD; Kenjiro Sato, MD; Takeo Onose, MD; Kanako Tsuji, MD; Ruri Abe, MD; Jun Takahashi, MD, PhD; Hiroaki Shimokawa, MD, PhD on behalf of the CHART-2 Investigators

Background: Recent trends in the clinical characteristics, management and prognosis of dilated cardiomyopathy (DCM) remain to be examined in Japan.

Methods and Results: We compared 306 and 710 DCM patients in the Chronic Heart Failure Analysis and Registry in the Tohoku District (CHART)-1 (2000–2005, n=1,278) and the CHART-2 (2006–present, n=10,219) Studies, respectively. Between the 2 groups of DCM patients, there were no significant differences in baseline characteristics. The prevalence of hypertension, dyslipidemia and diabetes mellitus were all significantly increased from the CHART-1 to the CHART-2 Study. The use of β-blockers and aldosterone antagonists was significantly increased, while that of loop diuretics and digitalis was significantly decreased in the CHART-2 Study. The 3-year mortality rate was significantly improved from 14% in the CHART-1 to 9% in the CHART-2 Study (adjusted HR, 0.60; 95% CI: 0.49–0.81; P=0.001). In particular, 3-year incidence of cardiovascular death was significantly decreased (adjusted HR, 0.26; 95% CI: 0.14–0.50, P<0.001), while that of HF admission was not (adjusted HR, 0.90; 95% CI: 0.59–1.37, P=0.632). The prognostic improvement was noted in patients with BNP <220 pg/ml, LVEF>40%, β-blocker use and aldosterone antagonist use.

Conclusions: Long-term prognosis of DCM patients has been improved, along with the implementation of evidence-based medication in Japan. (*Circ J* 2015; **79:** 1332–1341)

Key Words: Beta-blocker; Dilated cardiomyopathy; Lifestyle disease; Prognosis

Idiopathic dilated cardiomyopathy (DCM) is a disorder of the heart muscle in which the heart chambers are progressively enlarged or dilated.[1–3] The nationwide survey by the Japanese Ministry of Health, Labour and Welfare reported that the number of DCM patients in Japan was estimated to be 17,700 with a prevalence of 140/million in 1999.[4] Fuster et al reported that mortality in idiopathic DCM patients was 77% over 11 years between 1960 and 1973, while most of the deaths occurred during the first 2 years after diagnosis.[1] Recently, Merlo et al reported that an evidence-based therapeutic approach has improved the long-term prognosis of idiopathic DCM in the last 3 decades.[5] In Japan, it was reported that 5-year survival rate in idiopathic DCM improved from 62% in the 1980s to 90% in the 1990s.[6]

From 2000 to 2005, we conducted a multicenter prospective cohort of chronic heart failure (CHF) patients, named the Chronic Heart Failure Analysis and Registry in the Tohoku District-1 (CHART-1, n=1,278).[7,8] The CHART-1 Study found that the prognosis of CHF patients in Japan was equally poor compared with those in Western countries.[7,8] In 2006, we started the CHART-2 Study to elucidate the characteristics and prognosis of CHF patients in stages B–D.[8,9] In the CHART Studies, we reported that the use of renin angiotensin system inhibitors (RASI) and β-blockers for CHF patients was significantly increased, whereas that of loop diuretics and digitalis had decreased in the past years.[8,9] Recent trends in the clinical characteristics, management and prognosis of DCM patients in Japan, however, remain to be examined. In the present

Received August 24, 2014; revised manuscript received January 29, 2015; accepted February 16, 2015; released online April 2, 2015 Time for primary review: 36 days

Department of Cardiovascular Medicine (R.U., Y.S., K.N., M.M., S.T., T.Y., K.S., T.O., K.T., R.A., J.T., H.S.), Department of Evidence-based Cardiovascular Medicine (S.M., H.S.), Tohoku University Graduate School of Medicine, Sendai, Japan

The Guest Editor for this article was Hiroshi Ito, MD.

Mailing address: Yasuhiko Sakata, MD, PhD, Department of Cardiovascular Medicine, Tohoku University Graduate School of Medicine, 1-1 Seiryo-machi, Aoba-ku, Sendai 980-8574, Japan. E-mail: sakatayk@cardio.med.tohoku.ac.jp

ISSN-1346-9843 doi:10.1253/circj.CJ-14-0939

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

study, we thus examined the recent trends in baseline characteristics, treatment and long-term prognosis of DCM patients, by comparing the CHF database between the CHART-1 and CHART-2 Studies.

Methods

Study Design and Subjects

In the present study, a total of 1,016 DCM patients were enrolled from the database of the CHART-1 and the CHART-2 Studies (306 and 710 patients from the CHART-1 and CHART-2 Studies, respectively).[7–9] Both Studies are multicenter, prospective, hospital-based observational cohort studies of Japanese CHF patients. The CHART-1 Study was conducted between February 2000 and December 2005 and a total of 1,278 patients with CHF from the 26 hospitals (Tohoku University hospital and 25 affiliated hospitals) were enrolled.[7,8] The purpose of the CHART-1 Study was to elucidate the clinical characteristics, treatment and prognosis in Japanese CHF patients.[7,8] All patients had a structural disorder of the heart and were treated with standard therapy for CHF, including diuretics, digitalis, angiotensin-converting enzyme inhibitor, angiotensin receptor blocker and β-blocker. In 2006, we started the CHART-2 Study and successfully enrolled 10,219 consecutive patients, including 5,483 cardiovascular patients at high risk for development of HF (coronary artery disease or stage B)[10] and 4,736 patients with symptomatic CHF (stages C/D)[10] in the 24 hospitals (Tohoku University hospital and 23 affiliated hospitals). Tohoku University Hospital and 14 hospitals participated in both the CHART-1 and CHART-2 Studies, accounting for 74.0% and 75.8% of the total subjects enrolled, respectively. No patients enrolled in the CHART-1 Study were included in the CHART-2 Study. Diagnosis of CHF was based on the Framingham criteria,[11] while CHF stage was classified according to the ACCF/AHA HF Guidelines.[10]

The CHART-1 Study was approved by the committee of Tohoku University Hospital. The CHART-2 Study was approved by the human research committee of Tohoku University School of Medicine (conforming to the ethics guidelines of the 1975 Declaration of Helsinki), and also by the local ethics committee in each participating hospital and registered at Clinical Trials.gov (NCT00418041). Written informed consent was provided by all patients before enrollment. Information on medical history and baseline demographics, including medication and echocardiographic data, were collected at the time of enrollment by clinical research coordinators.

Definition of DCM

DCM was diagnosed by the attending physicians and/or the investigators at each hospital, based on the definition of DCM in the guidelines of the Japanese Circulation Society.[9] Briefly, DCM was diagnosed when a patient had global systolic dysfunction with dilated left ventricle (LV) after exclusion of known cardiac diseases, including ischemic cardiomyopathy, hypertensive heart disease, dilated phase of hypertrophic cardiomyopathy, cardiac sarcoidosis, myocarditis, amyloidosis, arrhythmogenic right ventricular cardiomyopathy, beriberi heart, alcoholic cardiomyopathy, non-compaction of ventricular myocardium, cardiomyopathy caused by muscular dystrophy, mitochondrial myopathy, chemical toxic cardiomyopathy, Fabry's disease, and postpartum cardiomyopathy.[9,12] Coronary angiography data were available in 98% of the patients enrolled from the CHART-2 study, in which absence of coronary artery stenosis was confirmed. No patients enrolled from the CHART-1 study had coronary angiography data in the database.[7,8]

Subjects

In the CHART-1 Study (n=1,278), 24 patients with missing data were excluded. Of these 1,254 patients, 306 patients (24.4%) were diagnosed as having DCM in the CHART-1 Study. In the CHART-2 Study (n=10,219), 5 patients with missing data were initially excluded. To make the selection bias minimal, we first selected patients from the CHART-2 Study according to the inclusion criteria of the CHART-1 Study. As a result, we selected 5,920 patients who met at least one of the following CHART-1 criteria: (1) LV ejection fraction (LVEF) <50%; (2) LV end-diastolic diameter (LVDd) ≥55 mm; or (3) at least one episode of congestive heart failure. From this population, 710 DCM patients (11.0%) were finally enrolled from the CHART-2 study. Finally, 306 and 710 DCM patients were enrolled from the CHART-1 and CHART-2 Studies, respectively.

Outcomes

The study endpoints were 3-year mortality, mode of death and 3-year hospitalization for worsening HF. Cardiovascular death was defined as death due to cardiovascular origins. Non-cardiovascular death was defined as death due to non-cardiovascular causes. For all patients, only the main mode of death was used. Hospitalization for worsening HF was defined as documentation of worsening HF requiring hospitalization. A patient admitted for worsening HF had to show signs and symptoms of HF and to require treatment with i.v. diuretics. Follow-up was made at least once a year by clinical research coordinators by means of review of medical records, surveys and telephone interviews.[8,9] All events were reviewed and assigned on consensus of at least 2 independent physicians from the members of the Tohoku Heart Failure Association, by reviewing case reports, death certificates, medical records and hospital course summaries provided by the investigators.

Statistical Analysis

Continuous variables are expressed as mean±SE or median (IQR), as appropriate. Discrete variables are expressed as n (%). Wilcoxon rank sum and Fisher's exact test were used to compare the characteristics between patients from the CHART-1 and CHART-2 Studies. Kaplan-Meier curves were plotted to evaluate the association between DCM and all-cause death, cardiovascular death or hospitalization for worsening HF. Comparison of the survival time between the 2 groups was performed using log-rank test. Multivariate Cox proportional hazards model was used to analyze the relationship between survival and prognostic indices. The covariates were selected as follows: first, the univariate Cox models were fitted for each of the CHART-1 and the CHART-2 patients separately, with candidate variables of sex, age, body mass index (BMI), systolic blood pressure, diastolic blood pressure, heart rate, New York Heart Association (NYHA) class, LVEF, LVDd, diabetes mellitus, dyslipidemia, atrial fibrillation, ventricular tachycardia, brain natriuretic peptide (BNP), estimated glomerular filtration rate (eGFR), β-blocker, RASI, aldosterone antagonist, and Ca channel blocker. Then, after the multivariate Cox models were fitted for each of the CHART-1 and the CHART-2 samples individually, using all the covariates with P<0.2 in each univariate model, the optimal subset of covariates was selected by stepwise backward elimination in each model. Finally, all the variables selected in either or both models were used as the final set of variables for the final

Table 1. Baseline DCM Patient Characteristics

	Total (n=1,014)		
	CHART-1 (n=306)	CHART-2 (n=710)	P-value
Age (years)	61.7±0.8	62.9±0.5	0.205
Male sex	222 (72.5)	517 (72.8)	0.939
Blood pressure (mmHg)			
Systolic	122.8±1.3	120.5±0.7	0.126
Diastolic	73.3±0.8	72.5±0.5	0.463
Heart rate (beats/min)	73.1±1.0	73.0±0.6	0.934
BMI (kg/m²)	23.4±0.3	23.5±0.2	0.787
NYHA classification			<0.001
I	40 (13.1)	135 (19.0)	
II	206 (67.3)	499 (70.4)	
III	57 (18.6)	71 (10.0)	
IV	3 (1.0)	4 (0.6)	
Laboratory data			
Hb (g/dl)	13.7±0.1	13.8±0.1	0.873
Anemia	77 (26.7)	159 (22.6)	0.164
BUN (mg/dl)	20.6±1.0	19.1±0.3	0.065
Cre (mg/dl)	1.03±0.06	1.00±0.03	0.651
eGFR (ml/min/1.73 m²)	67.7±1.4	66.4±0.9	0.451
BNP (pg/ml)	101.0 (41.3–259.5)	103.6 (42.9–254.6)	0.969
Echocardiography			
LVEF (%)	42.6±0.7	44.9±0.5	0.014
LVEF ≤40%	129 (42.6)	272 (38.6)	0.262
LVDd (mm)	61.1±0.5	58.8±0.3	<0.001
LVDs (mm)	48.8±0.5	46.0±0.4	<0.001
Comorbidity			
Hypertension	116 (37.9)	473 (66.7)	<0.001
Dyslipidemia	39 (12.7)	490 (69.0)	<0.001
Diabetes mellitus	43 (14.1)	145 (20.4)	0.017
Atrial fibrillation	107 (35.0)	292 (41.3)	0.059
Ventricular tachycardia	61 (19.9)	105 (14.8)	0.052
Medicine			
RASI	245 (80.1)	605 (82.5)	0.052
ACEI	203 (66.3)	407 (57.3)	0.008
ARB	48 (15.7)	222 (31.3)	<0.001
β-blockers	147 (48.0)	567 (79.9)	<0.001
Loop diuretics	213 (74.7)	449 (63.2)	<0.001
Digitalis	164 (55.8)	254 (35.8)	<0.001
Aldosterone antagonists	58 (20.2)	262 (36.9)	<0.001
Ca channel blockers	43 (14.6)	98 (13.8)	0.765
ICD/CRT-D	2 (0.7)	34 (4.8)	0.001

Data given as mean±SE, median (IQR) or n (%). ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body-mass index; BNP, brain natriuretic peptide; Ca, calcium; CRT-D, cardiac resynchronization therapy defibrillator; DCM, dilated cardiomyopathy; eGFR, estimated glomerular filtration rate; HF, heart failure; ICD, implantable cardioverter defibrillator; LVDd, left ventricular end-diastolic diameter; LVDs, left ventricular end-systolic diameter; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; RASI, renin angiotensin system inhibitor.

multivariate model. In the Cox models, we used the following covariates as binary variables: age (<70 and ≥70 years), LVEF (≤40 and >40%), BNP (<220 and ≥220 pg/ml), eGFR (≤50 and >50 ml/min/1.73 m²) and BMI (<18.5 and ≥18.5 kg/m²).[13] The split values of age, LVEF, BNP and eGFR were determined using classification and regression tree (CART) analysis.[14–17] We examined the associations between β-blocker or aldosterone blocker use and outcomes with inverse probability of treatment weighting (IPTW) using the propensity score.[18] In IPTW analysis, we used propensity score calculated with the following covariates: sex, systolic blood pressure, diastolic blood pressure, heart rate, LVDd, history of HF admission, hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, calcium channel blocker, RASI, loop diuretics, aldosterone antagonist, age, BNP, and eGFR. Two-sided P<0.05 was considered to be statistically significant. Interactions between

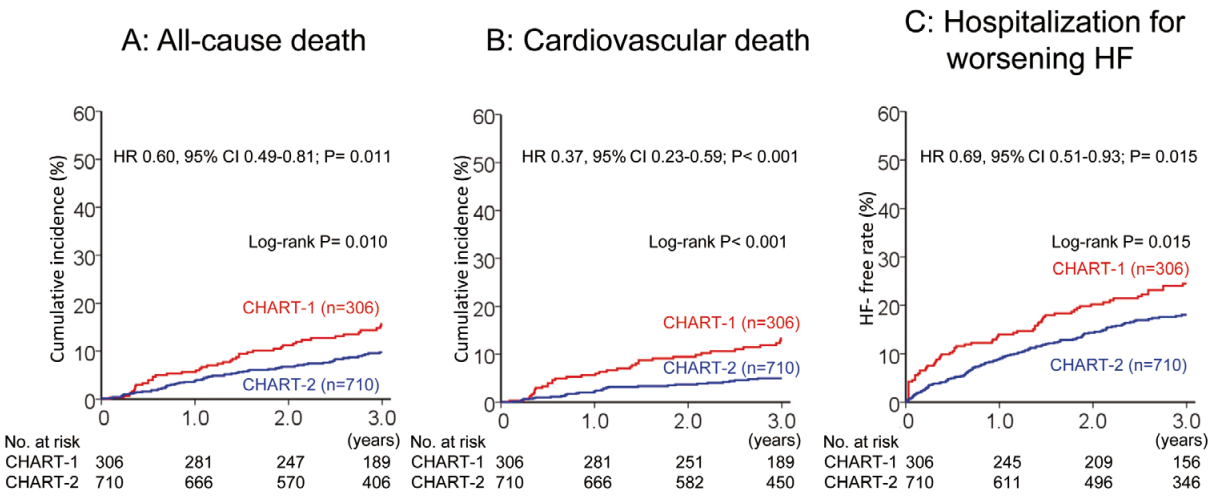

Figure 1. Kaplan-Meier survival curves for (**A**) all-cause death, (**B**) cardiovascular death and (**C**) hospitalization for worsening heart failure (HF).

several covariates were estimated using the Cox proportional hazard model, including interaction terms using the same variables chosen with the stepwise method. P-value for interaction <0.1 was considered to be statistically significant. All calculations were performed using SPSS 22.0 for Windows and R version 3.0.2.

Results

Baseline DCM Patient Characteristics

There were no significant differences in age, prevalence of male sex, heart rate, blood pressure or any other laboratory findings between the CHART-1 and the CHART-2 Studies (Table 1). In the echocardiography data, LVEF was more preserved and LVDd and LV end-systolic diameter were smaller in the CHART-2 patients. The prevalence of hypertension, dyslipidemia and diabetes mellitus was all increased from CHART-1 to CHART-2. While RASI use was similar at enrollment, the use of β-blockers and aldosterone antagonists was increased and use of loop diuretics and digitalis was decreased in CHART-2. Implantable cardioverter defibrillator/cardiac resynchronization therapy defibrillator (ICD/CRT-D) were more frequently used in CHART-2.

Incidence of Death and HF in DCM Patients

A total of 106 patients died during the 3-year follow-up (44 in CHART-1 and 62 in CHART-2). Crude 3-year mortality was significantly decreased from 14% in CHART-1 to 9% in CHART-2 (hazard ratio [HR], 0.60; 95% CI: 0.49–0.81, P=0.011; Figure 1A). Three-year cardiovascular death rate was also improved from 12% (n=32) in CHART-1 to 4.5% (n=37) in CHART-2 (HR, 0.37; 95% CI: 0.23–0.59, P<0.001; Figure 1B). Hospitalization for worsening HF was noted in 184 patients (69 in CHART-1 and 115 in CHART-2). Three-year HF admission rate was significantly decreased from 23% in CHART-1 to 16% in CHART-2 (HR, 0.69; 95% CI: 0.51–0.93, P=0.015; Figure 1C). After adjustment of the following variables, including systolic blood pressure, hypertension, age, LVEF, BNP, BMI, eGFR, β-blocker, and aldosterone antagonist, HR for each category was as follows: all-cause death, HR=0.60 (95% CI: 0.34–1.04, P=0.069), cardiovascular death, HR=0.26 (95% CI: 0.14–0.50, P<0.001) and HF admission, HR=0.90 (95% CI: 0.59–1.37, P=0.632).

Mode of Death in DCM Patients

Among the total 44 deaths in the CHART-1 Study, there were 37 cardiovascular deaths (84.1%) and 5 non-cardiovascular deaths (11.4%; Figure 2). The causes of the remaining 2 deaths were unknown. Among the total 62 deaths in CHART-2, 32 (51.6%) were cardiovascular deaths and 23 (37.1%) were non-cardiovascular deaths, while the causes of the remaining 7 deaths were unknown. Among the cardiovascular deaths, sudden death rate was significantly decreased from 5.2% in CHART-1 to 0.4% in CHART-2 (P<0.001). Incidence of death due to HF (from 5.6% to 3.2%, P=0.062) and stroke (from 1.0% to 0.4%, P=0.257) was non-significantly decreased, whereas non-cardiovascular death rate tended to increase (from 1.6% to 3.2%, P=0.107).

Predictors of All-Cause Death

Table 2 list the results of the multivariate Cox proportional hazard model for all-cause death. In CHART-1, 4 variables (age >70 years, NYHA III/IV, BNP ≥220 pg/ml and aldosterone antagonist) were selected using the stepwise multivariate Cox model, in which BNP ≥220 pg/ml and the use of aldosterone antagonist were significantly associated with all-cause death (Table 2A). In CHART-2, 7 variables (hypertension, age >70 years, LVEF ≤40%, BNP ≥220 pg/ml, BMI <18.5 kg/m^2, eGFR ≤50 ml/min/1.73 m^2 and β-blocker) were selected, and hypertension, age >70 years, LVEF ≤40%, BNP ≥220 pg/ml and β-blocker were significantly associated with all-cause death. The final model identified several factors that were significantly associated with decreased incidence of 3-year death, including NYHA III/IV, age ≥70 years, BNP ≥220 pg/ml, BMI <18.5 kg/m^2 and use of aldosterone antagonist in the CHART-1 Study, and age ≥70 years, BNP ≥220 pg/ml, eGFR <50 ml/min/1.73 m^2, and LVEF ≤40% in the CHART-2 study (Table 2B). We further examined the differences in 3-year

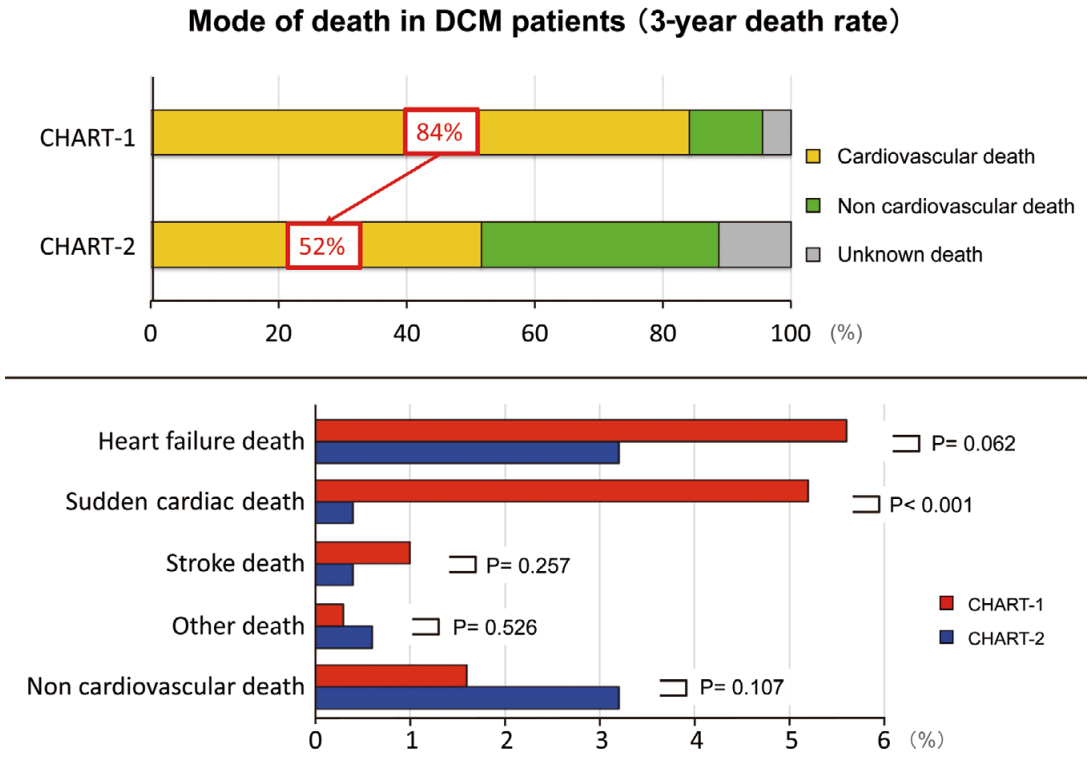

Figure 2. Mode of death in dilated cardiomyopathy (DCM) patients (3-year death rate).

Table 2. Prognostic Factors of All-Cause Death in DCM Patients

All-cause death (3-year death)	CHART-1			CHART-2		
	HR	95% CI	P-value	HR	95% CI	P-value
A. Multivariate Cox models by using stepwise method						
Age ≥70 years	2.25	1.01–4.98	0.046	1.85	1.06–3.25	0.032
BNP <220 pg/ml	0.37	0.16–0.84	0.017	0.21	0.11–0.40	<0.001
Aldosterone antagonists	4.64	2.15–9.99	<0.001			
NYHA III/IV	2.21	0.94–5.18	0.068			
Hypertension				0.48	0.28–0.84	0.010
LVEF >40%				0.49	0.27–0.91	0.023
BMI <18.5 kg/m^2				1.89	0.90–3.99	0.094
eGFR ≤50 ml/min/1.73 m^2				1.72	0.95–3.12	0.072
β-blockers				0.34	0.19–0.61	<0.001
B. Multivariate Cox models						
Hypertension	0.82	0.39–1.72	0.604	0.52	0.30–0.91	0.021
NYHA III/IV	2.47	1.12–5.43	0.024	1.19	0.63–2.27	0.587
Age ≥70 years	2.72	1.32–5.58	0.006	1.81	1.04–3.16	0.037
BMI <18.5 kg/m^2	0.12	0.02–0.91	0.040	1.94	0.92–4.11	0.082
BNP <220 pg/ml	0.39	0.18–0.85	0.018	0.22	0.12–0.41	<0.001
eGFR ≤50 ml/min/1.73 m^2	1.81	0.86–3.80	0.116	1.83	1.01–3.33	0.047
LVEF >40%	1.12	0.54–2.38	0.749	0.52	0.28–0.97	0.040
β-blockers	0.87	0.42–1.86	0.700	0.35	0.19–0.64	0.001
Aldosterone antagonists	3.18	1.59–6.35	<0.001	1.34	0.78–2.31	0.295

HR, hazard ratio. Other abbreviations as in Table 1.

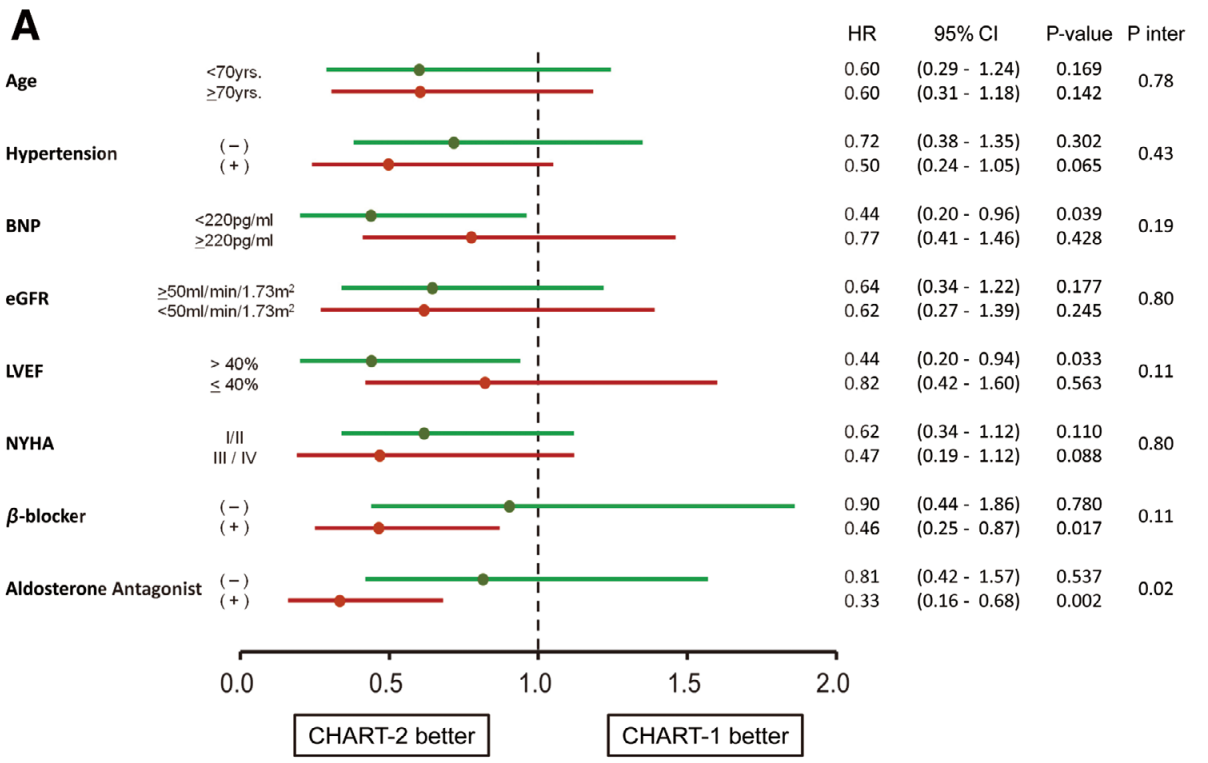

Figure 3. Forest plots for (**A**) overall survival and (**B**) incidence of heart failure in each subgroup (multivariate Cox proportional hazard model). BNP, brain natriuretic peptide; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

Table 3. Prognostic Impact of Medications in DCM Patients

All-cause death (3-year death)	HR	95% CI	P-value
A. β-blockers			
All patients (n=1,016)			
Overall	0.59	0.41–0.88	0.009
IPTW	0.65	0.48–0.89	0.007
CHART-1 (n=306)			
Overall	0.94	0.52–1.70	0.838
IPTW	1.42	0.78–2.59	0.254
CHART-2 (n=710)			
Overall	0.52	0.30–0.88	0.015
IPTW	0.61	0.42–0.87	0.006
B. Aldosterone antagonists			
All patients (n=1,016)			
Overall	1.75	1.20–2.57	0.004
IPTW	1.62	1.19–2.20	0.002
CHART-1 (n=306)			
Overall	3.28	1.81–5.96	<0.001
IPTW	4.55	2.44–8.47	<0.001
CHART-2 (n=710)			
Overall	1.45	0.88–2.39	0.144
IPTW	1.20	0.83–1.72	0.332

DCM, dilated cardiomyopathy; IPTW, inverse probability weighting.

mortality between CHART-1 and CHART-2 in the subgroups according to the cut-offs used in the Cox model. As a result, 3-year survival was better in CHART-2 in patients with BNP <220 pg/ml, LVEF >40%, using β-blockers and aldosterone antagonists (Figures S1,3A). In contrast, the incidence of HF hospitalization was similar between the CHART-1 and the CHART-2 Studies except for patients with reduced eGFR (Figure 3B).

On IPTW analysis using the propensity score, β-blocker use was independently associated with a lower mortality in the total population (HR, 0.65; 95% CI: 0.48–0.89; P=0.007) and in 710 patients from the CHART-2 Study (HR, 0.61; 95% CI: 0.42–0.87; P=0.006), but not in 306 patients from the CHART-1 Study (HR, 1.42; 95% CI: 0.78–2.59; P=0.254; Table 3A). In contrast, on IPTW analysis, aldosterone use was associated with increased mortality in the total population and in the CHART-1 Study, but not in the CHART-2 Study (Table 3B). In patients with LVEF >40%, IPTW analysis suggested no prognostic effect of β-blocker use in both the CHART-1 and the CHART-2 Studies (P-value for interaction=0.68), while in patients with LVEF ≤40%, β-blocker use was associated with better survival in the CHART-2, but not in the CHART-1 Study (P-value for interaction <0.01; Figure 4). IPTW analysis also suggested the prognostic benefits of β-blocker use in the CHART-2, but not in the CHART-1, Study, regardless of subgroup classification according to BNP level or aldosterone antagonist use (Figure 4).

Discussion

The novel findings of the present study are that (1) 3-year mortality of Japanese DCM patients has recently improved; (2) evidence-based medication for CHF has been implemented in Japan; (3) prevalence of lifestyle comorbidities (eg, hypertension, hyperlipidemia and diabetes mellitus) has been increasing in Japanese DCM patients; and (4) improvement in long-term prognosis of DCM patients was noted in the patients with BNP <220 pg/ml, LVEF >40%, β-blocker use and aldosterone antagonist use.

Improved Long-Term Prognosis of Japanese DCM Patients

The present study demonstrates that the crude 3-year incidence of all-cause death, cardiovascular death and admission for HF were all significantly decreased in the CHART-2 Study compared with the CHART-1 Study. In particular, 3-year mortality was decreased by approximately 40%, from 14% (4.6%/year) in the CHART-1 to 9% (3%/year) in the CHART-2 Study. Indeed, evidence-based medication for CHF has been implemented in Japan with the resultant improvement in long-term prognosis. The prescription rates of RASI, β-blockers and aldosterone antagonists were all increased in the CHART-2 compared with the CHART-1 Study. Thus, it is possible that the implementation of these evidence-based medications has contributed to the improvement of long-term mortality of DCM patients in the present study. This trend, along with increased use of RASI and β-blockers, is consistent with the previous report that 5-year mortality of DCM patients was decreased from 41% (8%/year) in 1982–1989 to 19% (3.8%/year) in 1990–2002 in Japan.[2] The present study further demonstrates that the trend of improvement in long-term prognosis of DCM patients has continued in the last 10 years in Japan.

Factors Contributing to Improvement of Long-Term Prognosis

In the present study with DCM patients, the CHART-2 patients had better clinical background, including LV function, compared with the CHART-1 patients, which might have contributed in part to the improved prognosis of the CHART-2 patients. Indeed, after adjustment for clinical background selected in the stepwise Cox regression analysis, the decreased incidence of all-cause death and HF admissions in the CHART-2 Study became insignificant, although there was a

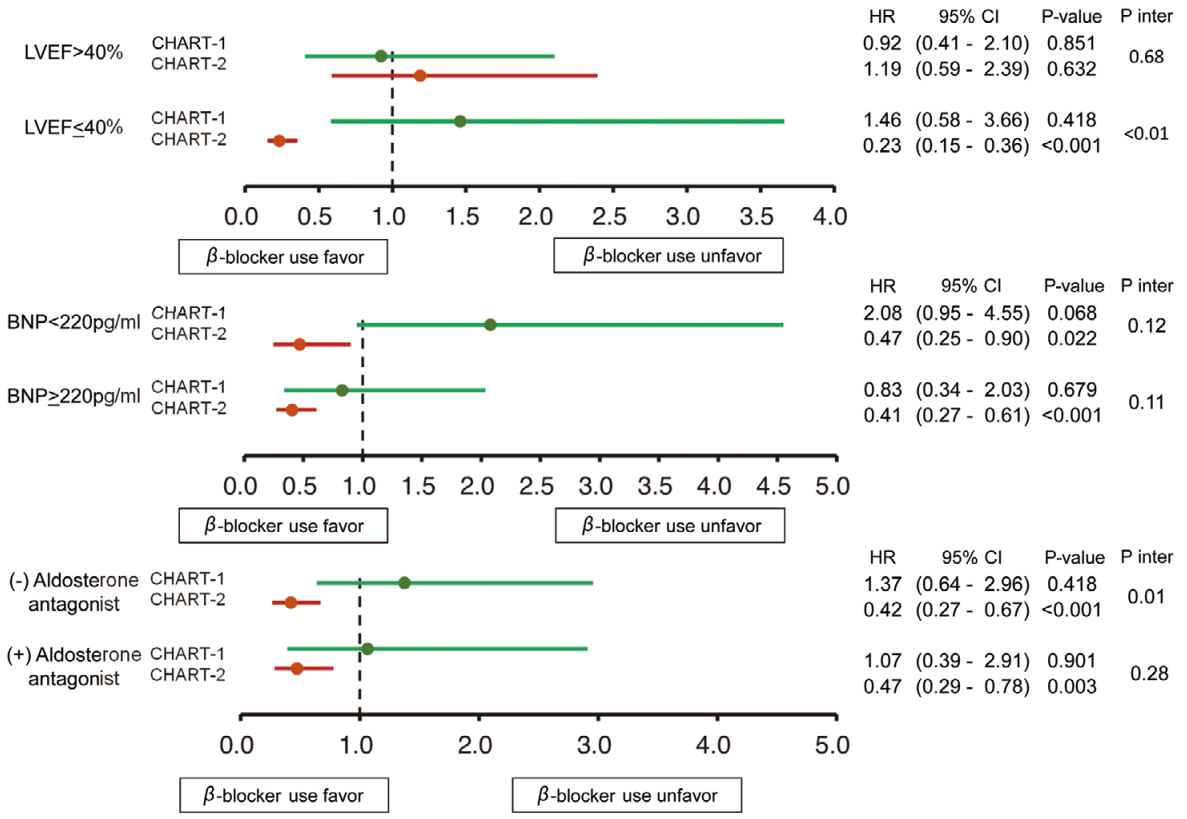

Figure 4. Inverse probability of treatment weighting analysis for each subgroup. BNP, brain natriuretic peptide; LVEF, left ventricular ejection fraction.

tendency for improved all-cause death (adjusted HR, 0.61; P=0.054) and the decreased incidence of cardiovascular death remained significant even after the adjustment (adjusted HR, 0.29; P<0.001). This finding, however, could be explained by the benefits of implementation of evidence-based medication, particularly, by that of β-blockers. In the present study, the use of β-blockers was markedly increased from 49% in CHART-1 to 81% in CHART-2, and the DCM patients treated with β-blockers had a better prognosis than those without them. Furthermore, the decrease in all-cause mortality was mainly associated with a decrease in cardiovascular death, specifically sudden death, supporting the notion that β-blockers were effective in improving the long-term prognosis of DCM patients in the present study. This is consistent with the previous reports that β-blockers improved LVEF and all-cause mortality in patients with CHF.[19–22] In addition, it is speculated that not only the prescription rates but also the dose of β-blockers was increased from the CHART-1 to the CHART-2 Studies, resulting in reduced mortality. Furthermore, it is conceivable that ICD/CRT-D treatment also played a significant role in preventing sudden cardiac death in the CHART-2 Study, although it is difficult to demonstrate its efficacy due to the small number of patients treated with ICD/CRT-D in the present study.

Subgroups With Improved Long-Term Prognosis

The present study demonstrated that the long-term prognosis of DCM patients was improved in several subgroups. In particular, the improvement was noted in patients with LVEF >40%, but not in those with LVEF ≤40%. It is difficult to explain the reason for this finding with regard to β-blocker use, because on IPTW analysis β-blockers improved prognosis over time from CHART-1 to CHART-2 in patients with LVEF ≤40% but not in those with LVEF >40%. This finding, however, is consistent with the previous findings that in-hospital mortality was improved over time between 2005 and 2010 in HF patients with preserved LVEF, but not in those with reduced LVEF,[23] and that HF patients with recovered LVEF had better prognosis than those with reduced LVEF or near-normal LVEF.[24,25] Furthermore, the present study also showed that the improvement was noted in the subgroup with BNP <220 pg/ml and that with aldosterone antagonist use. Interestingly, β-blocker use was associated with improved mortality in these subgroups, but not in those with BNP ≥220 pg/ml or those without aldosterone antagonist use, although the P-values for interaction were not significant. Thus, appropriate use of β-blockers might have played a role in the improvement of mortality in patients with BNP <220 pg/ml and in those with aldosterone antagonist use.

Increase in Lifestyle-Related Comorbidities

Another novel finding of the present study is that the prevalence of lifestyle-related comorbidities (eg, hypertension, dyslipidemia and diabetes mellitus) was increased from the

CHART-1 to the CHART-2 Study. The recent trend of westernization of clinical background in overall CHF patients in Japan has been previously reported,[7,9] and lifestyle-related diseases are emerging as comorbidities in DCM patients in Japan. Given that hypertension, dyslipidemia and diabetes are all recognized as coronary risk factors, this suggests that ischemic heart disease may stand out as one of the main causes of mortality and morbidity in DCM patients in the near future. Thus, more attention should be paid to the prevention of coronary artery disease through management of lifestyle-related comorbidities in current DCM practice.

Study Limitations

Several limitations should be mentioned for the present study. First, given that both the CHART-1 and CHART-2 Studies are prospective observational studies in the Tohoku district of Japan, we need to be cautious when extrapolating the present findings to other cohorts, particularly to those in other countries. Second, the diagnosis, evaluation, and management of DCM were made in each participating hospital, and thus there could be a selection and/or other bias in the present study. Finally, the number of the patients enrolled from the CHART-1 Study was relatively small, which might have limited the power to identify significant observations.

Conclusions

Three-year mortality of DCM patients has been significantly improved along with the implementation of evidence-based medication in Japan. Subgroup analysis, however, suggested that the improvement was concentrated in the subgroups with BNP <220 pg/ml, LVEF >40%, β-blocker use and aldosterone antagonist use.

Acknowledgments

We thank all members of the Tohoku Heart Failure Society and staff of the Department of Evidence-based Cardiovascular Medicine for their kind contributions (**Appendix**). This study was supported by Grants-in-Aid from a Research Grant from the Ministry of Health, Labour, and Welfare (Y.S., H.S.).

Disclosures

Conflict of Interest: The Department of Evidence-based Cardiovascular Medicine, Tohoku University Graduate School of Medicine, is supported in part by unrestricted research grants from Daiichi Sankyo (Tokyo, Japan), Bayer Yakuhin (Osaka, Japan), Kyowa Hakko Kirin (Tokyo, Japan), Kowa Pharmaceutical (Tokyo, Japan), Novartis Pharma (Tokyo, Japan), Dainippon Sumitomo Pharma (Osaka, Japan), and Nippon Boehringer Ingelheim (Tokyo, Japan). H.S. has received lecture fees from Bayer Yakuhin (Osaka, Japan), Daiichi Sankyo (Tokyo, Japan) and Novartis Pharma (Tokyo, Japan).

References

1. Fuster V, Gersh BJ, Giuliani ER, Tajik AJ, Brandenburg RO, Frye RL. The natural history of idiopathic dilated cardiomyopathy. *Am J Cardiol* 1981; **47:** 525–531.
2. Matsumura Y, Takata J, Kitaoka H, Kubo T, Baba Y, Hoshikawa E, et al. Long-term prognosis of dilated cardiomyopathy revisited: An improvement in survival over the past 20 years. *Circ J* 2006; **70:** 376–383.
3. Miura K, Matsumori A, Nasermoaddeli A, Soyama Y, Morikawa Y, Sakurai M, et al. Prognosis and prognostic factors in patients with idiopathic dilated cardiomyopathy in Japan: Results from a nationwide study. *Circ J* 2008; **72:** 343–348.
4. Japan Intractable Diseases Information Center. Dilated cardiomyopathy. http://www.nanbyou.or.jp/entry/301 (accessed July 31, 2014).
5. Merlo M, Pivetta A, Pinamonti B, Stolfo D, Zecchin M, Barbati G, et al. Long-term prognostic impact of therapeutic strategies in patients with idiopathic dilated cardiomyopathy: Changing mortality over the last 30 years. *Eur J Heart Fail* 2014; **16:** 317–324.
6. Azuma A, Matsuo A, Nakamura T, Kawasaki T, Yamamoto K, Hyogo M, et al. Improved survival of idiopathic dilated cardiomyopathy in the 1990s. *Jpn Circ J* 1999; **63:** 333–338.
7. Shiba N, Watanabe J, Shinozaki T, Koseki Y, Sakuma M, Kagaya Y, et al; CHART Investigators. Analysis of chronic heart failure registry in the Tohoku District: Third year follow-up. *Circ J* 2004; **68:** 427–434.
8. Shiba N, Nochioka K, Miura M, Kohno H, Shimokawa H; CHART-2 Investigators. Trend of Westernization of etiology and clinical characteristics of heart failure patients in Japan: First report from the CHART-2 Study. *Circ J* 2011; **75:** 823–833.
9. Sakata Y, Shimokawa H. Epidemiology of heart failure in Asia. *Circ J* 2013; **77:** 2209–2217.
10. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, et al; American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. 2013 ACCF/AHA guideline for the management of heart failure: A report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation* 2013; **128:** e240–e327, doi:10.1161/CIR.0b013e31829e8776.
11. McKee PA, Castelli WP, McNamara PM, Kannel WB. Natural history of congestive heart failure: The Framingham Study. *N Engl J Med* 1971; **285:** 1441–1446.
12. JCS Joint Working Group. Guidelines for management of dilated cardiomyopathy and secondary cardiomyopathy (JCS2011). http://www.j-circ.or.jp/guideline/pdf/JCS2011_tomoike_h.pdf (accessed July 31, 2014).
13. Nochioka K, Shiba N, Kohno H, Miura M, Shimokawa H. Both high and low body mass indexes are prognostic risks in Japanese patients with chronic heart failure: Implications from the CHART study. *J Card Fail* 2010; **16:** 880–887.
14. Takada T, Sakata Y, Miyata S, Takahashi J, Nochioka K, Miura M, et al; CHART-2 Investigators. Impact of elevated heart rate on clinical outcomes in patients with heart failure with reduced and preserved ejection fraction. A report from the CHART-2 Study. *Eur J Heart Fail* 2014; **16:** 309–316.
15. Yohannes Y, Hoddinott J. Classification and regression trees: An introduction. http://www.ifpri.org/sites/default/files/pubs/themes/mp18/techguid/tg03.pdf (accessed July 31, 2014).
16. Miura M, Sakata Y, Miyata S, Nochioka K, Takada T, Tadaki S, et al; CHART-2 Investigators. Usefulness of combined risk stratification with heart rate and systolic blood pressure in the management of chronic heart failure: A report from the CHART-2 Study. *Circ J* 2013; **77:** 2954–2962.
17. Breiman L, Friedman J, Stone JC, Olshen AR. Classification and regression trees. Monterey, CA: Wadsworth, 1984.
18. Austin PC. The performance of different propensity-score methods for estimating differences in proportions (risk differences or absolute risk reductions) in observational studies. *Stat Med* 2010; **29:** 2137–2148.
19. Bouzamondo A, Hulot JS, Sanchez P, Lechat P. Beta-blocker benefit according to severity of heart failure. *Eur J Heart Fail* 2003; **5:** 281–289.
20. CIBIS Investigators and Committees. A randomized trial of beta-blockade in heart failure. The Cardiac Insufficiency Bisoprolol Study (CIBIS). *Circulation* 1994; **90:** 1765–1773.
21. Hori M, Sasayama S, Kitabatake A, Toyo-oka T, Handa S, Yokoyama M, et al; MUCHA Investigators. 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* 2004; **147:** 324–330.
22. Heidenreich PA, Lee TT, Massie BM. Effect of beta-blockade on mortality in patients with heart failure: A meta-analysis of randomized clinical trials. *J Am Coll Cardiol* 1997; **30:** 27–34.
23. Steinberg BA, Zhao X, Heidenreich PA, Peterson ED, Bhatt DL, Cannon CP, et al; Get with the Guidelines Scientific Advisory Committee and Investigators. Trends in patients hospitalized with heart failure and preserved left ventricular ejection fraction: Prevalence, therapies, and outcomes. *Circulation* 2012; **126:** 65–75.
24. Basuray A, French B, Ky B, Vorovich E, Olt C, Sweitzer NK, et al. Heart failure with recovered ejection fraction. *Circulation* 2014; **129:** 2380–2387.
25. de Groote P, Fertin M, Duva Pentiah A, Goéminne C, Lamblin N, Bauters C. Long-term functional and clinical follow-up of patients with heart failure with recovered left ventricular ejection fraction after β-blocker therapy. *Circ Heart Fail* 2014; **7:** 434–439.

Appendix. The CHART-2 Study Investigators

1. Executive Committee

Hiroaki Shimokawa (Chair), Toshikazu Goto, Eiji Nozaki, Tetsuya Hiramoto, Mitsumasa Fukuchi, Kanichi Inoue, Atsushi Kato, Masafumi Sugi, Masatoshi Ohe, Tsuyoshi Shinozaki, Satoru Horiguchi, Hiroshi Kato.

2. Steering Committee

Kanichi Inoue, Tetsuya Hiramoto, Masahiko Ogata, Atsushi Kato, Shoichi Sato, Masafumi Sugi.

3. Collaborating Hospitals and Active Investigators by Prefecture

Aomori Prefecture

Shigeto Oyama (Towada City Hospital).

Iwate Prefecture

Eiji Nozaki, Akihiro Nakamura, Tohru Takahashi, Hideaki Endo, Shigehumi Fukui, Sota Nakajima (Iwate Prefectural Central Hospital). Makoto Nakagawa, Tetsuji Nozaki, Takuya Yagi (Iwate Prefectural Isawa Hospital).

Akita Prefecture

Satoru Horiguchi, Etsuko Fushimi, Yoshinao Sugai, Satoru Takeda, Kouhei Fukahori, Kentaro Aizawa (Hiraka General Hospital).

Yamagata Prefecture

Masatoshi Ohe, Takurou Tashima, Katsuhiko Sakurai, Tadashi Kobayashi (Kojirakawa Shiseido Hospital). Toshikazu Goto, Motoyuki Matsui, Yoshiaki Tamada, Tomoyasu Yahagi, Akio Fukui, Katsuaki Takahashi, Yoku Kikuchi (Yamagata Prefectural Central Hospital).

Miyagi Prefecture

Akihiko Sugimura, Junko Ohashi (Sendai Red Cross Hospital). Hiroyuki Kanno, Junji Kaneko (Katta General Hospital). Shu Suzuki, Kikuyo Takahashi (KKR Tohoku Kosai Hospital). Kenjiro Akai (Kurihara Central Hospital). Dai Katayose (Miyagi Rifu Ekisaikai Hospital). Sachio Onodera, Tetsuya Hiramoto, Seiji Komatsu, Masanobu Chida, Kaoru Iwabuchi, Masaharu Takeuchi, Hirokazu Yahagi, Nozomu Takahashi (Osaki Citizen Hospital). Keiji Otsuka, Yoshito Koseki, Masaki Morita (Saito Hospital). Tsuyoshi Shinozaki, Takeshi Ishizuka, Noriko Onoue, Nobuhiro Yamaguchi, Hiroshi Fujita (Sendai Medical Center). Atsushi Katoh, Shigeto Namiuchi, Tadashi Sugie, Kenya Saji, Toru Takii, (Sendai Open Hospital). Mitsumasa Fukuchi, Masahiko Ogata, Toshinori Tanikawa, Osamu Kitamukai (Sendai Tokushukai Hospital). Yasuharu Matsumoto (Shizugawa Public Hospital). Kanichi Inoue, Jiro Koyama, Tomoko Tomioka, Hiroki Shioiri, Yoshitaka Ito (South Miyagi Medical Center).Hiroshi Kato, Chikako Takahashi, Akiko Kawana (Tohoku Rosai Hospital).Yasuhiko Sakata, Kenta Ito, Masaharu Nakayama, Koji Fukuda, Jun Takahashi, Satoshi Miyata, Koichiro Sugimura, Kimio Sato, Yasuharu Matsumoto, Makoto Nakano, Takashi Shiroto, Ryuji Tsuburaya, Kotaro Nochioka, Hiroaki Yamamoto, Tatsuo Aoki, Kiyotaka Hao, Masanobu Miura, Masaki Kondo, Shunsuke Tatebe, Saori Yamamoto, Hideaki Suzuki, Kensuke Nishimiya, Nobuhiro Yaoita (Tohoku University Hospital).

Fukushima Prefecture

Masafumi Sugi, Yoshito Yamamoto, Sunao Toda, Yutaka Minatoya, Yusuke Takagi, Yuhi Hasebe, Taro Nihei (Iwaki Kyouritsu Hospital). Koji Fukuda (Watanabe Hospital).

4. Head Office and Coordinating Center

Yasuhiko Sakata, Yoshihiro Fukumoto, Jun Takahashi, Satoshi Miyata, Kotaro Nochioka, Masanobu Miura, Soichiro Tadaki, Ryoichi Ushigome, Takeshi Yamauchi, Kenjiro Sato, Kanako Tsuji, Takeo Onose, Ruri Abe, Chiharu Saga, Junko Suenaga, Yoko Yamada, Junko Kimura, Hiromi Ogino, Izumi Oikawa, Sanae Watanabe, Madoka Saga, Miki Washio, Keiko Nagasawa, Sachiko Nagasawa, Sachie Kotaka, Wakiko Komatsu, Reiko Hashimoto, Yasuko Ikeno, Tomoyuki Suzuki, Hiroko Hamada.

Supplementary Files

Supplementary File 1

Figure S1. Change in survival rate between CHART-1 and CHART-2 for (**A**) left ventricular ejection fraction (LVEF) > or ≤40%, (**B**) brain natriuretic peptide (BNP) < or ≥220 pg/ml, (**C**) presence of β-blockers and (**D**) presence of aldosterone antagonist.

Please find supplementary file(s);
http://dx.doi.org/10.1253/circj.CJ-14-0939