B	HFrEF (n=1,903)			HFpEF (n=2,779)		
	CHART-1 (n=543)	CHART-2 (n=1,360)	P-value	CHART-1 (n=463)	CHART-2 (n=2,316)	P-value
Age (years)	67.3±0.6	68.3±0.3	0.114	70.9±0.6	70.5±0.3	0.547
Male	381 (70.2)	999 (73.5)	0.155	261 (56.4)	1,413 (61.0)	0.069
BP (mmHg)						
Systolic	123.7±0.9	121.3±0.5	0.027	127.9±1.0	127.8±0.4	0.916
Diastolic	71.2±0.5	70.6±0.3	0.324	71.5±0.6	72.0±0.3	0.407
Heart rate (beats/min)	75.8±0.8	73.3±0.4	0.005	74.4±0.8	72.1±0.3	0.006
BMI (kg/m²)	22.7±0.2	22.8±0.1	0.616	23.2±0.2	23.5±0.1	0.193
NYHA classification			<0.001			<0.001
II	413 (76.1)	1,124 (82.6)		373 (80.6)	2,018 (87.1)	
III	125 (23.0)	215 (15.8)		85 (18.4)	280 (12.1)	
IV	5 (0.9)	21 (1.5)		5 (1.1)	18 (0.8)	
Laboratory data						
Hb (g/dl)	13.2±0.1	13.2±0.1	0.492	12.6±0.1	13.0±0.0	0.001
Anemia	180 (33.1)	498 (36.6)	0.168	215 (46.4)	877 (37.9)	0.001
BUN (mg/dl)	22.1±0.8	21.6±0.3	0.493	21.5±0.5	20.1±0.2	0.007
Cre (mg/dl)	1.08±0.04	1.17±0.03	0.087	1.10±0.04	1.03±0.02	0.088
eGFR (ml/min/1.73 m²)	61.5±1.0	57.8±0.6	0.002	58.2±1.1	60.3±0.5	0.064
BNP (pg/ml)	178.2 (83.7–393.2)	172.0 (71.6–374.0)	0.342	138.0 (58.7–282.0)	96.6 (40.9–218.0)	<0.001
Echocardiography						
LVEF (%)	37.8±0.4	37.9±0.3	0.925	63.4±0.5	65.1±0.2	<0.001
LVDd (mm)	60.6±0.4	58.9±0.3	<0.001	52.4±0.4	48.9±0.2	<0.001
LVDs (mm)	50.0±0.4	47.9±0.3	<0.001	35.1±0.4	31.5±0.2	<0.001
Comorbidity						
Hypertension	235 (43.3)	1,157 (85.1)	<0.001	233 (50.3)	2,046 (88.4)	<0.001
Dyslipidemia	102 (18.8)	1,100 (80.9)	<0.001	61 (13.2)	1,779 (76.8)	<0.001
Diabetes mellitus	108 (19.9)	497 (36.5)	<0.001	86 (18.6)	783 (33.8)	<0.001
Atrial fibrillation	194 (35.7)	502 (36.9)	0.636	229 (49.5)	1,027 (44.4)	0.046
Ventricular tachycardia	151 (27.8)	259 (19.1)	<0.001	65 (14.0)	161 (7.0)	<0.001
Etiology						
Ischemic heart disease	181 (33.3)	701 (51.5)	<0.001	88 (19.0)	1,048 (45.3)	<0.001
Cardiomyopathy	222 (40.9)	369 (27.1)	<0.001	112 (24.2)	275 (11.9)	<0.001
DCM	195 (35.9)	343 (25.2)		72 (15.6)	162 (7.0)	
HCM	6 (1.1)	20 (1.5)		29 (6.3)	95 (4.1)	
Other cardiomyopathy	21 (3.9)	6 (0.4)		11 (2.4)	18 (0.8)	
Medication						
β-blockers	184 (33.9)	870 (64.0)	<0.001	104 (22.5)	1,018 (44.0)	<0.001
RASI	385 (70.9)	1,061 (78.0)	0.001	304 (65.7)	1,619 (69.9)	0.078
ACEI	327 (60.2)	707 (52.0)	0.001	248 (53.6)	1,014 (43.8)	<0.001
ARB	61 (11.2)	399 (29.3)	<0.001	64 (13.8)	708 (30.6)	<0.001
Aldosterone antagonists	116 (22.4)	493 (36.2)	<0.001	66 (14.5)	491 (21.2)	0.001
Loop diuretics	729 (76.7)	2,038 (55.5)	<0.001	401 (78.6)	903 (66.4)	<0.001
Digitalis	478 (48.5)	920 (25.0)	<0.001	249 (47.2)	335 (24.6)	<0.001
CCB	126 (23.9)	356 (26.2)	0.318	162 (35.4)	1,032 (44.6)	<0.001
Statins	NA	515 (37.9)	NA	NA	817 (35.3)	NA
ICD/CRTD	6 (1.1)	72 (5.3)	<0.001	10 (2.2)	31 (1.3)	0.202

Data given as mean±SE, median (IQR) or n (%). HFpEF, HF with preserved ejection fraction; HFrEF, HF with reduced ejection fraction. Other abbreviations as in Table 1.

was decreased in the CHART-2 Study. Implantable cardioverter defibrillator (ICD)/cardiac resynchronization therapy defibrillator (CRTD) were more frequently used in CHART-2. Similar trends from CHART-1 to CHART-2 were noted in both ischemic and non-ischemic HF (**Table 2A**), and also in both HFrEF and HFpEF (**Table 2B**).

Temporal Trend in Long-Term Prognosis of Symptomatic HF

During the 3-year follow-up, a total of 771 patients died (236 and 535 in the CHART-1 and the CHART-2 Studies, respectively) and 923 were hospitalized for HF (302 and 621 in the CHART-1 and the CHART-2 Studies, respectively). Crude 3-year mortality was significantly decreased from 23.5% in CHART-1 to 14.6% in CHART-2 (hazard ratio [HR], 0.59; 95% CI: 0.50–0.69; P<0.001; **Figure 1A**). Three-year cardiovascular death rate was also improved from 17.4% (n=175) in CHART-1 to 7.5% (n=275) in CHART-2 (HR, 0.41; 95% CI: 0.34–0.50; P<0.001; **Figure 1B**). Also, 3-year HF admission

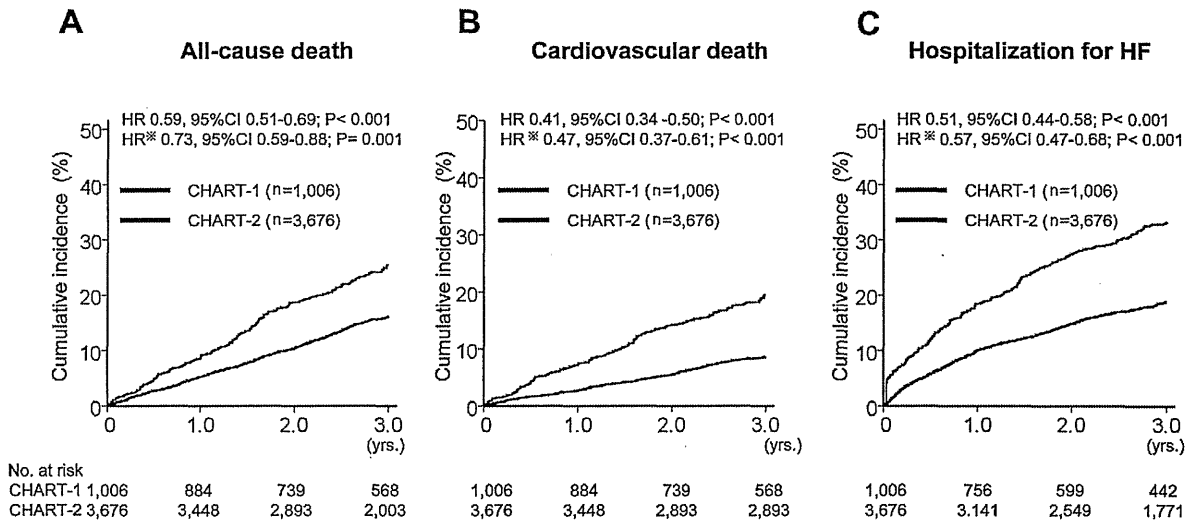

Figure 1. Temporal trend in long-term prognosis of symptomatic heart failure (HF). Kaplan-Meier curves for (**A**) all-cause death, (**B**) cardiovascular death and (**C**) hospitalization for worsening HF. *Adjusted for age, sex, hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation and ventricular tachycardia.

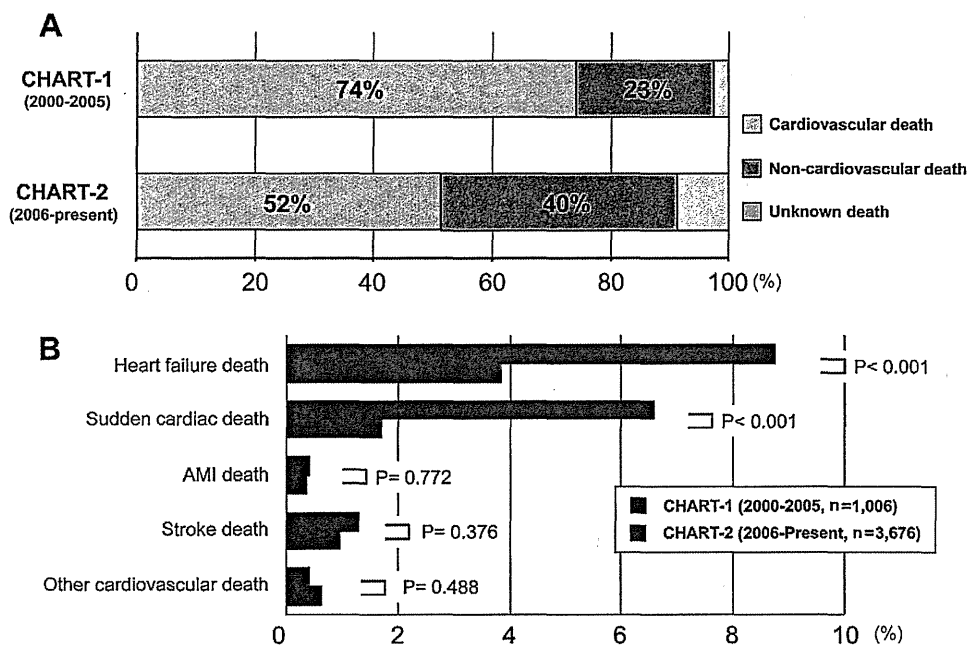

Figure 2. Temporal trends in mode of death in symptomatic heart failure patients. AMI, acute myocardial infarction.

rate was significantly decreased from 30.0% (n=302) in CHART-1 to 16.9% (n=621) in CHART-2 (HR, 0.51; 95% CI: 0.44–0.58; P<0.001; **Figure 1C**). After adjustment for clinical background, the CHART-2 patients still had improved prognosis compared with the CHART-1 patients for all-cause death (**Figure 1A**), cardiovascular death (**Figure 1B**) and HF admission (**Figure 1C**).

Temporal Trend in Mode of Death in Symptomatic HF

Among the 236 deaths in the CHART-1 Study, there were 175 cardiovascular deaths (74.1%) and 55 non-cardiovascular deaths (23.3%). The cause of the remaining 6 deaths was unknown (**Figure 2A**). Among the 535 deaths in the CHART-2 patients, 275 (51.4%) were cardiovascular deaths and 213 (39.8%) were non-cardiovascular deaths, while the cause of

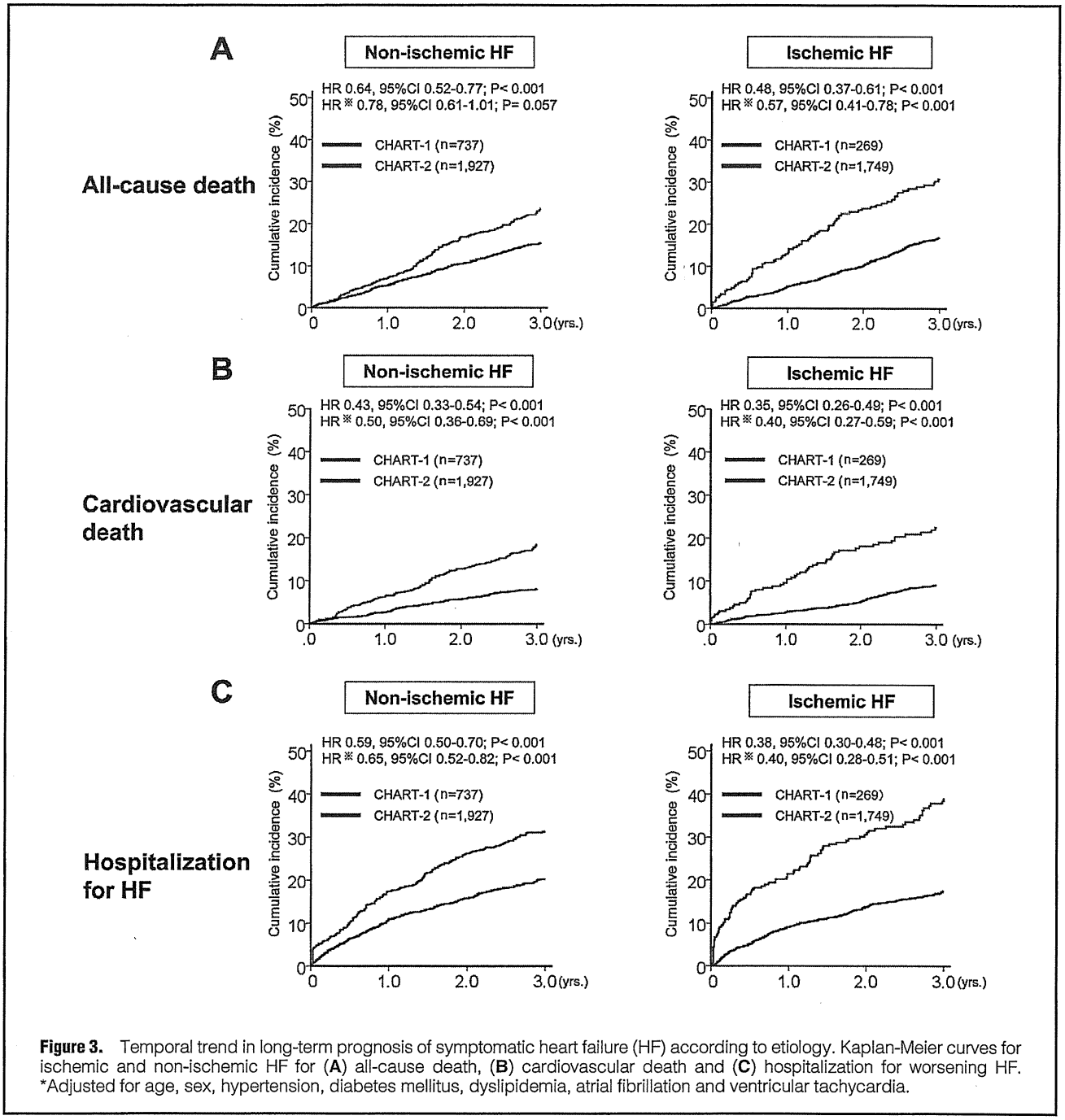

Figure 3. Temporal trend in long-term prognosis of symptomatic heart failure (HF) according to etiology. Kaplan-Meier curves for ischemic and non-ischemic HF for (**A**) all-cause death, (**B**) cardiovascular death and (**C**) hospitalization for worsening HF. *Adjusted for age, sex, hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation and ventricular tachycardia.

the remaining 47 deaths was unknown (**Figure 2A**). Among the cardiovascular deaths, the incidence of death due to HF (from 8.7 to 3.8%, P<0.001) and sudden cardiac death (from 6.6 to 1.7%, P<0.001) were markedly and significantly decreased, whereas the incidence of death due to acute myocardial infarction (from 0.4 to 0.4%, P=0.772) or stroke (from 1.3 to 1.0%, P=0.376) was unchanged (**Figure 2B**).

Difference in Long-Term Prognosis Between Non-Ischemic and Ischemic HF

We further examined the differences in 3-year mortality between the CHART-1 and the CHART-2 Studies in the subgroups of non-ischemic and ischemic HF patients. In both the non-ischemic and ischemic groups, the long-term prognosis of HF was improved from CHART-1 to CHART-2, including all-cause death (22 vs. 14%, and 29 vs. 15%; **Figure 3A**), cardiovascular death (16 vs. 7% and 20 vs. 8%; **Figure 3B**) and HF admission (28 vs. 18% and 35 vs. 16%; all P<0.001; **Figure 3C**). These trends of improved prognosis in non-ischemic and ischemic HF were generally unchanged after adjustment for clinical background (**Figure 3**).

Difference in Long-Term Prognosis Between HFpEF and HFrEF

The prevalence of HFpEF was increased from 46% in CHART-1 to 63% in CHART-2 (**Table 1**). In both the HFpEF and HFrEF

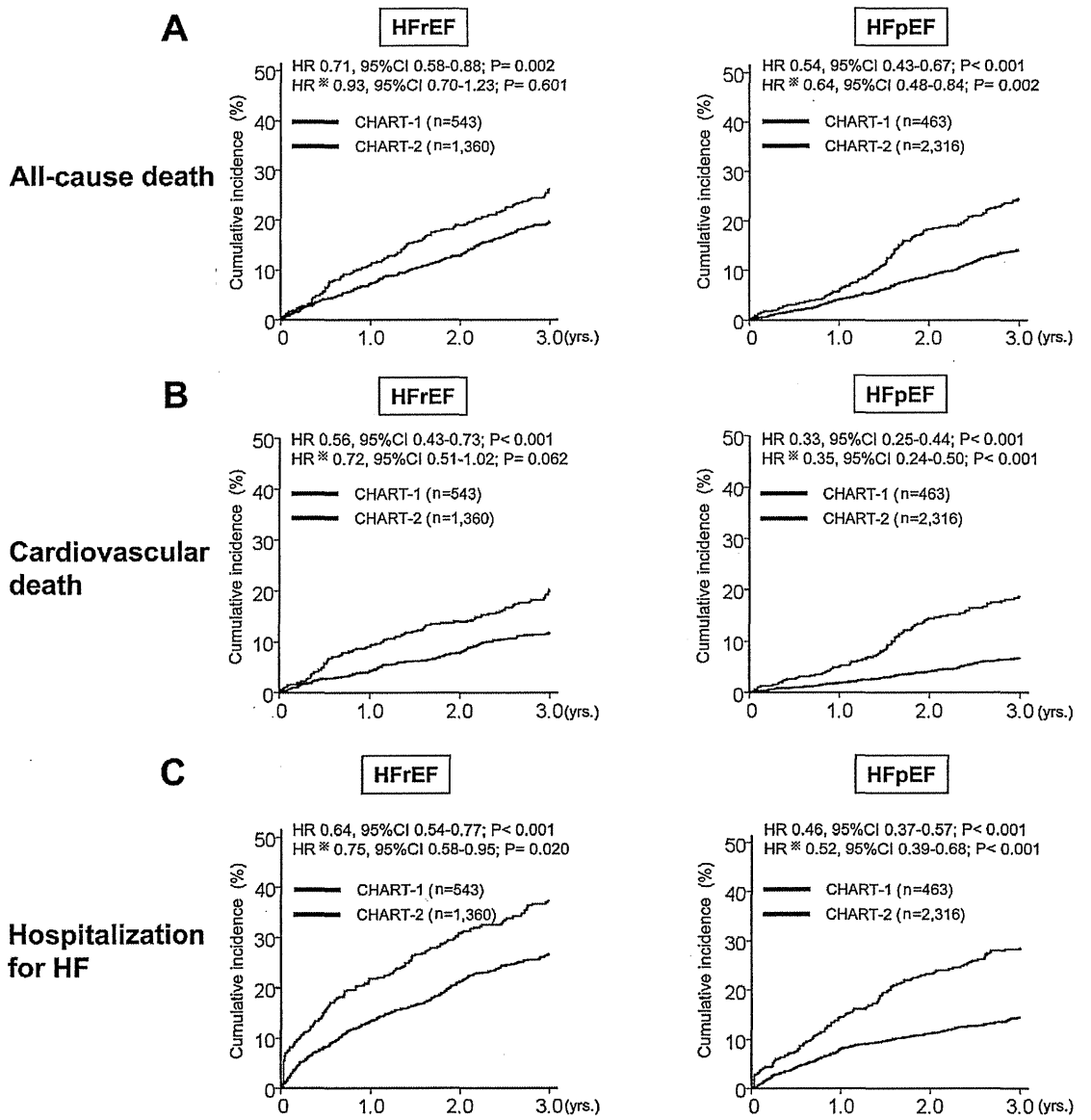

Figure 4. Temporal trend in long-term prognosis of symptomatic heart failure (HF) according to left ventricular ejection fraction (LVEF). Kaplan-Meier curves for HF with preserved EF (HFpEF; LVEF ≥50%) and HF with reduced EF (HRrEF; LVEF <50%) for (**A**) all-cause death, (**B**) cardiovascular death and (**C**) hospitalization for worsening HF. *Adjusted for age, sex, hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation and ventricular tachycardia.

subgroups, long-term prognosis of symptomatic HF was improved from CHART-1 to CHART-2, including all-cause death (HFrEF, 24 vs. 18%, P=0.002; HFpEF, 23 vs. 13%, P<0.001; **Figure 4A**), cardiovascular death (HFrEF, 18 vs. 10%, P<0.001; HFpEF, 17 vs. 6%, P<0.001; **Figure 4B**) and HF admission (HFrEF, 34 vs. 23%, P<0.001; HFpEF, 26 vs. 13%, P<0.001; **Figure 4C**). After adjustment for clinical background, however, the decrease in the incidence of all-cause death from CHART-1 to CHART-2 (adjusted HR [adjHR], 0.93; P=0.601) was no longer significant in the HFrEF group, whereas it remained significant in the HFpEF group (adjHR, 0.64, P=0.002). Similarly, the difference in the incidence of cardiovascular death between CHART-1 and CHART-2 became insignificant in the HFrEF groups after adjustment for clinical background (adjHR, 0.72; P=0.062), while there remained a significant difference in the HFpEF groups (adjHR, 0.35, P<0.001; **Figures 4A,B**).

Prognostic Factors in Symptomatic HF

Factors associated with all-cause death in the total population (n=4,682) selected using the stepwise multivariable Cox model are shown in **Table 3**. Age, BMI, heart rate, NYHA, SBP, DM, dyslipidemia, LVDd, BNP and eGFR were significantly associated with all-cause mortality. Using these factors as variables and adjusting for clinical background, the prognostic impact of each medication in the CHART-1 and the

Table 3. Multivariate Cox Predictors of All-Cause Death

	HR	95% CI	P-value
Age (per 10 years)	1.42	1.30–1.54	<0.001
BMI	0.97	0.95–0.98	<0.001
Heart rate	1.01	1.00–1.01	0.001
Systolic BP (per 10 mmHg)	0.93	0.89–0.96	<0.001
NYHA III/IV	1.62	1.34–1.95	<0.001
Diabetes mellitus	1.37	1.15–1.64	<0.001
Dyslipidemia	0.70	0.59–0.84	<0.001
LVDd	1.01	1.00–1.02	0.012
BNP (per 100 pg/ml)	1.08	1.06–1.10	<0.001
eGFR (per 10 ml/min/1.73 m^2)	0.93	0.89–0.96	<0.001

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

CHART-2 patients (**Figure 5**) was determined on the multivariate Cox modeling. Given that β-blockers and statins tended to improve the prognosis of the CHART-2 patients (**Figure 5A**), we further examined their prognostic impact in the HFpEF and HFrEF subgroups. In the HFrEF group, use of β-blockers was associated with decreased incidence of all-cause death in CHART-2 (**Figure 5B**), whereas, in the HFpEF group, statin use was associated better prognosis in CHART-2 but not in CHART-1 (**Figure 5C**). Use of RASI, aldosterone antagonists, loop diuretics, digitalis or calcium channel blockers was not associated with all-cause mortality in CHART-1 or CHART-2 (**Figure 5**).

Discussion

The novel findings of the present study are that in symptomatic HF patients in Japan: (1) the prevalence of IHD and lifestyle-related diseases (eg, hypertension, hyperlipidemia and DM) has increased; (2) the prevalence of HFpEF has increased in both ischemic and non-ischemic HF; (3) evidence-based medications have been implemented more often; and (4) the 3-year incidence of all-cause death, cardiovascular death and admission for HF has decreased. To the best of our knowledge, this is the first study on the temporal trend of symptomatic HF in Japan.

Increased Prevalence of Ischemic HF

We have previously reported a trend in the westernization of HF etiologies and implementation of evidence-based medications in the CHART Studies, in which a broad spectrum of HF patients in Japan was enrolled.[3,6] In the present study, in order to obtain further insights into the temporal trends in HF management in Japan, we examined a total of 4,682 symptomatic HF patients from the CHART-1 (n=1,006) and the CHART-2 (n=3,676) Studies with the same inclusion criteria. In the present study, we not only confirmed the trend in westernization of HF etiology and better implementation of evidence-based medications in symptomatic HF patients, as we previously reported,[3,6] but also obtained several new findings.

One of the most important findings was the marked increase in prevalence of ischemic HF: it had increased from 27% in CHART-1 to 48% in CHART-2. In Japan, Tsutsui et al reported that the prevalence of IHD was 30% in 2004,[15] which is similar to that (27%) in the CHART-1 Study, in which patients were enrolled between 2000 and 2004. In contrast, the prevalence of IHD in the CHART-2 Study, in which patients were enrolled between 2006 and 2010, was markedly increased to 48%. Thus, the prevalence of IHD in Japanese patients with symptomatic HF has already reached the same level as in Western countries (44–59%).[16–20]

Increased Prevalence of HFpEF

Another important finding of the present study was the increase in the prevalence of HFpEF in Japan. Although recent studies reported that the prevalence of HFpEF has increased worldwide, the increase from 46% to 63% in the CHART Studies is remarkable. For example, in the Framingham Heart Study, the prevalence of HF with LVEF ≥50% had increased from 33% in 2000 to 39% in 2010.[21] Thus, the present study demonstrated that the higher prevalence of HFpEF in the Japanese population has recently become more evident. In addition, it should be noted that the prevalence of IHD with LVEF ≥50%, but not with LVEF <50%, dramatically increased in the CHART-2 Study, indicating the rapid increase in HFpEF in ischemic HF, along with the westernization of clinical characteristics of symptomatic HF in Japan. It is possible that the recent changes in lifestyle and advances in coronary intervention for acute myocardial infarction have caused the increase in HFpEF in IHD.[22–25] Interestingly, however, the prevalence of HFpEF was also increased in patients without IHD, possibly reflecting a trend in HF in the aged populations as well.[1–3]

Temporal Trend in HF According to Etiology and LV Function

Although we have previously reported the increased prevalence of lifestyle-related disease and implementation of evidence-based medications in Japanese HF patients,[3,6] it has been unclear whether these trends were related to HF etiology (ischemic vs. non-ischemic) or LV function (HFrEF vs. HFpEF). In the present study, we found a similar trend in westernization of the prevalence of comorbidities and better implementation of evidence-based medications, regardless of HF etiology or LV function. Thus, it should be underlined that prevention of future ischemic events is an emerging issue in symptomatic HF patients regardless of HF etiology or LV function. In particular, patients with HFpEF and those with non-ischemic HF should be given more attention, given that the use of evidence-based medications was lower in these patients, even in the CHART-2 Study.

Improved Long-Term Prognosis of Japanese Symptomatic HF Patients

We recently reported that long-term prognosis of DCM patients has been improved, along with the implementation of evidence-based medications in Japan.[26] There have been few reports, however, that examined the temporal trends in clinical outcome of Japanese patients with symptomatic HF in general. In

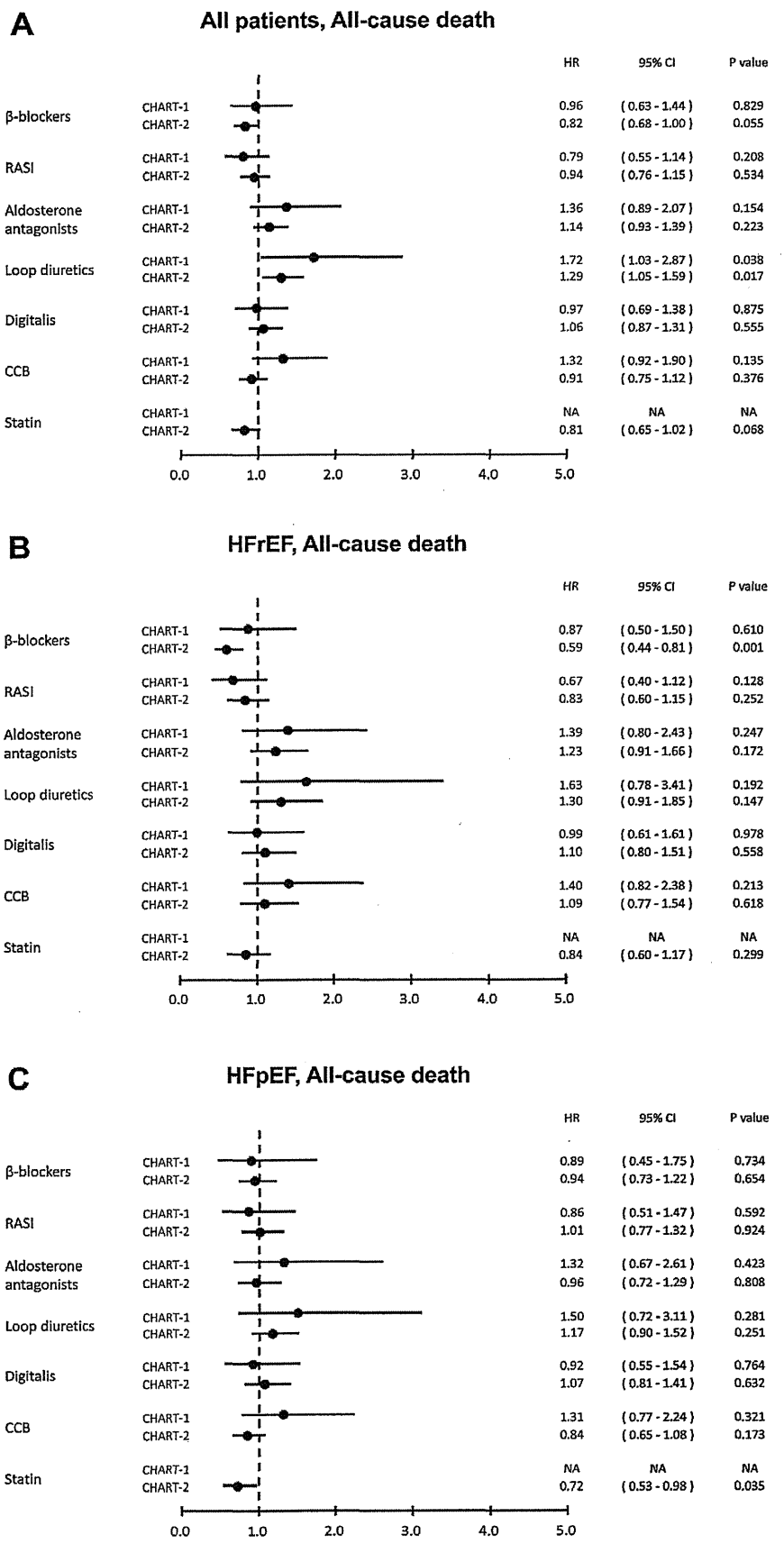

Figure 5. Effects of medications on long-term prognosis of symptomatic heart failure (HF). Forest plots for effect of each medicine for all-cause death in (**A**) all patients, (**B**) HF with reduced ejection fraction (HFrEF), and (**C**) HF with preserved ejection fraction (HFpEF). Multivariate Cox proportional hazard model. *Adjusted for age, body mass index, heart rate, systolic blood pressure, left ventricular end-diastolic diameter, brain natriuretic peptide, estimated glomerular filtration rate, New York Heart Association, diabetes mellitus, dyslipidemia. CCB, calcium channel blockers; RASI, renin-angiotensin system inhibitors.

the present study, we examined the temporal trend in long-term prognosis along with the changes in clinical characteristics and management of Japanese patients with symptomatic HF. Indeed, the present study has shown that 3-year incidences of all-cause death, cardiovascular death and admission for HF were all significantly decreased from CHART-1 to CHART-2. Importantly, the decreased incidence of the 3 events remained significant in the overall population, even after adjustment for clinical background, suggesting that implementation of evidence-based medicine played a major role independently of westernization of patient clinical characteristics.

Many previous studies examined the prognosis of HF,[27–30] but most of the studies focused on prognosis after hospitalization for acute HF, and there have been few reports on the prognosis of CHF. In the Framingham cohort, it was reported that the 5-year mortality rate was 65% (13%/year) in male HF patients surviving at least 90 days after the diagnosis of HF,[16] and that 5-year mortality was decreased from 70% (14%/year) in 1950–1969 to 59% (12%/year) in 1990–1999.[31] There are few reports, however, regarding the improvement of prognosis in HF patients after 2000, namely, in the era of evidence-based medicine. In this sense, the present study has provided important evidence that the prognosis of HF has been improved after 2000: the 3-year mortality was improved from 24% (8%/year) in CHART-1 to 15% (5%/year) in CHART-2 in the present study. It should be noted, however, that in the HFrEF subgroup, improvement of all-cause mortality from CHART-1 to CHART-2 became insignificant after adjustment for clinical background. Thus, further implementation of evidence-based management including use of newer drugs such as ivabradine;[32] ICD/CRTD and exploration of better management are required for HFrEF patients.[33–34]

Temporal Trend in Mode of Death

The present study demonstrated that the prevalence of cardiovascular death was decreased, whereas that of non-cardiovascular death was increased from CHART-1 to CHART-2. One of the explanations for this observation is that implementation of evidence-based medicine has mainly reduced cardiovascular death. Another explanation is the increase in the prevalence of HFpEF in symptomatic HF from CHART-1 to CHART-2, given that, in HFpEF patients, the prevalence of sudden death was lower and that of non-cardiovascular death higher as compared with HFrEF patients.[35]

In the present study, it was also noted that the rate of sudden cardiac death was significantly decreased from CHART-1 to CHART-2. Implementation of evidence-based medications might have played a significant role in decreasing the rate of sudden cardiac death.[27–30] In addition, it is conceivable that ICD/CRTD treatment prevented sudden cardiac death in the CHART-2 Study, because the prevalence of patients with ICD/CRTD was increased. The underuse of ICD/CRTD for HF, however, remains an important problem worldwide.[33,36,37] Thus, more effort is needed to achieve appropriate use of ICD/CRTD in order to further reduce sudden death in patients with symptomatic HF.

Medications Contributing to Improvement of Long-Term Prognosis

The CHART-2 patients had better clinical characteristics compared with the CHART-1 patients, which might have contributed in part to the improved prognosis of the CHART-2 patients. Given that the CHART Studies are observational, the patients had already been treated with pharmacologic medications at the time of registration. Thus, reduced BNP, lower NYHA class and higher prevalence of preserved LVEF in the CHART-2 Study were likely, at least in part, due to more frequent implementation of evidence-based medication. The prescription rates of β-blockers, RASI and aldosterone antagonists were all increased in the CHART-2 Study as compared with the CHART-1 Study. Along with these changes, 3-year prognosis, particularly 3-year cardiovascular mortality, was decreased. Previous studies reported that the use of β-blockers, RASI and aldosterone antagonists significantly reduced the risk of cardiovascular death and sudden cardiac death in patients with HF, particularly in those with HFrEF.[27–30] In the present study, however, the prognostic impacts of RASI and aldosterone antagonists were not significant in the CHART-1 or the CHART-2 Study. In contrast, β-blockers tended to improve all-cause mortality in the overall population in CHART-2 but not in CHART-1. Furthermore, on subgroup analysis the use of β-blockers was associated with improved mortality in HFrEF patients, but not in HFpEF patients, in the CHART-2 Study. Thus, in the present study, the reduced mortality in the HFrEF patients could be, at least in part, attributable to better implementation of β-blockers in the CHART-2 Study. In contrast, the use of statins may have improved the mortality from CHART-1 to CHART-2 in HFpEF patients, although no data on statin use were available in the CHART-1 Study. In the present study, the use of statins was significantly associated with reduced mortality in the CHART-2 patients. Given that statin use is associated with decreased incidence of all-cause death, mainly that in sudden death and non-cardiovascular death in HFpEF patients,[14] the decrease in sudden death and non-cardiovascular death in HFpEF patients could be attributable to an increase in statin use from CHART-1 to CHART-2. Although we have no data on the use of statin in the CHART-1 Study, it is likely that the prevalence of HF treated with statins increased from CHART-1 to CHART-2 along with the increase in the prevalence of IHD.

Study Limitations

Several limitations should be mentioned for the present study. First, given that both the CHART-1 and the 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 prognostic impact of medications was analyzed based on the initial data at enrollment, and we did not include information on the dose and adherence of these drugs during the follow-up period.

Conclusions

The long-term prognosis of symptomatic HF patients has been significantly improved along with the implementation of evidence-based medications in Japan. Also, the prevalence of ischemic HF and that of HFpEF have markedly increased in Japan.

Acknowledgments

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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

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Supplementary Files

Supplementary File 1

Appendix S1. CHART-2 Study Investigators

Please find supplementary file(s);
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Letter to the Editor

A deletion mutation in myosin heavy chain 11 causing familial thoracic aortic dissection in two Japanese pedigrees

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To The Editor:

In addition to the genes involved in syndromic types of thoracic aortic aneurysm and/or dissection (TAAD) (eg. *FBN1* in Marfan syndrome, *TGFBR1/TGFBR2* in Loeys–Dietz syndrome), several genes such as *MYH11* and *ACTA2* have been implicated in familial non-syndromic TAAD [1–4]. Here, we identified a deletion mutation in *MYH11* gene causing familial thoracic aortic dissection (TAD) in two independent Japanese pedigrees.

Pedigree #1 (Fig. 1a): A 78-year-old Japanese man (II-3) with a potent family history of TAD was referred to our hospital for evaluation of possible aortic diseases, however, routine evaluation including echocardiography and CT/MRI showed normal findings. His oldest sister and youngest sister (II-1 and II-6) have survived TAD under medical intervention, whereas the second sister (II-5) died suddenly due to an aortic event at 46 years old. The daughter of the youngest sister (II-6) also died suddenly from TAD in spite of intensive care while in the later stage of her pregnancy with her youngest daughter (IV-3), who was successfully delivered by caesarian section. This daughter (IV-3) was diagnosed with patent ductus arteriosus (PDA). None of aforementioned family members had any clinical skeletomuscular manifestations.

Pedigree #2: The proband was a Japanese woman who was diagnosed with type II DeBakey dissection at the age of 54 years. Her mother had died suddenly (aged 60) from acute type A aortic dissection. She did not have any skin features such as thin and translucent skin, easy bruising, or livedo reticularis, and there were no skeletal, pulmonary or ocular features seen in Marfan syndrome. Transthoracic echocardiography revealed no other cardiac abnormalities.

Genomic DNA was extracted from peripheral blood or saliva. All coding exons of *MYH11*, *ACTA2*, *FBN1*, *TGFBR1*, and *TGFBR2* were amplified from genomic DNA with the use of primer sets previously described (http://genome.cse.ucsc.edu/cgi-bin/hgGene). PCR-products were sequenced with a BigDye Terminator v3.1 cycle-sequencing system on an ABI Prism 3100xl Genetic Analyzer (Applied Biosystems). The PCR products of the exon where a deletion variant was identified were subcloned into T-vector pMD20 using a Mighty TA-cloning Kit (TaKaRa Bio) and sequenced for the confirmation of the variant. Genetic analysis was approved by the ethics committee of The University of Tokyo. A written informed consent was obtained after providing a detailed explanation of the purpose of this analysis.

In the direct sequencing analysis, a heterozygous in-frame deletion (c.3766_3768delAAG, p.K1256del) of *MYH11* (NM_002474.2) was detected in each pedigree (Fig. 1b). This variant was confirmed by the direct-sequencing of subcloned PCR products spanning this variant (Fig. 1c). In one pedigree, all relatives affected by TAD had this variant, whereas clinically unaffected adult relatives did not (Fig. 1a). This deletion has not been reported as a common variant and/or rare variant in the public genomic database on Caucasian, African, and Asian populations (dbSNP (build 142, http://www.ncbi.nlm.nih.gov/SNP/), Exome Sequencing Project (ESP) (http://evs.gs.washington.edu/EVS/), Human Genetic Variation Database (http://www.genome.med.kyoto-u.ac.jp/SnpDB/), or 1000 Genomes Project (http://www.1000genomes.org)). Furthermore, this variant was not reported to be a causative mutation for any disorder (OMIM (http://www.ncbi.nlm.nih.gov/omim/), ClinVar

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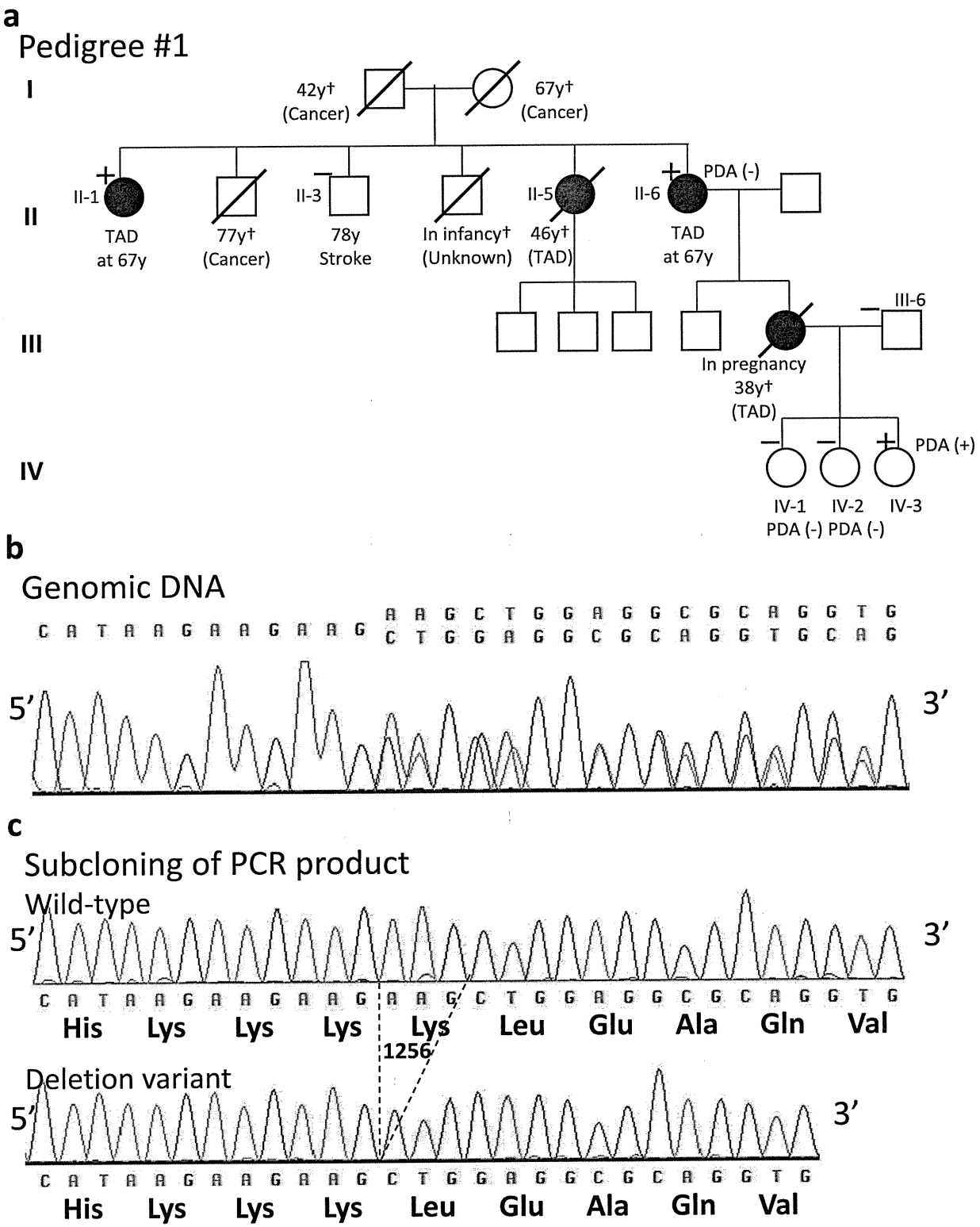

Fig. 1. a. One pedigree with thoracic aortic dissection in this study. Square: male, circle: female, solid: affected by thoracic aortic dissection, open: unaffected by thoracic aortic dissection, diagonal line: deceased, TAD: thoracic aortic dissection, PAD: patent ductus arteriosus, +: presence of heterozygous *MYH11* del1256K variant, −: absence of *MYH11* del1256K variant. b. A deletion mutation in *MYH11* gene (NM_002474.2 > NP_002465.1) in each pedigree. An AAG triplet is deleted in a heterozygous manner. c. Sequence analyses of subcloned PCR product amplified from genomic DNA of an affected member. Predicted amino acid sequences are shown along with nucleotide sequences.

(http://www.ncbi.nlm.nih.gov/clinvar/)). Finally, a recently-published huge exome database ExAC (http://exac.broadinstitute.org/) reported 1 heterozygote of this variant out of 4326 East-Asians, suggesting that this variant is very rare. This deletion variant is located in exon 28 of *MYH11*, which is a hot-spot for causative mutations of familial TAAD identified so far in Caucasians. This region is responsible for the stability of the α-helical coiled-coil structure in the rod domain of smooth muscle myosin heavy chain. The lysine residues of K1253_K1256 in myosin-11 isoform SM1A (NP_002465.1) which this in-frame deletion affects are completely conserved in the evolution of

vertebrates from zebrafish to human. Using the in silico prediction software SIFT (Sorts Intolerant From Tolerant) (http://sift.bii.a-star.edu.sg/www/SIFT_indels2.html), this deletion variant was classified as "damaging".

Genetic analysis of *ACTA2*, *FBN1*, *TGFBR1*, and *TGFBR2* did not reveal any significant variant that is thought to function as a causative variant.

Here, in two independent Japanese pedigrees of familial TAD, a deletion variant of *MYH11* was identified. Recently, the identical *MYH11* variant was reported in a Dutch family with TAAD and PDA, in which its causality remains inconclusive due to the incomplete co-segregation with the disease [5]. However, several lines of evidence strongly support causality. First, co-segregation of this variant with TAD was clearly shown in pedigree #1. A pediatric case with this variant (IV-3 in pedigree #1) was affected by PDA, which was reported to co-exist with TAAD in *MYH11* mutation carriers [2,3]. Second, this variant was very rare in control genomic databases (1 heterozygote of this variant out of 4326 East-Asians in ExAC database). Third, this variant occurred at a hot-spot for causative mutations in a previously implicated gene *MYH11*. Loss of 24 amino acids (Q1241_L1264del) due to a 72-bp deletion within *MYH 11* exon 28 was reported to cause TAAD and PDA in an American family [2]. In addition, a missense mutation Leu1264Pro in *MYH11* exon 28 was reported to cause TAAD and PDA in another Caucasian family [3]. Fourth, this variant affected a highly conserved amino acid residue (Lys1256) located in the functional rod domain of myosin-11 [6,7]. Finally, this variant was predicted by in silico prediction software to damage the function of the encoded protein. Based on our conservative criteria for pathogenicity, this *MYH11* K1256del variant is thought to be a causative mutation for TAD.

In conclusion, we have reported a *MYH11* mutation causing familial TAD in two Japanese pedigrees, which is the first report in Japanese subjects. Further genetic analyses are warranted to establish the clinical usefulness of re-sequencing of *MYH11* gene, especially its hot-spot, for clarification of the genetic background in TAAD cases.

Conflict of interest

The authors have no conflict of interest to declare.

Acknowledgments

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Original article

Early vs. late reverse ventricular remodeling in patients with cardiomyopathy

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ABSTRACT

Background: Predictors of left ventricular reverse remodeling (LVRR) and differences in the time taken to achieve LVRR remain unclear.
Methods: We consecutively registered 129 patients with severe cardiomyopathy admitted with heart failure (HF). Patients were followed for a median of 778.0 days (IQ: 457.0, 1078.0). LVRR was defined as a decrease in indexed left ventricular systolic dimension of at least 15% additional to a 25% improvement in left ventricular ejection fraction at outpatient check-up compared with discharge. LVRR accomplishment within 400 days was defined as early-LVRR opposing the remaining late-LVRR patients. Primary endpoint was a composite of all-cause mortality and HF re-hospitalization.
Results: LVRR was observed in 51 patients (39.5%). Baseline predictors for LVRR were age younger than 60 years (OR, 3.27; 95% CI 1.04–10.37, $p = 0.043$), no history of previous HF hospitalization (OR, 0.32; 95% CI 0.12–0.86, $p = 0.025$), and systolic blood pressure (sBP) >100 mmHg at discharge (OR, 4.39; 95% CI 1.39–13.81, $p = 0.011$). Overall, there were 51 endpoint events [LVRR 11 (21.6%) vs. non-LVRR 40 (49.4%), $p < 0.001$]. LVRR was a significant predictor of favorable prognosis (HR, 3.77; 95% CI 1.68–8.47, $p < 0.001$). Notably, 41 (80.4%) patients qualified for early-LVRR. Early-LVRR was associated with better prognosis compared with late-LVRR [early-LVRR 6 (14.6%) vs. late-LVRR 5 (50.0%), $p = 0.066$]. Among assessed variables, sBP >100 mmHg at discharge was a significant predictor of early-LVRR (OR, 10.87; 95% CI 1.19–100.0, $p = 0.034$).
Conclusion: Prognosis was improved in patients who achieved LVRR. Early-LVRR tended to be an advantage in terms of long-term prognosis. Higher sBP was a predictor not only for all-LVRR but also early-LVRR.

Introduction

Prognosis of heart failure (HF) has drastically improved over the past decade, yet its prognosis, particularly in patients with advanced cardiomyopathy remains limited. The majority of HF patients undergo left ventricular remodeling; a process by which mechanical, neurohormonal, and possibly genetic factors alter ventricular size, shape and function [1]. The eventual change in the ventricle becomes a threat to overall hemodynamics [2]. Recently, left ventricular reverse remodeling (LVRR) defined as a decrease in dimensions and modification of the shape of the heart resulting in a significant improvement in pump function, has been defined as a clinical entity and is observed in about one third of cardiomyopathy patients [3–8]. In several of the studies, prognosis has been proved to be better among patients who have achieved LVRR.

However, LVRR is a heterogeneous process, and its clinical implications may vary over time. Previous studies have suggested that higher systolic blood pressure (sBP) is a predictor of LVRR [6], but not many have used multivariate analysis for further investigation. Furthermore, given that left ventricular remodeling continues for months after the initial insult [9], LVRR at the early phase may play a more important role compared to remodeling occurring at the later phase. Despite the timing of remodeling being a major objective in this field, previous studies have not examined chronological relationships between LVRR and HF prognosis. In addition, little is known about LVRR in the modern

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Asian HF population. Nevertheless, it is known that beta-blockers and other HF-related medications in Japan are administered at lower doses than in Western facilities, and therefore it is essential to analyze a study population in Japan because these medical agents play an important role in LVRR [10,11].

The objective of this study was to determine early clinical characteristics that predict LVRR. We also sought to identify differences in time to LVRR achievement in a long-term follow-up study. LVRR is an important predictor of long-term prognosis in patients with advanced cardiomyopathy, and further delineation of its process will aid their risk stratification. We also suggest defining the appropriate interval for LVRR after acute decompensation, as it may be essential for predicting prognosis.

Methods

Study population

We enrolled 325 consecutive HF patients with post-acute decompensation who were admitted to Keio University Hospital from June 2005 to February 2011. Patients were followed up at the outpatient clinic of our institute after discharge. Informed consent was obtained from all subjects in accordance with the Keio Hospital admission policies. Of the 325 patients, 69 were excluded on the basis of etiology: valvular disease, sarcoidosis, tachycardia, takotsubo cardiomyopathy, pericarditis, myocarditis, congenital heart disease, right ventricular failure, and miscellaneous infiltrative etiologies.

The remaining 256 patients with idiopathic dilated cardiomyopathy, hypertrophic cardiomyopathy, hypertensive cardiomyopathy, and ischemic cardiomyopathy were assessed. We subsequently excluded 30 patients whose left ventricular ejection fraction (LVEF) was preserved at admission and 2 patients who received cardiac resynchronization therapy. In total, follow-up echocardiogram was not obtained in 196 patients of the 325 patients within 400 days of discharge. Clinical and echocardiographic data were available for 129 patients at mid-term follow-up. A flowchart of the inclusion criteria is shown in Supplementary Figure 1.

Clinical evaluation and biomarker measurements

Clinical data including New York Heart Association functional class, heart rate, sBP, body mass index (BMI), and serum hemoglobin concentration and creatinine level were determined by standard laboratory methods. The estimated glomerular filtration rate (eGFR) was calculated using the Cockcroft–Gault formula.

The plasma brain natriuretic peptide (BNP) level and other biomarkers were measured before discharge and 6 months after initial admission for HF. Commercially available kits were used to measure BNP (Shionogi, Tokyo, Japan) and cardiac troponin T (cTnT; Roche Diagnostics, Tokyo, Japan). The lower limit of detection for cTnT was 0.01 ng/ml.

In the evaluation of prescribed medication, the dosage of each beta-blocker was converted to carvedilol equivalent dose (Supplementary Table 2) (e.g. titer of bisoprolol against carvedilol is 5:1).

Echocardiographic study

Conventional M-mode, two-dimensional, and Doppler variables were measured in all patients at discharge and at the outpatient clinic during follow-up in accordance with guidelines of the American Society of Echocardiography [12]. Left atrial and ventricular diameters, along with wall thicknesses were measured using M-mode echocardiography at the parasternal long-axis acoustic window. LVEF was graded by two dedicated echocardiographers, using the Teicholz method and the biplane method of disks. Referencing these calculations, the LVEF was determined in accordance with the American Society of Echocardiography recommendations [12]. Mitral regurgitation was semi-quantitatively graded considering the regurgitant jet area on color Doppler imaging. Mitral regurgitation with a jet area $>4\ cm^2$ was considered significant. All measurements were obtained from the mean of 3 beats for patients with sinus rhythm. The standard measurement for heart failure patients with atrial fibrillation was to average the measurement of five cardiac cycles or to measure the representative cardiac cycle. All echocardiograms at our facility were recorded according to the recommended protocol of the American Society of Echocardiography. The quality check was performed by the two board-certified echocardiologists assigned to the laboratory.

Criteria of reverse remodeling

LVRR was defined as the presence of a decrease in indexed left ventricular systolic dimension of at least 15% with addition to 25% improvement in LVEF at outpatient check-up compared with measurements at discharge. Algorithm for LVRR classification is shown in Fig. 1. Patients who completed LVRR by the first

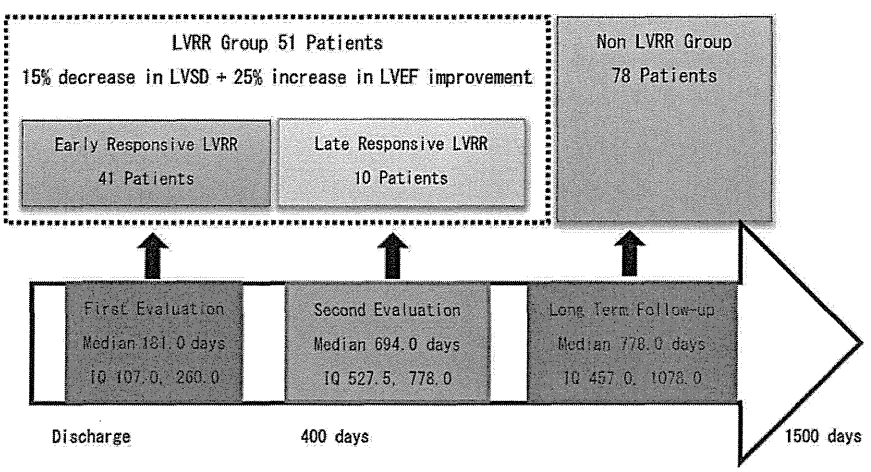

Fig. 1. Classification according to timing of LVRR accomplishment. LVRR, left ventricular reverse remodeling; LVSD, left ventricular systolic dimension; LVEF, left ventricular ejection fraction.

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evaluation within 400 (365 ± 35) days from discharge were classified as the early responsive LVRR group. Patients who completed LVRR at the second evaluation between 400 days and 1500 days from discharge were classified as the late responsive LVRR group. We defined the LVRR group as a combination of the early and late-LVRR groups. Patients who did not accomplish LVRR throughout the follow-up period were defined as the non-LVRR group.

Follow-up data and endpoints

Follow-up information was obtained from medical records and direct inquiries of patients or the patients' families via mail or telephone. In the case of death, the final follow-up was considered to be the date of death. The primary endpoint was a composite of all-cause mortality and hospitalizations for HF. Patients were followed up for a maximum period of 1500 days.

Statistical analysis

Continuous variables are expressed as mean ± SD, and categorical variables as percentages. Between-group continuous and categorical variables were assessed using an unpaired Student's *t*-test and chi-square test, respectively. Log-transformed value of BNP was used in Cox-proportional hazards models and logistic regression models. Each variable was evaluated for its association with LVRR by univariate analysis. Clinically relevant factors and significant variables with a *p*-value of <0.10, namely age younger than 60 years, history of previous hospitalization for HF, atrial fibrillation, sBP >100 mmHg at discharge, plasma BNP and cTnT at discharge, hemoglobin concentration at discharge, and left atrial dimension at discharge were included in a stepwise logistic regression.

Survival curves were drawn by the Kaplan–Meier method, and the curves were compared by the log-rank test. A multivariate Cox regression analysis was performed to adjust for the impact of LVRR and known predictors of long-term prognosis. We also included variables that were statistically significant according to univariate analysis. Variables other than LVRR that were included in the multivariate model were: age, history of previous admission, etiology, BNP, and cTnT levels at discharge, prescription of angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB) at discharge, and beta-blocker prescription at discharge.

All results with a *p*-value of <0.05 were considered statistically significant. All analyses were performed using SPSS, version 19.0 (SPSS Inc., Chicago, IL, USA).

Results

Study population

The 129 study patients had a mean age of 63.5 ± 15.1 years; 80.6% were male, and 72.1% had a non-ischemic etiology. LVRR was observed in 51 patients (39.5%). Differences between the LVRR group and non-LVRR group are detailed below. The baseline characteristics of the study patients are noted in Table 1. BNP, hemoglobin, and eGFR measurements at 6 months from discharge are displayed in Supplementary Table 3. The first echocardiographic evaluation was performed at a median of 181.0 days (IQ: 107.0, 260.0). Variables at the first echocardiographic evaluation are shown in Supplementary Table 4.

Outcomes

The median duration of follow-up was 778 days (IQ; 457.0, 1078.0). Overall, there were 50 re-admissions for HF, 12 deaths, and 51 composite events including both endpoints. The number of events in the LVRR and non-LVRR groups was 11 (21.6%) and 40 (49.4%), respectively. Kaplan–Meier survival curves for both groups are shown in Fig. 2. Patients in the LVRR group had a significantly better long-term prognosis compared with those in the non-LVRR group (log-rank test, $p < 0.001$).

Predictors of mortality according to the multivariate Cox proportional hazards models are shown in Table 2. Compared with the LVRR group, the risk of death due to re-hospitalization for HF

Table 1
Baseline characteristics of patients by LVRR.

Variable	Total (*n* = 129)	LVRR (*n* = 51)	Non-LVRR (*n* = 78)	*p*-Value
Age, years	63.5 ± 15.1	59.1 ± 17.6	66.3 ± 12.6	0.012
Male, *n* (%)	104 (80.6)	40 (78.4)	64 (82.0)	0.259
BMI at discharge, kg/m^2	23.3 ± 4.1	24.0 ± 4.6	22.7 ± 3.6	0.120
Non-ischemic etiology, *n* (%)	93 (72.1)	40 (78.4)	53 (67.9)	0.194
History of past HF admission, *n* (%)	63 (48.8)	17 (33.3)	46 (59.0)	0.004
AF, *n* (%)	40 (31.0)	11 (21.6)	29 (37.2)	0.061
III or IV NYHA functional class at admission, *n* (%)	93 (72.1)	37 (72.5)	56 (71.8)	0.587
sBP at admission, mmHg	129.3 ± 28.7	135.4 ± 28.3	125.4 ± 28.5	0.596
sBP >100 mmHg at admission, *n* (%)	115 (89.1)	50 (98.0)	65 (83.3)	0.010
sBP at discharge, mmHg	105.7 ± 16.4	110.9 ± 15.3	102.3 ± 16.3	0.634
sBP >100 mmHg at discharge, *n* (%)	87 (67.4)	40 (78.4)	47 (60.3)	0.025
BNP at admission, pg/ml	698.7 ± 618.6	684.4 ± 658.7	708.1 ± 595.4	0.558
BNP at discharge, pg/ml	302.7 ± 290.3	238.6 ± 301.1	343.5 ± 277.6	0.641
cTnT >0.10 ng/ml at discharge, *n* (%)	29 (22.5)	7 (13.7)	22 (28.2)	0.144
Hb at admission, g/dl	13.2 ± 2.4	13.8 ± 2.8	12.8 ± 2.1	0.008
Hb at discharge, g/dl	13.4 ± 2.4	14.0 ± 2.6	13.0 ± 2.3	0.101
eGFR at admission	45.0 ± 17.2	48.0 ± 18.0	43.0 ± 16.4	0.964
eGFR at discharge	42.8 ± 16.6	45.5 ± 18.0	41.0 ± 15.5	0.771
LV end-systolic dimension, mm	52.7 ± 12.8	53.7 ± 11.9	52.0 ± 13.4	0.124
LV end-diastolic dimension, mm	63.1 ± 10.8	63.5 ± 10.3	62.9 ± 11.2	0.348
LVEF, %	28.2 ± 8.0	27.6 ± 6.5	28.5 ± 8.8	0.044
LA dimension, mm	45.5 ± 9.2	43.3 ± 8.6	46.9 ± 9.4	0.481
Any ACEi/ARB exposure, *n* (%)	106 (82.2)	43 (84.3)	63 (80.8)	0.302
Any beta-blocker exposure, *n* (%)	118 (91.5)	48 (94.1)	70 (89.8)	0.476
Dose of beta-blocker, mg of carvedilol	8.9 ± 5.6	7.9 ± 4.8	9.6 ± 6.0	0.137

LVRR, left ventricular reverse remodeling; BMI, body mass index; HF, heart failure; AF, atrial fibrillation; NYHA, New York Heart Association; sBP, systolic blood pressure; BNP, brain natriuretic peptide; cTnT, cardiac troponin T; Hb, hemoglobin; eGFR, estimated glomerular filtration rate; LV, left ventricular; LVEF, left ventricular ejection fraction; LA, left atrial; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

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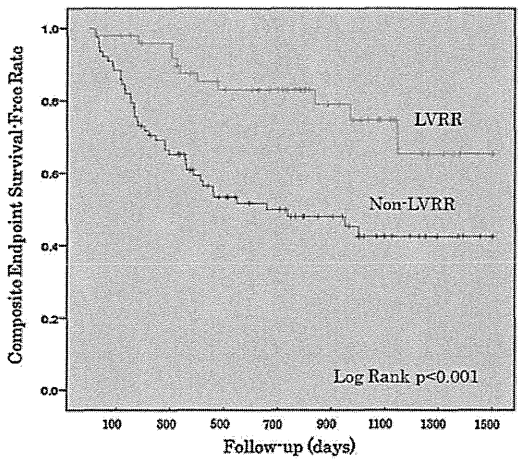

Events	LVRR (n=51)	Non-LVRR (n=78)	Total (n=129)	p-value
HF readmission, n (%)	10 (19.6)	40 (51.3)	50 (38.8)	<0.001
Death, n (%)	2 (3.9)	10 (12.8)	12 (9.3)	0.066
Composite endpoint, n (%)	11 (21.6)	40 (51.3)	51 (39.5)	<0.001

Fig. 2. Long-term prognosis event curve of patients according to LVRR groups. LVRR, left ventricular reverse remodeling; HF, heart failure.

among the non-LVRR group was remarkably greater [hazard ratio (HR), 3.77, 95% CI 1.68–8.47], indicating an association between LVRR and improved prognosis. LVRR was one of the strongest predictors among known predictors including age (HR, 1.01, 95% CI 0.98–1.04), previous hospitalization for HF (HR, 1.63, 95% CI 0.83–1.83), and biomarkers such as BNP or cTnT at discharge (HR, 1.90, 95% CI 1.25–2.89 and HR, 1.98, 95% CI 1.04–3.78). Besides differences in long-term outcome, the LVRR group was also shown to have lower BNP levels at 6 months after discharge compared with the non-LVRR group (140.5 ± 243.9 vs. 401.3 ± 352.1, $p = 0.004$) (Supplementary Table 3).

Table 2
Cox-proportional hazard model of death or HF hospitalization.

Variables	HR	95% CI	p-Value
No LVRR establishment	3.03	1.37–6.71	0.006
Age	1.01	0.98–1.04	0.414
Previous HF hospitalization	1.63	0.83–3.20	0.153
Non-ischemic etiology	0.85	0.40–1.83	0.679
BNP at discharge, pg/ml	1.90	1.25–2.89	0.003
cTnT >0.10 ng/ml at discharge	1.98	1.04–3.78	0.036
Any ACEi/ARB exposure	0.57	0.28–1.18	0.130
Any beta-blocker exposure	0.45	0.14–1.42	0.172

Adjusted for listed variables.
LVRR, left ventricular reverse remodeling; HF, heart failure; BNP, brain natriuretic peptide; cTnT, cardiac troponin T; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

Predictors of LVRR

Among the variables assessed at the initial evaluation, univariate analysis showed that predictors associated with LVRR included age younger than 60 years, no history of hospitalization for HF, atrial fibrillation, higher sBP at discharge, lower plasma BNP concentration at discharge, higher hemoglobin concentration at discharge, and smaller left atrial dimension at discharge (Table 3). None of the prescribed medications were relevant for predicting LVRR achievement, including beta-blockers. In the multivariate analysis, among notable predictors, no previous history of hospitalization for HF and sBP >100 mmHg at discharge were proven to be significantly associated with LVRR.

Early-response LVRR vs. late-response LVRR

Of the 51 patients in the LVRR group, 41 (80.4%) qualified for early-response LVRR. The characteristics of the early- and late-LVRR groups are noted in Table 4. Most measurements proved to be

Table 3
Baseline predictors of left ventricular reverse remodeling ($n = 129$).

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	p-Value	OR	95% CI	p-Value
Age younger than 60 years	2.13	1.02–4.43	0.044	2.53	0.79–8.10	0.117
Female	1.25	0.52–3.03	0.611			
Non-ischemic etiology	1.72	0.76–3.85	0.197			
History of previous HF admission	0.35	0.17–0.72	0.005	0.34	0.12–0.92	0.033
BMI at discharge, kg/m^2	1.09	0.98–1.19	0.118			
AF	0.47	0.21–1.04	0.064	0.54	0.18–1.58	0.257
Hypertension	1.39	0.68–2.86	0.366			
III or IV NYHA functional class at admission	1.27	0.54–2.94	0.588			
sBP at discharge, mmHg	1.03	1.01–1.06	0.005			
sBP >100 mmHg at discharge	2.25	1.11–5.63	0.027	3.28	1.05–10.28	0.042
BNP at admission, pg/ml	0.83	0.60–1.16	0.280			
BNP at discharge, pg/ml	0.54	0.37–0.81	0.002	0.75	0.46–1.22	0.240
cTnT >0.10 ng/ml at discharge	0.40	0.16–1.03	0.059	0.88	0.24–3.25	0.849
Hb at admission, g/dl	1.18	1.01–1.37	0.035			
Hb at discharge, g/dl	1.18	1.01–1.37	0.032	1.19	0.94–1.50	0.144
eGFR at admission	1.02	0.99–1.04	0.109			
eGFR at discharge	1.02	0.99–1.04	0.137			
LAD at discharge, mm	0.95	0.90–1.00	0.041	0.97	0.91–1.03	0.367
LVDd at discharge, mm	1.00	0.97–1.04	0.742			
LVDs at discharge, mm	1.00	0.98–1.04	0.450			
LVEF at discharge	0.99	0.94–1.03	0.549			
Any ACEi/ARB exposure	1.69	0.61–4.76	0.306			
Any beta-blocker exposure	2.04	0.40–11.11	0.389			
Dose of beta-blocker, mg of carvedilol	0.94	0.88–1.01	0.119			

HF, heart failure; BMI, body mass index; AF, atrial fibrillation; NYHA, New York Heart Association; sBP, systolic blood pressure; BNP, brain natriuretic peptide; cTnT, cardiac troponin T; Hb, hemoglobin; eGFR, estimated glomerular filtration rate; LAD, left atrial dimension; LVDd, left ventricular dimension diastolic phase; LVDs, left ventricular dimension systolic phase; LVEF, left ventricular ejection fraction; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

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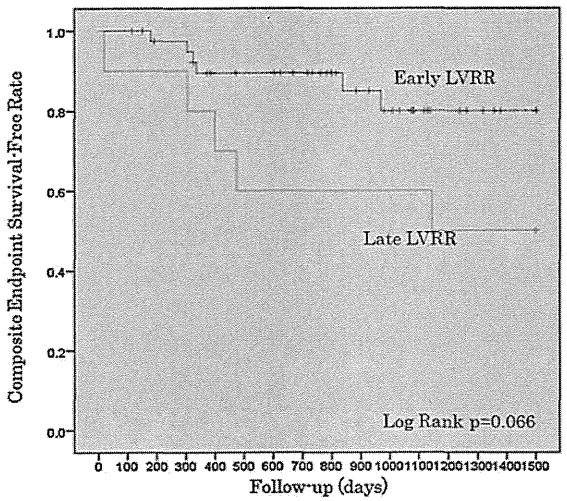
Table 4
Baseline characteristics of early and late responsive LVRR patients.

Variable	Early LVRR (n=41)	Late LVRR (n=10)	p-Value
Age, years	60.7 ± 16.5	52.8 ± 21.6	0.242
Male, n (%)	32 (78.0)	8 (80.0)	0.633
BMI at discharge, kg/m^2	24.5 ± 4.8	21.8 ± 3.1	0.343
Non-ischemic etiology, n (%)	31 (75.6)	9 (90.0)	0.302
History of past HF hospitalization, n (%)	14 (3.4)	3 (30.0)	0.560
Hypertension, n (%)	21 (51.2)	2 (20.0)	0.066
AF, n (%)	8 (19.5)	3 (30.0)	0.367
III or IV NYHA functional class at admission, n (%)	30 (73.2)	7 (70.0)	0.665
sBP at admission, mmHg	138.9 ± 28.6	119.6 ± 21.9	0.455
sBP >100 mmHg, at admission, n (%)	41 (100.0)	9 (90.0)	0.184
sBP at discharge, mmHg	113.0 ± 13.6	101.6 ± 19.8	0.074
sBP >100 mmHg at discharge, n (%)	35 (85.4)	5 (50.0)	0.017
BNP at admission, pg/ml	639.4 ± 589.4	889.2 ± 929.0	0.148
BNP at discharge, pg/ml	204.0 ± 277.0	373.0 ± 368.4	0.094
Troponin T >0.10 ng/ml, at discharge, n (%)	6 (14.6)	1 (10.0)	0.583
Hb at admission, g/dl	13.8 ± 2.9	13.6 ± 2.7	0.792
Hb at discharge, g/dl	14.1 ± 2.6	13.5 ± 2.3	0.645
eGFR at admission	49.8 ± 16.4	40.8 ± 22.9	0.449
eGFR at discharge	47.0 ± 17.0	39.4 ± 21.9	0.169
LV end-systolic dimension, mm	52.0 ± 10.3	60.9 ± 15.6	0.462
LV end-diastolic dimension, mm	62.2 ± 8.9	68.7 ± 14.3	0.460
LVEF, %	28.0 ± 6.0	26.1 ± 8.6	0.136
LA dimension, mm	43.6 ± 9.0	42.3 ± 7.2	0.991
Any ACEi/ARB exposure, n (%)	36 (87.8)	7 (70.0)	0.678
Any beta-blocker exposure, n (%)	40 (97.6)	8 (80.0)	0.331
Dose of beta-blocker, mg of carvedilol	8.0 ± 4.8	7.3 ± 4.5	0.908

LVRR, left ventricular reverse remodeling; BMI, body mass index; HF, heart failure; AF, atrial fibrillation; NYHA, New York Heart Association; sBP, systolic blood pressure; BNP, brain natriuretic peptide; Hb, hemoglobin; eGFR, estimated glomerular filtration rate; LV, left ventricular; LVEF, left ventricular ejection fraction; LA, left atrial; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.



	Early (n=41)	Late (n=10)	p-value
HF readmission, n (%)	5 (12.2)	5 (50.0)	0.002
Death, n (%)	1 (2.4)	1 (10.0)	0.396
Composite endpoint, n (%)	6 (14.6)	5 (50.0)	0.066

Fig. 3. Long-term prognosis event curve of early vs. late LVRR patients. LVRR, left ventricular reverse remodeling; HF, heart failure.

similar between the two groups with the exception of sBP >100 mmHg at discharge [35 (85.4%) vs. 5 (50.0%), $p = 0.017$]. Mean age of the two groups was 60.7 ± 16.5 years and 52.8 ± 21.6 years ($p = 0.242$), respectively. There was no significant difference in the prescription rate [40 (97.6%) vs. 8 (80.0%), $p = 0.331$] or in the dose of beta-blocker used (8.04 ± 4.84 mg vs. 7.32 ± 4.47 mg, $p = 0.908$). Besides baseline variables, BNP measurements at the first evaluation were also significantly different between the groups (87.6 ± 109.7 pg/ml vs. 430.3 ± 506.0 pg/ml, $p < 0.001$).

Kaplan–Meier curves of the composite endpoint and event rates are shown in Fig. 3. The early-response group tended to be associated with better prognosis compared with the late-LVRR group. The results obtained when early LVRR was defined as beneficial response within 1 year were consistent with those obtained within 400 days. We performed an additional analysis including 47 patients, excluding 4 in whom follow-up echocardiography was not performed within 1 year; the early LVRR group had better prognosis (Supplementary Figure 2).

Among the variables assessed at the initial evaluation, univariate analysis showed that predictors associated with early LVRR included sBP at discharge (Table 5). None of the prescribed medications were relevant for predicting early-LVRR.

Table 5
Baseline predictors of early ventricular reverse remodeling among the patients with ventricular reverse remodeling (n=51).

Variable	Univariate analysis		
	OR	95% CI	p-Value
Age younger than 60 years	0.52	0.13–2.13	0.365
Female	1.13	0.20–6.26	0.893
BMI at discharge	1.18	0.95–1.46	0.129
Non-ischemic etiology	0.34	0.04–3.06	0.339
History of past HF hospitalization	0.83	0.18–3.70	0.803
Hypertension	4.42	0.83–23.47	0.081
AF	0.57	0.12–2.69	0.473
III or IV NYHA functional class at admission	1.05	0.18–5.88	0.956
sBP at admission, mmHg	1.03	1.00–1.07	0.074
sBP >100 mmHg at admission	–	–	–
sBP at discharge, mmHg	1.06	1.00–1.12	0.052
sBP >100 mmHg at discharge	7.14	1.52–33.3	0.013
BNP at admission, pg/ml	0.67	0.33–1.37	0.274
BNP at discharge, pg/ml	0.64	0.33–1.24	0.186
cTnT >0.10 ng/ml, at discharge	1.54	0.16–14.50	0.704
Hb at admission, g/dl	1.02	0.80–1.31	0.878
Hb at discharge, g/dl	1.08	0.83–1.42	0.555
eGFR at admission	1.03	0.99–1.08	0.160
eGFR at discharge	1.03	0.98–1.08	0.228
LV end-systolic dimension, mm	0.94	0.88–1.00	0.057
LV end-diastolic dimension, mm	0.94	0.88–1.01	0.100
LVEF, %	1.05	0.93–1.19	0.444
LA dimension, mm	1.02	0.94–1.10	0.677
Any ACEi/ARB exposure	1.03	0.10–10.20	0.981
Any beta-blocker exposure	5.00	0.28–88.53	0.272
Dose of beta-blocker, mg of carvedilol	1.04	0.86–1.24	0.708

BMI, body mass index; HF, heart failure; AF, atrial fibrillation; NYHA, New York Heart Association; sBP, systolic blood pressure; BNP, brain natriuretic peptide; cTnT, cardiac troponin T; Hb, hemoglobin; eGFR, estimated glomerular filtration rate; LA, left atrial; LV, left ventricular; LVEF, left ventricular ejection fraction; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

Discussion

In our study, over a third of patients showed reverse remodeling at the mid-term evaluation and prevalent LVRR. Prognosis was

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improved in patients with LVRR, and it was a strong independent predictor of both re-hospitalization for HF and death. Without LVRR, the risk for HF events was approximately threefold greater compared with patients who achieved LVRR. Importantly, our study showed a higher impact of LVRR on outcomes among early responders (LVRR within 400 days).

The incidence of LVRR in our cohort was in accordance with most previous studies with the exception of studies performed after cardiac resynchronization therapy, where it reaches 50–60% [4,7,8,13,14]. LVRR was defined as a 15% decrease in LVSD (left ventricular systolic dimension) with a 25% improvement in LVEF. Previous studies have included other criteria for LVRR, including increment of LVEF, an absolute limit of diameter length of left ventricular dimension post-LVRR, or a limited EF percentage post-LVRR [3–6,14]. Patients who achieved LVRR by our definition also had improved clinical features, such as shortened LV diameter and increased EF. Kawaii et al. have also shown parallel modifications in both systolic and diastolic LV dimensions, LVEF, and LV mass [14–27] (Supplementary Table 1).

In terms of time to achieve LVRR, most previous studies have not considered LVRR and the time interval from discharge to response. Our study indicated that patients with late-LVRR had worse outcomes compared with patients with early-LVRR. Late-LVRR was associated with lower sBP, and an unfavorable hemodynamic pattern may apply to chronic changes in LVRR establishment.

Recent investigations have indicated the sole effects of beta-blockers beneficially attributing to LVRR. It is thought that a favorable increase in sarcoplasmic reticulum Ca^{2+} ATPase, and alpha-myosin heavy chain encoding genes is the underlying cause of this favorable reaction [15]. However, the prescription rate and approved dosages of beta-blockers are lower in Japan compared with Western countries [10,11]. In our cohort, the mean dose of beta-blockers was approximately 8.5 mg (carvedilol equivalent), which is less than the recommended target dosage in Western countries (e.g. 25–50 mg twice daily). Beta-blockers play an essential role in the LVRR process, and there seems to be a different threshold for LVRR in Japanese patients, because the overall prevalence of LVRR is similar to that in Western countries. The efficiency of beta-blockers differs according to ethnicity, and the Japanese in particular require a low dose compared to their Western counterparts. We have previously investigated whether beta-blocker dose was increased after discharge using information from a registry including 158 patients [19], and we found that the dose of beta-blocker was the same in 53.2% of the patients during a median follow-up of 1.5 years (interquartile range, 0.6–2.6 years).

Elderly patients who had previously experienced HF events were less likely to achieve LVRR despite generalized treatment of our cohort. Repeat HF hospitalizations are known to be representative of the severity of cardiac conditions. Setoguchi et al. concluded that the number of HF events can be used to triage patients according to disease stage [20]. We assume that patients without LVRR are in an advanced stage compared with LVRR patients. Other inverse predictors of LVRR included sBP <100 mmHg and a lower hemoglobin level at discharge. Patients whose sBP is decreased at discharge compared with that at admission may be less likely to tolerate after-load treatment subsequent to hospital stay. Merlo et al. also emphasized the association between LV recovery and higher blood pressure [6]. Anemia is a common co-morbidity factor with HF; anemia may reflect renal failure resulting from failure to reduce overload of the heart [21–23]. Although there were no differences in renal dysfunction at baseline, eGFR measurements tend to be worsening in non-LVRR patients at 6 months post-admission (Supplementary Table 3). We suggest that monitoring of renal function at outpatient clinics may be essential for LVRR establishment.

Limitations

We cannot exclude the possibility of residual confounding by unmeasured or unknown variables. Many patients were not adequately assessed to meet our inclusion criteria or lost to follow-up, limiting the number of subjects in our study. Therefore we were obliged to set a novel time period for determining early vs. late-LVRR. Subjects were selected from a single university hospital and stable patients may have gone to community hospitals for outpatient check-ups. LVEF and left ventricular systolic dimension at discharge were worse in LVRR patients compared with non-LVRR patients, which is in accordance with findings from previous studies [24,25]. We were unable to provide explanations for this contradiction. The diameter of the left ventricle assessed by two-dimensional echocardiography does not accurately represent the true volume of the left ventricle. Artificial causes can also detract from an accurate echocardiographic evaluation [26].

Finally, a considerable number of events occurred before 400 days from discharge, indicating that LVRR may be a result, rather than a cause of cardiac events. A prospective study may clarify the causal relationship between LVRR and preferable prognosis. One of our major limitations is that our study has a retrospective design.

Conclusion

The incidence of LVRR in our study was similar to that in Western individuals despite low-dose beta-blocker treatment. Prognosis was improved in patients who achieved LVRR. In addition, early response to treatment was a major advantage in terms of long-term prognosis. Higher sBP at discharge was most importantly associated with LVRR besides other predictors such as younger age, no history of previous HF hospitalization, and hemoglobin level at discharge. We also suggest sBP >100 mmHg is a predictor of early establishment of LVRR.

Disclosures

None.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jjcc.2015.07.021.

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Clinical Characteristics of Definite or Suspected Isolated Cardiac Sarcoidosis: Application of Cardiac Magnetic Resonance Imaging and ^{18}F-Fluoro-2-deoxyglucose Positron-Emission Tomography/ Computerized Tomography

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ABSTRACT

Background: Isolated cardiac sarcoidosis (iCS) is difficult to diagnose in patients without histologic evidence of sarcoidosis. We aimed to clarify the clinical characteristics of iCS, including imaging features on cardiac magnetic resonance imaging (MRI) and ^{18}F-fluoro-2-deoxyglucose positron-emission tomography/computerized tomography (FDG-PET/CT) scans. We also reviewed the therapeutic effect of corticosteroids and determined the long-term prognosis.

Methods and Results: We retrospectively reviewed 83 consecutive patients with suspicious CS from 1997 to 2013. Systemic sarcoidosis with CS (sCS, n = 30) and iCS (n = 11) were diagnosed according to clinical criteria. In iCS cases, sarcoidosis was not detected in any other organs. The clinical features did not significantly differ between sCS and iCS cases, except for ejection fraction, which was lower in iCS ($P = .025$). Nine sCS and 4 iCS cases showed late gadolinium enhancement, and the lesions tended to be on the epicardial side (76.9% $P = .011$) and septal wall (52.9% $P < .001$). The coefficient of variance for the myocardial standardized uptake value of FDG-PET/CT was higher in sCS (0.32 ± 0.13; n = 19) and iCS (0.32 ± 0.09; n = 7) than in control cases (n = 31; $P < .001$). B-Type natriuretic peptide level was improved after prednisolone treatment in both groups. Kaplan-Meier curve indicated that prognosis was not different between sCS and iCS cases.

Conclusions: The clinical cardiac characteristics of iCS cases were similar to those of sCS. Cardiac MRI and FDG-PET, noninvasive imaging modalities, could be useful modalities to detect myocardial involvement in the cases with definite or suspected iCS. (*J Cardiac Fail 2015;21:313–322*)

Key Words: Isolated cardiac sarcoidosis, left ventricular dysfunction.

Sarcoidosis is a systemic inflammatory disease characterized by the formation of noncaseating granulomas in multiple organs.[1] Granulomatous infiltration of the myocardium in cardiac sarcoidosis (CS) can lead to sudden death[2–4]; however, another report indicated that only 40%–50% of patients who were found to have CS at autopsy had clinical evidence of the condition during their lifetime.[5] The prompt diagnosis of CS is an important clinical topic and enables the initiation of therapy before the occurrence of fatal complications.[6] We reported a case of isolated CS (iCS) in 2000,[7] but there have been few studies on iCS.[8-10]

There are 2 main problems in the diagnosis of iCS. First, the diagnostic sensitivity of endomyocardial biopsy is 20%–30% because of sampling errors.[11] Moreover, a greater proportion of patients present with nonspecific findings on

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endomyocardial biopsy, such as interstitial fibrosis. If a sarcoid granuloma is present in patients in the early phase, sarcoidosis is gradually replaced by fibrosis.[12] Furthermore, only a few biomarkers exhibit specificity for CS, because sarcoidosis presents with a weak systemic immunologic response despite the associated extensive local inflammation.[1] Serum angiotensin-converting enzyme and lysozyme levels have been accepted as diagnostic aids in sarcoidosis, but they do not increase in all cases. The utility of troponin T in the diagnosis of CS has been reported[13]; however, no studies since then have reported on the phenomenon. Therefore, managing cases clinically suspected as iCS without histologic manifestation is a critical issue for therapy, particularly when prescribing prednisolone.

Recent studies have focused on the usefulness of cardiac magnetic resonance imaging (MRI)[14] and ^{18}F-fluoro-2-deoxyglucose positron-emission tomography (FDG-PET) for CS diagnosis.[15] On cardiac MRI, late gadolinium enhancement (LGE) can be used to identify myocardial fibrosis, and in cases of CS this modality shows mid-to-epicardial wall enhancement in the thinning septal or posterior wall.[16,17] FDG-PET has been generally used in inflammatory cardiovascular diseases.[18] FDG is an analogue of glucose and is taken up by leukocytes that are activated by cytokines during systemic immunologic responses to inflammatory diseases.

Here, we aimed to identify common features in patients with clinically suspected iCS according to conventional guidelines. Furthermore, CS-specific features were investigated based on cardiac MRI findings and compared with those of iCS. A secondary aim was to quantitatively assess FDG uptake during FDG-PET/computerized tomography (CT) to identify iCS cases. We further assessed the therapeutic effect of prednisolone and compared the long-term outcomes in sCS and iCS cases.

Materials and Methods

Study Patients, Clinical Classification, and Clinical Assessment

We performed a retrospective review of our database of 11,033 patients who were referred to the Department of Cardiovascular Medicine of Tokyo Medical and Dental University from 1997 to 2013; 83 consecutive patients who were referred for CS or sarcoidosis as an initial diagnosis were identified. The patients had undergone electrocardiography and echocardiography and were diagnosed according to the 2006 version of the Diagnostic Standard and Guideline for Sarcoidosis by the Japan Society of Sarcoidosis and Other Granulomatous Disorders[4] (Table 1). Patients who had undergone endomyocardial biopsy were assessed for the presence of not only noncaseating granulomas but also myocarditis and other cardiomyopathies. All cases of iCS were evaluated the presence or absence of systemic involvement with ophthalmologic examination and close inspection of skin. They were examined with the use of chest X-ray, chest CT, gallium scintigraphy, and/or FDG-PET/CT. The cases were divided into 3 groups: (i) systemic sarcoidosis with CS (sCS), (ii) definite or suspected iCS, and (iii) systemic sarcoidosis without CS (Fig. 1).

If sarcoidosis was not present in the other organs, iCS was determined based on the presence of granulomas in the myocardium (histologic iCS). If a patient fulfilled the clinical criteria for CS (Table 1; Fig. 1) but did not have any histologic manifestations, he or she was assessed to ascertain whether ischemic heart disease had been ruled out by means of coronary angiography or coronary CT angiography. Additionally, suspected iCS patients who had been examined by means of cardiac MRI or FDG-PET were included if they met each criterion for CS.

Suspected iCS cases were further investigated for systemic reactions of sarcoidosis. The conventional guidelines refer to 6 systemic reactions of sarcoidosis.[4] Moreover, the lysozyme level and sustained increase of troponin levels were reviewed. After the classification, we compared differences in therapeutic backgrounds, including the use of intracardiac devices and cardiac involvement, between the sCS and iCS groups. The study protocol was approved by the Institutional Ethics Review Committee of Tokyo Medical and Dental University, and informed consent was obtained from each patient for this study and initiation of corticosteroids.

Cardiac MRI Studies

Cardiac MRI was performed at the Cardiovascular Imaging Clinic and Tokyo Medical and Dental University. At Tokyo Medical and Dental University, the images were acquired during repeated breath-holds with the use of a 1.5-T scanner (Excelart Vantage powered by Atlas; Toshiba Medical Systems) with a phased-array coil. The cardiac MRI procedure involved the use

Table 1. Clinical Diagnosis of Guidelines for Diagnosis of Cardiac Sarcoidosis (2006)—Japan Society of Sarcoidosis and Other Granulomatous Disorders

(1) Major criteria
  (a) Advanced atrioventricular block.
  (b) Basal thinning of the interventricular septum.
  (c) Positive ^{67}gallium uptake in the heart.
  (d) Depressed ejection fraction of the left ventricle (ejection fraction $<50\%$).
(2) Minor criteria
  (a) Abnormal electrocardiography findings: ventricular arrhythmias, complete right bundle branch block, axis deviation, abnormal Q-wave.
  (b) Abnormal echocardiography: regional abnormal wall motion or morphological abnormality (ventricular aneurysm, wall thickening).
  (c) Nuclear medicine: perfusion defect detected by ^{201}thallium or ^{99m}technetium myocardial scintigraphy.
  (d) Gadolinium-enhanced cardiac MR imaging: delayed enhancement of myocardium.
  (e) Endomyocardial biopsy: interstitial fibrosis or monocyte infiltration over moderate grade.
1. 2 or more of the 4 major criteria are satisfied.
2. 1 in 4 of the major criteria and 2 or more of the 5 minor criteria satisfied.