Ⅲ. 研究成果の刊行物・別刷

Both High and Low Body Mass Indexes are Prognostic Risks in Japanese Patients With Chronic Heart Failure: Implications From the CHART Study

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ABSTRACT

Background: Prognostic impact of body mass index (BMI) in Japanese patients with chronic heart failure (HF) remains unclear.

Methods and Results: We examined the relationship between BMI and the prognosis of Japanese HF patients in the Chronic Heart Failure Analysis and Registry in the Tohoku District (CHART) study. The study sample was 972 Japanese chronic HF patients (mean age, 68.2 ± 13.5; male 65.2%). We categorized them into 5 groups; BMI <18.5, 18.5 to 22.9, 23.0 to 24.9 (reference), 25.0 to 29.9, and ≥30.0. Using a Cox hazards model, the relationships between BMI and deaths or admission for worsening HF were studied in detail. Mean follow-up period was 3.4 ± 1.7 years. Multivariate analysis showed that, as compared with reference group (BMI 23.0 to 24.9), hazard ratios (HR) for all-cause death showed a U-shaped association with 1.70 (95% confidence interval; 1.04–2.76), 1.23 (0.85–1.78), 1.26 (0.84–1.90), and 2.75 (1.51–5.00) among those with BMI<18.5, 18.5 to 22.9, 25.0 to 29.9, and ≥30.0, respectively. There were significant and suggestive U-shaped associations between BMI and cardiac-cause death or admission for worsening HF.

Conclusions: Both high and low BMIs were associated with increased outcomes, suggesting that extreme obesity is not beneficial in improving the prognosis of Japanese chronic HF patients. (*J Cardiac Fail 2010;16:880–887*)

The prognosis of patients with chronic heart failure (HF) is still poor despite recent development in the treatment of HF.[1] Therefore, management of risk factors is one of the first-line strategies to improve the prognosis and quality of life in chronic HF patients. In patients with chronic HF, body mass index (BMI; kg/m^2) has been used for evaluation and management of the disorder, and low BMI was consistently associated with the increased death.[2,3] Furthermore, increased BMI has been recognized as an important risk factor for the development of HF in general.[4–7] However, in established HF patients, the relationship between higher BMI and the risk of death or morbidity is unclear.[3,8–17] Previous studies suggested that patients with high BMI had lower rate of death,[8–14] as is the case with patients with end-stage renal disease,[18] malignant tumors,[19] and elderly individuals.[20] In contrast, other studies showed that there is no,[15] or no significant[3,16,17] relationships between higher BMI and the risk of death in patients with HF.

Although the prognostic effect of higher BMI in HF patients remains unclear, the European Society of Cardiology and American College of Cardiology/American Heart Association guidelines for management of HF recommend that HF patients with obesity should reduce their weight to improve the prognosis.[21,22]

Therefore, in the present study, we examined the association of BMI and the prognosis of Japanese chronic HF patients to clarify the prognostic significance of BMI and to identify the optimal BMI level in our chronic HF patient cohort, named the Chronic Heart Failure Analysis and Registry in the Tohoku District (CHART).[23]

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Methods

The CHART Study and the Study Sample

The study design and the major results of our CHART study have been reported previously.[23–25] Briefly, the CHART Study was a multicenter, prospective cohort study conducted between February 2000 and December 2005 that evaluated the clinical characteristics and prognoses in Japanese patients with chronic HF. A total of 1278 patients with stable chronic HF were enrolled who met at least 1 of the following 3 predefined inclusion criteria; (1) left ventricular ejection fraction (LVEF) <50%, (2) left ventricular end-diastolic diameter ≥55 mm, or (3) at least one episode of congestive HF.[23] The diagnosis of HF was based on the criteria of the Framingham study.[26] All information, including medical history, height, weight, laboratory data, and echocardiography data, were compiled into a computer database at the time of enrollment and we then performed a follow-up survey every year. The follow-up period was 3.4 ± 1.7 years. The outcomes of the present study were all-cause death, cardiac-cause death, and admission for worsening HF. Cardiac-cause death was defined as deaths from cardiovascular disease including HF and sudden death. Admission for worsening HF was defined as unexpected admission for treatment of HF. The mode of death and the events of admission for worsening HF were determined by the physicians in attendance. Of the 1278 patients enrolled in our CHART study, 177 patients (13.8%) without a clear history of HF and 129 patients (10.1%) who did not have BMI records were excluded. Therefore, the present study sample was 972 chronic HF patients with sufficient data.

Data and Statistical Analysis

All continuous variables are shown as mean ± standard deviation. BMI was calculated as body weight in kilograms divided by the square of the height in meters (kg/m^2). Estimated glomerular filtration rate was calculated using the simplified modification of diet in renal diseases formula.[27] Chronic kidney disease (CKD) was defined as baseline estimated glomerular filtration rate <60 mL/min/1.73 m^2.[28] Anemia was defined as hemoglobin <12 g/dL in females and <13 g/dL in males, based on the World Health Organization (WHO) definition.[29]

To evaluate the risk of outcomes, we categorized the study sample into 5 groups with different BMI based on the WHO definitions: <18.5, 18.5 to 22.9, 23.0 to 24.9 (reference), 25.0 to 29.9, and ≥30.0.[30] BMI was used as a categorical variable for statistical analyses in the present study. Comparisons of data among the 5 groups were performed by analysis of variance test in continuous variables and by chi-square test in dichotomous variables. Kaplan-Meier curves were plotted to evaluate the association between BMI and outcomes. We also constructed the following 4 Cox proportional hazard regression models: (a) unadjusted, (b) age- and sex- adjusted, (c) age-, sex-, and selected covariates-adjusted, and (d) fully adjusted. In the model (c), we included the following covariates; age, sex, New York Heart Association (NYHA) class, ischemic etiology, history of admission for HF, LVEF, and anemia. In the fully adjusted model (d), in addition to the covariates used in the model (c), we adjusted for treatment (β-blocker, angiotensin-converting enzyme inhibitor, and angiotensin II receptor blocker), hypertension,[31] hyperlipidemia,[32] diabetes mellitus,[33] left ventricular hypertrophy, [34] atrial fibrillation (AF),[35] and CKD[36] that were considered to be in the causal pathway between BMI and outcomes. Continuously, we examined the relationship between BMI and all-cause death stratified by LVEF ≥50% or <50%. We conducted all analyses using IBM SPSS Statistics 18.0. A 2-sided P value of <.05 was considered to be statistically significant.

Results

Baseline Characteristics

Mean age was 68.2 ± 13.5 years and male patients accounted for 65.2% in the study sample (n = 972). Figure 1 shows the distribution of BMI in the present study sample by sex. The mean BMI (median) of the present study was 23.0 ± 3.7 (22.8) kg/m^2 and 87.1% of the study sample had their BMIs between 18.5 and 29.9. The BMI < 18.5 group accounted for 9.1% (n = 88) and the percentage of the BMI ≥30.0 group accounted for 3.8% (n = 37) of the study sample. Table 1 shows the baseline characteristics of the patients. As compared with the BMI 23.0 to 24.9 group (reference), the BMI <18.5 group was characterized by older age (73.0 ± 12.8 years), higher percentage of females (58.0%) and of ischemic etiology (33.0%), more severe symptoms (NYHA III or IV, 36.4%), and lower hemoglobin level. In contrast, the BMI ≥ 30.0 group was characterized by younger age (60.8 ± 17.2 years) and higher prevalence of hypertension (75.7%) and of preserved LVEF (LVEF ≥50%, 59.5%). The prevalence of other important cardiovascular risks, such as hyperlipidemia and diabetes mellitus, tended to be higher in patients with higher BMI. In contrast, there were no significant differences in prevalence of AF and CKD among the 5 groups.

BMI and the Death in Patients With Chronic HF

During the mean follow-up of 3.4 ± 1.7 years, 285 patients (29.3%, 184 males and 101 females) died. Figure 2 shows Kaplan-Meier curves describing the relationships between BMI and outcomes. The BMI ≥ 30.0 group and the BMI <18.5 group showed the higher event rates for all-cause death and cardiac-cause death compared with the BMI 23.0 to 24.9 group (reference) with the lowest event rates (log-rank P < .001).

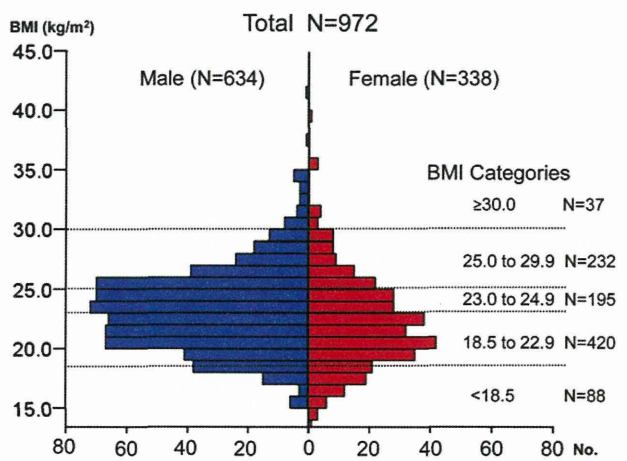

Fig. 1. The distribution of body mass index (BMI) in the study sample stratified by sex.

Table 1. Baseline Characteristics of 972 HF Patients Stratified by BMI Categories

	BMI Categories					
	<18.5 n = 88	18.5 to 22.9 n = 420	23.0 to 24.9 n = 195	25.0 to 29.9 n = 232	≥30.0 n = 37	*P* Value
BMI (kg/m^2)						
Mean (SD)	17.1 (1.2)	20.9 (1.3)	23.9 (0.6)	26.6 (1.3)	32.8 (2.8)	
Median (IQR)	17.4 (1.0)	20.9 (0.9)	23.9 (0.6)	26.2 (0.6)	31.9 (1.3)	
Age (y)	73.0 ± 12.8	69.8 ± 13.1	67.4 ± 12.3	65.6 ± 13.7	60.8 ± 17.2	<.001
Male (%)	42.0	63.1	70.3	73.3	67.6	<.001
Follow-up (y)	2.99 ± 1.74	3.36 ± 1.75	3.75 ± 1.65	3.59 ± 1.77	2.87 ± 1.63	.001
NYHA III or IV (%)	36.4	23.1	12.3	15.1	16.2	<.001
Hypertension (%)	45.5	42.4	48.7	56.0	75.7	<.001
Hyperlipidemia (%)	10.2	14.3	19.0	17.2	24.3	.16
Diabetes mellitus (%)	14.8	17.6	22.1	25.0	27.0	.09
History of admission for HF (%)	29.5	23.8	34.9	29.5	32.4	.02
Atrial fibrillation (%)	37.5	39.8	48.7	42.7	32.4	.16
Etiology						.052
Ischemic (%)	33.0	26.4	23.1	30.6	24.3	
Valvular (%)	26.1	26.0	22.6	13.4	10.8	
LVH (%)	38.6	40.0	39.5	44.8	45.9	.68
Measurement						
LVDD (mm)	55.1 ± 9.1	56.0 ± 9.9	55.6 ± 9.6	56.2 ± 10.1	58.9 ± 11.5	.39
LVDD >55 mm (%)	50.0	51.9	51.0	53.0	62.2	.77
LVEF (%)	49.6 ± 15.7	51.2 ± 16.7	52.1 ± 14.4	52.7 ± 16.0	51.5 ± 17.1	.56
LVEF ≥50% (%)	46.6	47.8	55.7	59.1	59.5	.03
Hemoglobin (g/dL)	11.7 ± 1.9	12.6 ± 2.1	13.5 ± 2.0	13.5 ± 2.1	13.8 ± 2.4	<.001
Anemia or not (%)	65.9	48.2	27.7	29.4	35.1	<.001
Creatinine (mg/dL)	1.1 ± 0.9	1.2 ± 1.3	1.0 ± 0.5	1.0 ± 0.5	0.9 ± 0.3	.03
CKD or not (%)	23.9	27.7	18.5	23.6	21.6	.17
Medical therapy						
ACE-I or ARB (%)	69.3	66.7	76.4	76.3	73.0	.04
β-blocker (%)	34.1	30.0	28.2	28.0	40.5	.49
Loop diuretic (%)	77.8	78.3	68.5	72.9	84.4	.07
Spironolactone (%)	22.2	20.2	21.2	24.8	31.3	.50
Ca blocker (%)	27.1	26.3	35.4	35.4	27.0	.07
Digitalis (%)	50.6	48.9	50.8	42.6	29.7	.08

HF, heart failure; IQR, interquartile range; NYHA, New York Heart Association; LVH, left ventricular hypertrophy; LVDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; CKD, chronic kidney disease; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker. Results are expressed as mean ± standard deviation (SD).

Table 2 shows results of the Cox proportional hazard models for the development of all-cause death and cardiac-cause death. In the unadjusted model (a), as compared with the BMI 23.0 to 24.9 group (reference), the BMI<18.5 group, the BMI 18.5 to 22.9 group, the BMI 25.0 to 29.9 group, and the BMI ≥ 30.0 group showed 147%, 70%, 37%, and 170% increase in the risk for all-cause death, respectively (each *P* value; <.001, <.001, .12, and .001).

In the fully adjusted model (d), as compared with the BMI 23.0 to 24.9 group (reference), the hazard ratios (HR) for all-cause death of the BMI<18.5 group, BMI 18.5 to 22.9 group, BMI 25 to 29.9 group, and the BMI ≥30.0 group were 1.70 (95%CI; 1.04–2.76), 1.23 (0.85–1.78), 1.26 (0.84–1.90), and 2.75 (1.51–5.00), respectively. In the model (d), as compared with the model (c), HR for all-cause death in the BMI <18.5 group was influenced by including the following covariates: hypertension, hyperlipidemia, diabetes mellitus, left ventricular hypertrophy, AF, CKD, and treatment, but the HR for all-cause death in the BMI ≥30.0 group remained robust (Table 2).

We also constructed the Cox models between BMI and all-cause death stratified by LVEF ≥ 50% or <50% (Table 3). In the fully adjusted model (d), a 91% increase in the risk of all-cause death among the BMI <18.5 group with LVEF ≥50% was observed; however, it did not reach statistical significance (Table 3). Otherwise, the BMI ≥ 30.0 group with LVEF ≥ 50% showed significant 187% increase in the risk of all-cause death. Similar trend was also observed in patients with LVEF <50% as shown in the Table 3.

Of 285 deaths, 221 deaths (77.5%) were due to cardiac cause. The HRs (95%CI) for cardiac-cause death in the fully adjusted model (d) were 1.78 (1.02–3.09) and 2.99 (1.56–5.76) in the BMI <18.5 group and the BMI ≥ 30.0 group, as compared with the BMI 23.0 to 24.9 group (reference) (Table 2). Results also showed a U-shaped association between HRs and BMI with the lowest HR in the BMI 23.0 to 24.9 group not only in all-cause death, but also in cardiac-cause death.

BMI and the Risk of Admission for Worsening HF in Patients With Chronic HF

Admission for worsening HF was noted in 309 patients (31.8%) during the study period. Kaplan-Meier curves for admission for worsening HF was plotted in Fig. 2. Patients in the BMI 23.0 to 24.9 group (reference) had the lowest events rate for admission for worsening HF (Fig. 2).

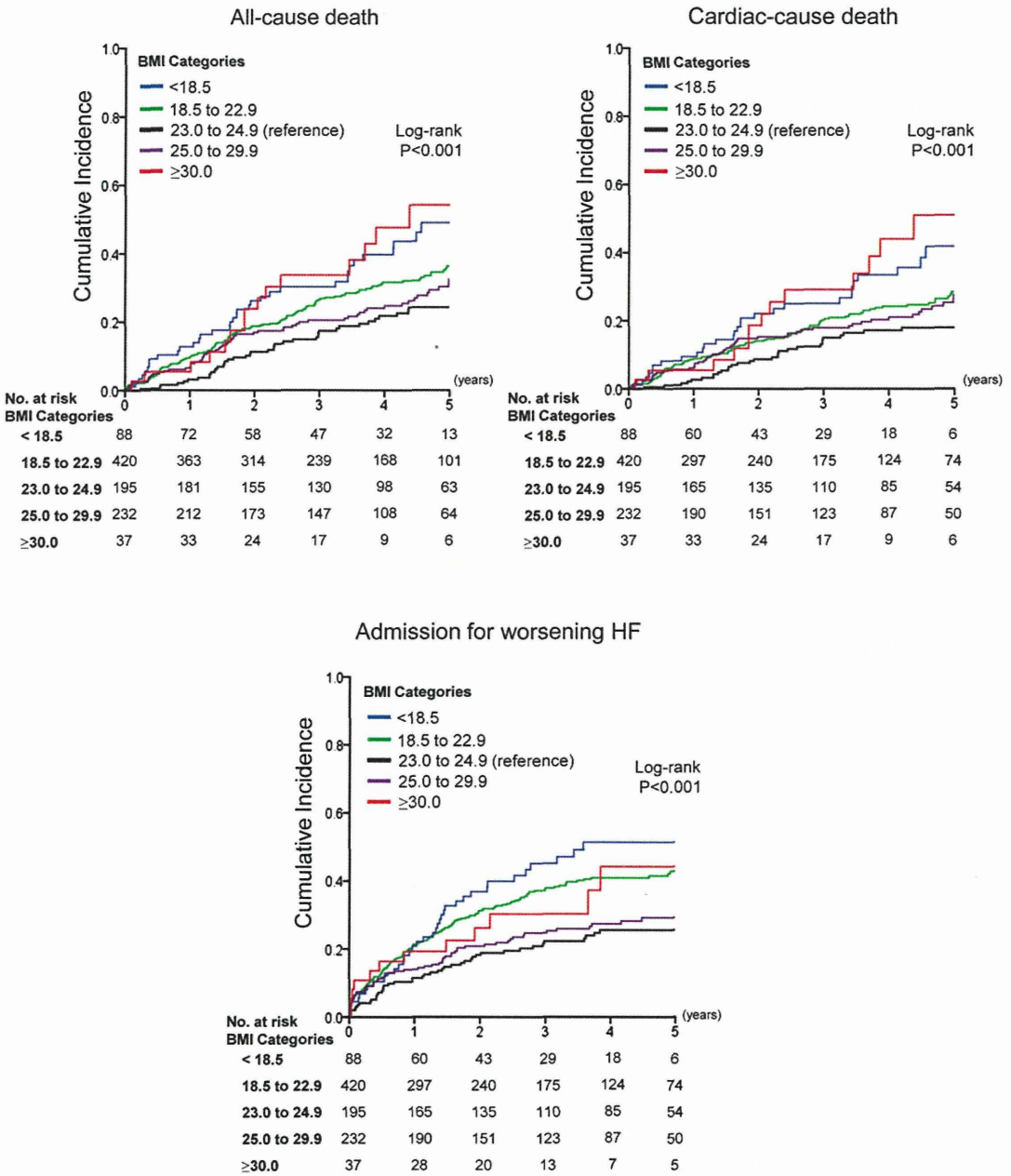

Fig. 2. Kaplan-Meier curves categorized by body mass index (BMI) levels in Japanese patients with chronic heart failure (HF), for all-cause death, cardiac-cause death, and admission for worsening HF.

Results of Cox regression models between BMI and the risk for admission for worsening HF were shown in Table 2. In the unadjusted model (a), as compared with the BMI 23.0 to 24.9 group (reference), the BMI < 18.5 group, the BMI 18.5 to 22.9 group, the BMI 25.0 to 29.9 group, and the BMI ≥ 30.0 group showed 142%, 91%, 19%, and 89% increase in the risk of admission for worsening HF, respectively (each *P* value; <.001, <.001, .38, and .04). This trend was also observed in the age- and sex- adjusted model (b). In the fully adjusted model (d), HRs (95% CI) were 1.44 (0.90–2.29), 1.44 (1.02–2.04), 1.15 (0.77–1.72), and 2.02 (1.07–3.82), suggesting that there was a U-shaped association between BMI and admission for worsening HF.

Discussion

We have shown that Japanese chronic HF patients with BMI 23.0 to 24.9 had the lowest all-cause death, cardiac-cause death, and admission for worsening HF. Both patients with lower or higher BMI had heightened risk of adverse outcomes and the association between BMI and the HRs for outcomes showed a U-shaped profile.

Low BMI and Prognosis of Japanese HF Patients

We showed that lower BMI was associated with increased risk for all-cause death, cardiac-cause death, and admission

Table 2. Cox Proportional Hazard Models for All-cause Death, Cardiac-cause Death, and Admission for Worsening HF

	No. of Events (%)	No. of Events/ 100 Person-year	(a) Unadjusted			(b) Age- and Sex-adjusted			(c) Age-, Sex-, and Covariates-adjusted			(d) Fully Adjusted		
			HR	95% CI	*P* Value	HR	95% CI	*P* Value	HR	95% CI	*P* Value	HR	95% CI	*P* Value
All-cause death														
BMI categories														
<18.5	36 (40.9)	13.7	2.47	1.57 − 3.88	<.001	1.94	1.22 − 3.08	.005	1.36	0.86 − 2.16	.19	1.70	1.04 − 2.76	.03
18.5 to 22.9	131 (31.2)	9.3	1.70	1.19 − 2.42	<.001	1.53	1.07 − 2.18	.02	1.18	0.84 − 1.67	.34	1.23	0.85 − 1.78	.27
23.0 to 24.9 (reference)	40 (20.5)	5.5	1.00			1.00			1.00			1.00		
25.0 to 29.9	62 (26.7)	7.4	1.37	0.92 − 2.04	.12	1.41	0.94 − 2.09	.94	1.22	0.83 − 1.79	.32	1.26	0.84 − 1.90	.26
≥30.0	16 (43.2)	15.1	2.70	1.51 − 4.83	.001	3.12	1.74 − 5.60	< .001	2.42	1.36 − 4.31	.003	2.75	1.51 − 5.00	.001
Cardiac-cause death														
BMI categories														
<18.5	29 (33.0)	11.0	2.63	1.58 − 4.39	<.001	2.09	1.24 − 3.53	.006	1.35	0.80 − 2.28	.25	1.78	1.02 − 3.09	.04
18.5 to 22.9	97 (23.1)	6.9	1.67	1.11 − 2.52	.01	1.52	1.01 − 2.29	.05	1.13	0.76 − 1.68	.55	1.17	0.76 − 1.80	.47
23.0 to 24.9 (reference)	30 (15.4)	4.1	1.00			1.00			1.00			1.00		
25.0 to 29.9	51 (22.0)	6.1	1.58	0.96 − 2.36	.08	1.54	0.98 − 2.42	.06	1.29	0.84 − 2.00	.25	1.38	0.87 − 2.19	.17
≥30.0	14 (37.8)	13.2	3.12	1.65 − 5.88	<.001	3.42	1.80 − 6.49	<.001	2.60	1.39 − 4.87	.003	2.99	1.56 − 5.76	.001
Admission for worsening HF														
BMI categories														
<18.5	38 (43.2)	14.5	2.42	1.57 − 3.74	<.001	1.99	1.28 − 3.10	.002	1.20	0.77 − 1.86	.42	1.44	0.90 − 2.29	.13
18.5 to 22.9	155 (36.9)	10.7	1.91	1.37 − 2.67	<.001	1.82	1.30 − 2.54	.001	1.31	0.95 − 1.79	.10	1.44	1.02 − 2.04	.04
23.0 to 24.9 (reference)	44 (22.6)	6.1	1.00			1.00			1.00			1.00		
25.0 to 29.9	59 (25.4)	7.0	1.19	0.81 − 1.76	.38	1.23	0.83 − 1.82	.29	1.01	0.70 − 1.86	.95	1.15	0.77 − 1.72	.49
≥30.0	13 (35.1)	12.3	1.89	1.02 − 3.51	.04	2.09	1.12 − 3.90	.02	1.58	0.86 − 2.92	.14	2.02	1.07 − 3.82	.03

BMI, body mass index; HF, heart failure; HR, hazard ratio; CI, confidence interval. In the model (c), we adjusted the model by age, sex, New York Heart Association class, ischemic etiology, history of admission for HF, left ventricular ejection fraction, and anemia. In the fully adjusted model (d), in addition to the covariates used in the model (c), we adjusted for the following covariates; treatment (β-blocker, angiotensin-converting enzyme inhibitor, and angiotensin II receptor blocker), hypertension, hyperlipidemia, diabetes mellitus, left ventricular hypertrophy, atrial fibrillation, and chronic kidney disease.

Table 3. Cox Proportional Hazard Models Stratified by LVEF for All-cause Death

	No. of Events (%)	No. of Events/100 Person-year	(a) Unadjusted			(b) Age-and Sex- adjusted			(c) Age-, Sex-, and Covariates-adjusted			(d) Fully Adjusted		
			HR	95% CI	*P* Value	HR	95% CI	*P* Value	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Patients with LVEF ≥50%														
BMI categories														
<18.5	21 (51.2)	16.9	3.20	1.75 – 5.86	.01	2.38	1.26 – 4.47	.01	1.59	0.83 – 3.06	.16	1.91	0.98 – 3.70	.06
18.5 to 22.9	69 (34.7)	9.9	1.88	1.15 – 3.07	.01	1.63	0.99 – 2.66	.052	1.21	0.74 – 1.97	.44	1.29	0.77 – 2.15	.34
23.0 to 24.9 (reference)	21 (19.4)	5.3	1.00			1.00			1.00			1.00		
25.0 to 29.9	28 (20.6)	5.4	1.03	0.59 – 1.82	.92	1.06	0.60 – 1.87	.83	1.02	0.59 – 1.76	.95	1.13	0.64 – 1.99	.68
≥30.0	10 (45.5)	14.2	2.70	1.27 – 5.73	.01	3.45	1.60 – 7.43	.002	2.94	1.38 – 6.28	.005	2.87	1.31 – 6.29	.01
Patients with LVEF <50%														
BMI categories														
<18.5	15 (31.9)	10.8	1.81	0.92 – 3.57	.09	1.52	0.76 – 3.05	.24	1.08	0.54 – 2.14	.83	1.49	0.71 – 3.13	.29
18.5 to 22.9	59 (27.2)	8.3	1.44	0.86 – 2.41	.17	1.36	0.81 – 2.26	.25	1.04	0.62 – 1.72	.89	1.17	0.68 – 2.04	.57
23.0 to 24.9 (reference)	19 (22.1)	5.8	1.00			1.00			1.00			1.00		
25.0 to 29.9	32 (34.0)	10.2	1.77	1.00 – 3.12	.05	1.87	1.06 – 3.32	.03	1.40	0.80 – 2.45	.25	1.67	0.91 – 3.05	.10
≥30.0	6 (40.0)	16.7	2.73	1.09 – 3.57	.03	3.16	1.24 – 8.02	.02	1.80	0.71 – 4.56	.21	3.00	1.15 – 7.85	.03

BMI, body mass index; LVEF, left ventricular ejection fraction; HR, hazard ratio; CI, confidence interval. In the model (c), we adjusted the model by age, sex, New York Heart Association class, ischemic etiology, history of admission for HF, and anemia. In the fully adjusted model (d), in addition to the covariates used in the model (c), we adjusted for the following covariates; treatment (β-blocker, angiotensin-converting enzyme inhibitor, and angiotensin II receptor blocker), hypertension, hyperlipidemia, diabetes mellitus, left ventricular hypertrophy, atrial fibrillation, and chronic kidney disease.

for worsening HF in Japanese chronic HF patients. Results were consistent with previous studies using Western HF patients.[2,3]

The recent report from the CHARM Study showed that patients with lower BMI had a graded increase in risk of all-cause death as compared with patients with BMI between 30.0 and 34.9, who had the lowest HR for death.[3] Underweight, which is frequently observed in HF patients, has been considered to be associated with malnutrition and wasting that are related to chronically increased inflammatory status.[37] In patients with advanced HF, the release of pro-inflammatory cytokines is increased, leading to the development of protein-energy malnutrition that might be the major mechanism of this reverse relationship between lower BMI and poor prognosis in chronic HF patients.[2,3,37]

High BMI and Prognosis of Japanese HF Patients

In the present study, we showed that higher BMI was associated with the increased risk for all-cause death, cardiac-cause death, and admission for worsening HF, suggesting that extreme obesity was associated with poor prognosis in Japanese patients with chronic HF. Elevated BMI is associated with hemodynamic overload, increased metabolic demand, and increased peripheral resistance, all of which could cause LV remodeling.[12,38] And it was also reported that high BMI was associated with enhanced neurohumoral activation and increased oxidative stress.[39]

Several previous studies have shown inconsistent results with the present study. Oreopoulos et al reported in their meta-analysis of 9 observational studies that both overweight patients (BMI 25.0 to 29.9) and obese patients (BMI ≥30.0) were associated with lower all-cause death, concluding that such obese status might be protective.[14] However, Alla et al observed no significant association between high BMI and the mortality of chronic HF patients,[15] and Kenchaiah et al showed that in the CHARM Study, compared with HF patients with BMI between 30.0 and 34.9, patients with BMI ≥35 had a 17% increased risk of death, but did not reach statistical significance probably because of the small sample size, overadjustment for covariates, or both.[3]

Our result supports the recommendation of the European Society of Cardiology and American College of Cardiology/American Heart Association guidelines for management of HF, which advise for HF patients with obesity to reduce their weight for better prognosis.[21,22]

Optimal BMI Level to Improve Prognosis of Japanese HF Patients

We demonstrated that the association between BMI and all-cause death or cardiac-cause death showed a U-shaped profile with the lowest event rate at between 23.0 and 24.9 in Japanese chronic HF patients. The shape of the association between BMI and admission for worsening HF also suggested a U-shaped profile. We were unable to evaluate the association between BMI and noncardiac death because of the small number of events (event number; 7 in the BMI <18.5 group, 34 in the BMI 18.5 to 22.9 group, 10 in the BMI 23.0 to 24.9

group, 11 in the BMI 25.0 to 29.9 group, and 2 in the BMI ≥30.0 group).

In the present study, optimal BMI level was shifted to the lower levels than previous studies in Western countries. Although the detailed mechanism of this discrepancy is unclear and may be attributed to complex clinical conditions, we speculate that it was due to anthropometrical characteristics of the Japanese population. In general, Asian population has lower BMI compared with Western population and hence the distribution of BMI is shifted toward lower BMI levels.[40] In 2007, the Organization for Economic Co-operation and Development reported that adult individuals with BMI ≥30.0 accounted for about 32% of the US adult population; however, the percentage of adult obese individuals was only 3% in Japan.[41] This lower rate of the population with BMI ≥30.0 may influence the distribution of BMI in our study sample.

Japanese individuals have a high percentage of adipose tissue at a lower BMI[42] and have a higher rate of beta-3 adrenergic receptor gene mutation, which might be associated with more likelihood of weight gain.[43,44] Excessive deposition of adipose tissue causes insulin resistance and prolonged inflammatory responses,[45] which may lead to the development of cardiovascular disease and death at lower BMI levels in Japanese populations. In this sense, Japanese HF patients might be a more "fat-sensitive" population and might be more susceptible to adverse cardiovascular effects caused by obesity compared with Western HF patients.

Limitations of the Study

Several limitations should be mentioned for the present study. First, the sample size of the present study was relatively small, especially in patient with BMI ≥30.0, which could cause possible selection bias. Second, we excluded the patients who did not have BMI data (n = 129). The mean age of patients without BMI data was 72.3 ± 11.1 years and male accounted for 62.0%. When we constructed the unadjusted survival curves using Kaplan-Meier method, the cumulative incidence rates between the group with BMI data and that without BMI data were not statistically significant (data not shown). Therefore, we believe that the exclusion of patients without BMI data did not influence the major findings of the present study. Third, in the Cox hazard models, we did not include other important variables, especially chronic obstructive pulmonary diseases and peripheral edema that were shown to have close interactions with BMI[4,12] because of limited data availability. Fourth, we did not account for changes in BMI during follow-up.

Conclusions

Despite the study limitations, the present results from our CHART study imply that both high and low BMI are associated with increased death and hospitalization for HF in Japanese chronic HF patients. Further studies should be performed to evaluate the optimal BMI level for better prognosis and quality of life in chronic HF patients.

Disclosures

None.

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Review

Chronic kidney disease and heart failure—Bidirectional close link and common therapeutic goal

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Summary Chronic kidney disease (CKD) is common and the estimated prevalence is about 9–13% in the general adult population. CKD is defined by the presence of kidney damage or decreased glomerular filtration rate. Individuals with CKD have a far greater likelihood of cardiovascular death than progression to end-stage renal disease. Heart failure (HF) is a complex clinical syndrome that can result from any structural or functional cardiac disorder and the prevalence is reported to be 2–3% in the general population. The prognosis of HF patients is still poor despite recent advances in HF treatment. Both diseases are major and growing public health problems because aging of the population contributes to the increasing incidence of those diseases. More than 40% of HF patients have CKD and the close relationship between CKD and HF worsens their prognoses. All physicians must evaluate kidney function using estimated glomerular filtration rate calculated by the new Japanese equation in patients with HF. Accurate evaluation of pathophysiology between the two diseases and appropriate intervention are necessary to improve the prognosis of patients with the diseases.

Contents

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Introduction

Chronic kidney disease (CKD) is an extensive public health problem which should be recognized properly by every healthcare provider. The US National Kidney Foundation Kidney Disease Outcome Quality Initiative proposed the concept of CKD and established the definition and classification in 2002 [1].

Studies from the USA, Europe, Australia, and Asia showed that the prevalence of CKD is about 9–13% in the general population [2–5]. The incidence and prevalence of patients with CKD including end-stage renal disease (ESRD) have doubled in the past 10 years in the USA [6]. Many patients with CKD die from cardiovascular disease (CVD) and patients who need renal replacement therapy are fewer, except in those with ESRD [7]. CKD is more prevalent in patients with CVD or with CVD-related risk factors, such as hypertension, diabetes mellitus, dyslipidemia, and metabolic syndrome. Furthermore, CKD is a significant aggravating factor in patients with these conditions and is also an important prognostic risk for them [8].

Heart failure (HF) is also a serious and expanding public health matter and is one of the leading causes of mortality in most developed countries. More than 5 million patients have HF and over 550,000 patients are newly diagnosed with HF every year in the USA [9]. The European Society of Cardiology reports that there are at least 15 million patients with HF in 51 European countries, which have a total population of more than 900 million [10]. The prevalence of HF is approximately 2–3% and rises sharply in elderly populations, and it has been increasing because of the progressive aging of the population and the decreased mortality of patients who survived the first coronary event [11]. The total estimated costs for managing HF were reported to be 27.9 billion dollars in the USA in 2005, and 905 million pounds in the UK in 2000 [11,12]. Approximately 50% of HF patients die at 4 years and 40% of admitted patients with HF are dead or readmitted within 1 year despite the recent improved treatment for HF [10].

Patients with HF usually have much co-morbidity such as arterial hypertension, diabetes mellitus, chronic obstructive pulmonary disease, anemia, cachexia, gout, and renal insufficiency, and such co-morbidity aggravates the condition of HF. Renal dysfunction is especially common in HF patients, and anemia, hyperkalemia, low serum albumin, and uses of renin-angiotensin-system (RAS) inhibitors, aldosterone antagonists, and diuretics are associated with such disorder [10]. The prevalence of renal impairment increases with age, HF severity, a history of hypertension, or diabetes.

Such close interaction between kidney and heart has been called "cardiorenal syndrome (CRS)" and this connection is observed to be the most strong in patients with HF. It seems to be mediated by not only the decreased cardiac output but also by the effects of the activated RAS, the imbalance between nitric oxide and reactive oxygen species, inflammation, anemia, and the increased sympathetic nervous activity.

This brief review describes the close relationship and pathophysiology between CKD and HF, and summarizes treatment strategies in HF patients with CKD.

Table 1 Definition of chronic kidney disease [1].

Criteria
1. Kidney damage for ≥3 months, as defined by structural or functional abnormalities of the kidney, with or without decreased GFR, manifest by either: Pathological abnormalities; or Markers of kidney damage, including abnormalities in the composition of the blood or urine, or abnormalities in imaging tests
2. GFR < 60 ml/min/1.73 m^2 for ≥3 months, with or without kidney damage

GFR, glomerular filtration rate.

Definitions of CKD and HF: progressive disorders

The diagnosis of CKD is easily given by the existence of kidney damage or decreased glomerular filtration rate (GFR) for three months or more. GFR is estimated using the formula including serum creatinine level, age, sex, and ethnicity irrespective of cause of the disease. The definition and classification stages of CKD are shown in Tables 1 and 2 [1]. CKD is considered to be a disease that progresses from mild to

Table 2 CKD classification based on severity [1].

Stage	Description	GFR (ml/min/1.73 m^2)
1	Kidney damage with normal or ↑ GFR	≥90
2	Kidney damage with mild ↓ GFR	60–89
3	Moderate ↓ GFR	30–59
4	Severe ↓ GFR	15–29
5	Kidney failure	<15 (or dialysis)

CKD, chronic kidney disease; GFR, glomerular filtration rate; ↑, increased; ↓, decreased.

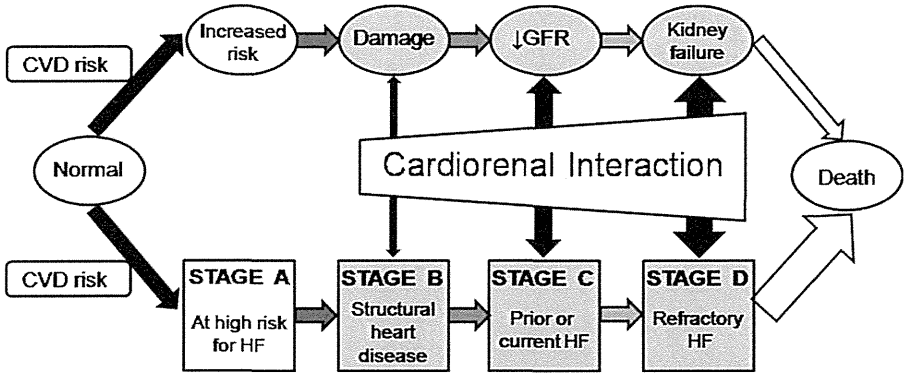

Figure 1 Cardiorenal interaction and stage classification in the initiation and progression of chronic kidney disease and heart failure [1,11]. CVD, cardiovascular disease; HF, heart failure; GFR, glomerular filtration rate.

severe condition as shown in Fig. 1, which is the conceptual model of the course of CKD.

HF is a complex clinical syndrome that can be caused by any structural or functional cardiac disorder that impairs the pump function of the heart [11]. There have been many definitions of HF proposed to date [13]. The common and most important feature of HF syndrome includes symptoms, signs, and objective evidence of a structural or functional abnormality (Table 3). It must be emphasized that HF is not equal to left ventricular dysfunction and HF is characterized by specific symptoms in the past medical course and signs revealed by the physical examination. The Writing Committee of the AHA/ACC Heart Failure Guidelines developed a new stage classification of HF in 2001, which includes 4 stages presenting the development and progression of the HF syndrome (Fig. 1). Stage A denotes patients with CVD risks such as hypertension, diabetes mellitus, metabolic syndrome, etc. and without any geometric or functional disorder in the left ventricle. In contrast, patients who are asymptomatic but show left ventricular hypertrophy and/or left ventricular dysfunction are indicated as Stage B. When patients have symptoms of HF caused by underlying structural heart disease in the current or past medical status, those are considered to reach Stage C. Finally Stage D specified patients with refractory HF who may need mechanical circulatory support or heart transplantation [11].

Both classifications of CKD and HF have the same characteristics which clearly show the progressive manner of diseases and these classifications can provide a reliable and objective tool to identify patients on the way of developing the diseases (Fig. 1). Furthermore, they can indicate the recommendation for treatments which are considered to be appropriate at each stage of illness and are expected to prevent advancement from one stage to the next.

Patients in the clinical intersection between CKD and HF are at a high risk for poor outcomes. Inter-relationships of CKD and HF include common characteristics, such as common risk factors, bidirectional effects of one disease process on the progression of the other, adverse effects on one disease process when investigating the other, and treatment biases potentially influenced by both diseases. Those clinical and pathophysiological links will be more expanded as the stage progresses and will aggravate the severity of the diseases more seriously (Fig. 1).

Table 3 Definition of heart failure [10].

Heart failure is a clinical syndrome in which patients have the following features:
Symptoms typical of heart failure
(breathlessness at rest or on exercise, fatigue, tiredness, ankle swelling)
and
Signs typical of heart failure
(tachycardia, tachypnoea, pulmonary rales, pleural effusion, raised jugular venous pressure, peripheral edema, hepatomegaly)
and
Objective evidence of a structural or functional abnormality of the heart at rest
(cardiomegaly, third heart sound, cardiac murmurs, abnormality on the echocardiogram, raised natriuretic peptide concentration)

HF in patients with CKD

The overlap between CKD and other chronic diseases, most notably diabetes, hypertension, chronic obstructive pulmonary disease, and CVD is common. The annual data report of the United States Renal Data System (USRDS) in 2009 reported that the prevalence of CVD reached 63% in CKD patients compared to 5.8% of those without CKD, and it graded the association with both CKD severity and age [6]. While CKD is a risk multiplier for the development of CVD, the largest hazard occurs for HF. Compared with patients without CKD, the relative risk for the development of HF was 1.45 and 1.68 in patients with CKD of stage 1–2 and 3–5, respectively, when evaluating Medicare patients age 66 and older [6]. The event rate of HF diagnosis in those patients was the highest among all CVD and it was 56 events per 1000 patient years for patients without CKD and 176 for those with CKD of stage 3–5. Age-adjusted survival of CKD patients with HF was poor; one-year mortality of patients with CKD of stage 3–5 was nearly 25% although that of those without CKD was 17% [6].

Table 4 Prevalence and hazard of chronic kidney disease in patients with chronic heart failure.

Ref. no.	Study	Year	No. of pts	NYHA	Age, years	Male, %	EF, %	BP or HTN	DM, %	RASi, %	eGFR < 60,%	Follow-up	Outcome	Adjusted hazard comparing with pts without CKD for the outcome
17	SOLVD-T	2000	2,161	I–IV	60.7	81.5	24.7	40.4%	24.9	50.3	35.7	–	All-cause mortality	1.41 for eGFR <60[a]
18	PRIME-II	2000	1,906	III–IV	64.7	80.4	26.2	121.6/ 75.1 mmHg	20.7	91.6	49 (eGFR ≤ 58)	277 days (median)	All-cause mortality	1.91 for eGFR 44–58 2.85 for eGFR <44
19	DIG	2002	585	II/III: 85%	65	73.9	35	128.3/ 75.3 mmHg	40.3	88	50 (eGFR ≤ 63.8)	2.6 years (median)	All-cause mortality	1.6 for eGFR 47–64[a] 2.1 for eGFR 18–48[a]
20	McClellan	2002	665	–	75.7	40	38.4	66%	44	54	38[b]	–	All-cause mortality	1.24 at 1-year mortality[b]
21	UK-HEART	2002	553	II/III: 98%	62.7	76	42	–	0	82	–	–	All-cause mortality	1.09 in each 10 μmol/l increase of creatinine
22	CHARM	2006	2,680	II–IV	65.3	66.6	38.5	128.2/ 73.6 mmHg	37.2	45.5	36	34.4 months	CV death + HF hospitalization	1.54 for eGFR 45–59.9 1.86 for eGFR <45
23	ANCHOR	2006	59,772	–	71.8	54.2	NA	61%	32.4	24	39.2	2.07 years (median)	All-cause mortality + HF hospitalization	1.39 for eGFR 30–44 2.28 for eGFR 15–29
24	CHART	2008	920	II–IV	68.3	65.1	49.3[c]	39.2%[c]	19.3[c]	69.1[c]	42.7	3.45 years	All-cause mortality + HF hospitalization	1.31 for eGFR 30–59 1.56 for eGFR <30
25	JCARE-CARD	2009	2,013	1.8 (mean)	71.5	58.7	44.8	54.5%	30.7	ACEi: 36.7 ARB: 46.1	70.3	2.4 years	All-cause mortality	1.26 for eGFR 30–59 2.48 for eGFR <30

EF, ejection fraction; BP, mean blood pressure; HTN, hypertension; DM, diabetes mellitus; RASi, renin–angiotensin-system inhibitor; eGFR, estimated glomerular filtration rate (ml/min/1.73 m^2); pts, patients; CKD, chronic kidney disease; HF, heart failure; CV, cardiovascular; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

[a] ml/min.

[b] CKD was defined by serum creatinine of ≥1.4 mg/dl for women and ≥1.5 mg/dl for men.

[c] Data were retrieved from the previous study that included 1154 patients.

Unadjusted all-cause mortality evaluating Medicare patients age 66 and older showed the declining trend in patients with CKD during the past 10 years. However, relative risk of mortality was almost 3 times higher when CVD accompanied CKD [6]. Approximately 50% of CKD patients died of complications of CVD before they reached ESRD [14]. Keith et al. revealed that death was more common than progression to ESRD by evaluating more than 28,000 patients with CKD from a health maintenance organization [7]. Only about 20% of patients with stage 4 CKD had progressed to dialysis, whereas 46% had died of cardiovascular complications.

CVD accounted for 43.7% of the all-causes of death in dialysis patients in the USRDS database in 2005–2007 [6]. The percentage of HF as a cause of mortality was 5.3%, however event rates for congestive HF in dialysis patients reached 270 per 1000 patient years [6]. A report from the HEMO study indicated that HF prevalence in ESRD patients is about 40% [15].

The prevalence and incidence of HF, and the percentage of mortality due to HF in patients with mild to moderate CKD is not well described, because such patients have a broad spectrum of characteristics including CKD stage, age, and cardiovascular risks. Kottgen et al. studied the role of impaired kidney function as a risk factor for incident HF evaluating 14,857 middle-aged individuals without HF who were enrolled in The Atherosclerosis Risk in Communities Study [16]. Crude HF incidences were 5.7, 5.9, and 17.7 per 1000 person-years in those with estimated GFR $\geq$ 90, 60–89, and <60 ml/min/1.73 m^2, respectively, and a greater decline in kidney function during the follow-up period occurred in individuals concomitant with HF hospitalization/death compared to those who did not develop HF.

CKD in patients with HF

CKD is common in patients with HF. Table 4 shows the major publications including our report describing the prognosis and characteristics of chronic HF patients with CKD that were published after 2000 [17–25]. CKD was present in 35–70% of HF patients evaluated in cohort studies or subanalyses of randomized controlled trials. Furthermore, the comorbidity of CKD was associated with increased hospitalization due to worsening HF and all-cause/cardiovascular deaths. The hazard ratio for all-cause mortality in HF patients with moderate to severe CKD was about 1.3–2.9 compared to those without CKD (Table 4). The prognostic impact of CKD was observed in a broad spectrum of HF patients [22], however Ahmed et al. reported accompanying CKD was more strongly associated with mortality in patients with preserved ejection fraction than in those with reduced ejection fraction [26].

One of the major mechanisms of worsening renal function in patients with HF is considered to be long-term reduced renal perfusion. However, estimated GFR in HF patients with preserved ejection fraction was similar compared with that in those with reduced ejection fraction [27] and the ESCAPE trial revealed that renal congestion might be a more important factor for renal impairment compared to increased pulmonary artery pressure [28]. Other contributing factors of hypoperfusion are the increased vasoconstrictive mediators (epinephrine, angiotensin, endothelin) and pharmacotherapy-related effects including diuresis-associated hypovolemia, RAS inhibitors, and drug-induced hypotension [29]. Other possible mechanisms of kidney–heart interaction are shown in Table 5.

Table 5 Proposed mechanism in cardiorenal interaction.

Common factors for heart and kidney
Traditional cardiovascular risk factors
Smoking
Obesity
Hypertension
Diabetes
Dyspilidemia
Other risk factors
Malnutrition
Genetic risk factors
Humorally mediated factors
Elevated sympathetic nervous system
Elevated renin-angiotensin system
Other common factors
Inflammation
Endothelial dysfunction
Immune mediated damage
Oxidative stress
Coagulation imbalance
Treatment related factors
Undertreatment
Toxic agents
Organ-specific factors
Hemodynamics mediated factors
Decreased cardiac output (heart)
Renal hypoperfusion (heart)
Elevated venous pressure (heart)
Sodium and water retention (kidney)
Hypertension (kidney)
Other specific factors
Brain natriuretic peptide (heart)
Anemia (kidney)
Uremic solute retention (kidney)
Calcium and phosphate abnormality (kidney)
Electrolyte, acid-base imbalances (kidney)

Acute kidney injury in patients with acute heart failure

Acute heart failure (AHF) is defined as a rapid onset or change in the signs and symptoms of HF, which may be either new HF or worsening of pre-existing chronic HF. Although AHF is usually characterized by pulmonary congestion, acutely reduced cardiac output and tissue hypoperfusion are also important hemodynamic aspects, which sometimes cause multiorgan failure. A rapid worsening of cardiac function also leads to acute kidney injury

Table 6 Proposed definitions of cardiorenal syndrome [34].

CRS type 1 (acute CRS)
Abrupt worsening of cardiac function (e.g. acute cardiogenic shock or decompensated congestive heart failure) leading to acute kidney injury
CRS type II (chronic CRS)
Chronic abnormalities in cardiac function (e.g. chronic congestive heart failure) causing progressive and permanent chronic kidney disease
CRS type III (acute renocardiac syndrome)
Abrupt worsening of renal function (e.g. acute kidney ischemia or glomerulonephritis) causing acute cardiac disorder (e.g. heart failure, arrhythmia, ischemia)
CRS type IV (chronic renocardiac syndrome)
Chronic kidney disease (e.g. chronic glomerular disease) contributing to decreased cardiac function, cardiac hypertrophy and/or increased risk of adverse cardiovascular events
CRS type V (secondary CRS)
Systemic condition (e.g. diabetes mellitus, sepsis) causing both cardiac and renal dysfunction

CRS, cardiorenal syndrome.

(AKI) and pre-morbid chronic renal dysfunction has been reported as a common precursor for AKI in HF patients [30,31]. Worsening renal function, defined as a rise in serum creatinine level >0.3 mg/dl, during hospitalization for HF is observed in 20–30% of HF patients [29]. Any change in serum creatinine has been reported to be associated with longer hospital stay, increased costs, and increased short-term/long-term mortality [29]. Lower estimated GFR on HF admission was also an independent predictor for long-term mortality in AHF patients [32]. The mechanisms of the relationship are multiple and complex including persistent vasoconstriction, high renal venous pressure, elevated intra-abdominal pressure, adenosine and tubuloglomerular feedback, and medicine perturbing intrarenal hemodynamics (Table 5) [29,33].

Classification of cardiorenal syndrome

The bidirectional natures of heart and kidney interaction represent the pathophysiological basis for a clinical entity that has been called cardiorenal syndrome (CRS) (Fig. 1). Ronco et al. proposed the new classification of CRS to help physicians characterize groups of patients, to provide the rationale for specific management strategies, and to allow the design of future clinical trials [34]. They defined CRS as a pathophysiologic disorder of the heart and kidneys whereby acute or chronic dysfunction of 1 organ may induce acute or chronic dysfunction of the other, and divided CRS into 5 different subtypes (Table 6). The proposed mechanism of kidney–heart interaction is also shown in Table 5. The benefit and validity of using this classification should be confirmed in future studies.

Anemia in patients with CKD and/or HF

Anemia develops relatively early in the disease course of CKD and worsens with CKD severity. McClellan et al. reported that anemia was present in 47.7% in 5222 enrolled patients with CKD [35] and the prevalence of anemia was strongly associated with decreased GFR. The major mechanisms of the development of anemia are decreased erythropoietin production and increased erythropoietin resistance, and other causes include decreased red blood cell life span due to uremic toxins, chronic blood loss caused by platelet dysfunction, nutritional deficiencies [36], iron deficiency, and elevated inflammatory cytokines [37] that may cause bone marrow suppression.

Anemia also frequently occurred in HF patients, with reports ranging widely from 9.0% to 79.1% [38,39], but the majority of studies described more than 20% [40]. Previous reports suggested that decreased hemoglobin level was associated with increased rates of death and HF-related admission [23]. Anemia observed in HF patients mainly is attributed to kidney-related factors described above, and is also related with bone marrow suppression by frequent angiotensin-converting enzyme (ACE) inhibitor use in HF patients [41]. Because CKD and anemia frequently co-exist and worsen the prognosis in patients with HF, CRS is also named as "cardio-renal-anemia syndrome" [40].

Whether the correction of anemia using erythropoiesis-stimulating agents is beneficial or not in patients with CKD or HF is still controversial. Previous trials have reported that the complete normalization of hemoglobin levels in CKD patients did increase adverse outcomes, although it might improve cardiac function [42]. The CHOIR study revealed the surprisingly higher rates of adverse events in CKD patients targeted for the high hemoglobin level (13.5 g/dl) compared with those in the low hemoglobin group (11.3 g/dl) [43]. The CREATE and the TREAT studies also showed that the complete correction of hemoglobin level did not demonstrate any improvement in cardiovascular events [44,45]. Meanwhile, some previous studies evaluating patients with HF showed a beneficial impact of anemia correction on HF symptoms, left ventricular ejection fraction, and quality of life [46,47]. However, in a recent trial in HF patients (STAMINA-HeFT), darbepoetin alfa treatment did not significantly improve exercise duration, NYHA functional class, or even health-related quality of life [48]. A large-scale, double-blind, randomized morbidity and mortality trial (RED-HF) is currently ongoing and it may demonstrate the impact of anemia correction on mortality in those patients [49].

Treatments of CKD patients with HF and of HF patients with CKD

A complete description or details of treatment in patients with CKD or HF are beyond the scope of this article, which may appear in the authoritative clinical practice guidelines for the treatment of CKD or HF [1,10,11]. The following part highlights the issue regarding the treatment using RAS inhibitors, which is the most commonly recommended therapy in patients with HF or CKD.

Reduction of proteinuria or albuminuria by treatment is associated with the slowing of the progression of CKD and is associated with reducing the cardiovascular events [50–52]. Major clinical practice guidelines recommended RAS inhibitors as the first-line therapy for patients with proteinuric nephropathy [53–55]. However, several researchers indicated that RAS blockade was not effective in patients with early-stage CKD [56,57]. Furthermore, O'Hare et al. estimated that 40.6% of the US population older than 70 years had stage 3 or 4 CKD, most of whom were diagnosed only by the decreased estimated GFR with lower urinary protein excretion. They noted that such a population was poorly represented in randomized controlled trials of CKD progression [58] and thus, whether there is a benefit of RAS inhibitors in such elderly CKD patients is still unknown.

Many studies have shown that the use of ACE inhibitors increased survival in HF patients with reduced left ventricular function [59–61]. Angiotensin II receptor blockers (ARB) provide comparable beneficial effect on cardiovascular outcomes in those patients [62,63]. Several researchers have shown that the beneficial effect of RAS inhibition on HF and CKD seems to be independent to lowering blood pressure (BP) [64,65].

Whether the interventions aimed at lowering BP by way of RAS inhibition and lowering protein excretion are beneficial simultaneously to both cardiovascular and renal outcome is still controversial. The IDNT trial revealed that the relative risk for reaching a renal end point progressively decreased with the lowering in achieved systolic BP using irbesartan, and the group below 120 mmHg did not show the increased risk [64]. However, the risk for both all-cause mortality and cardiovascular mortality rose in patients who achieved less than 120 mmHg of systolic BP by a relative risk of 3.05 and 4.06, respectively, and the decrements of diastolic BP were significantly associated with the increased rate of myocardial infarction [65]. Meanwhile, the RENAAL trial showed that patients with more than 30% reduction in urine protein excretion were associated with a significantly reduced risk for renal outcome compared with those without such a reduction. Furthermore, the reduction in proteinuria was also associated with reduced cardiovascular event rates [51].

Medical recommendations in treating HF patients with renal impairment

Because HF patients with CKD have been not adequately represented in randomized controlled trials of HF, most treatments in such patients are not usually prescribed in an evidence-based manner. The following recommendations must be validated in future studies [10,11].

1. General principles
   (1) Evaluate the CKD stage using estimated GFR and urine albumin:creatinine ratio.
   (2) Check etiology of CKD.
   (3) Control BP appropriately using anti-hypertensive medicines including RAS-inhibitors and/or beta-blockers (<130/80 mmHg).
   (4) Appropriate management of other traditional cardiovascular risks including diabetes, dyslipidemia, smoking, etc. is necessary.
   (5) Check all CKD-related risks including anemia, serum electrolyte abnormality, serum albumin level, renotoxic agents, etc.
   (6) When using ACE inhibitors/ARB, contraindications in patients must be checked thoroughly and consider reducing dose in patients with moderate-severe CKD.
   (7) Aldosterone antagonists should be used with caution as they may cause significant hyperkalemia.
   (8) Renal dysfunction is usually associated with impaired clearance of HF medicines. The start or maintenance doses should be reduced and plasma levels must be monitored frequently to avoid toxicity, if possible.
   (9) HF patients with CKD often have excessive salt and water retention, which needs more intensive diuretic treatment. In patients with severe CKD, loop diuretics are more effective than thiazide diuretics.
2. AHF Patients with AKI (CRS Type 1)
   (1) Evaluate status of cardiac output and renal congestion.
   (2) A gradual diuresis is recommended and extracorporeal ultrafiltration may be considered in case of severely decreased diuretic responsiveness [66].
   (3) Close monitoring of renal function and hyperkalemia is necessary especially when RAS inhibitors are used [67].
   (4) The administration of beta-blockers is not recommended until the patient has stabilized physiologically [68].
   (5) The radiocontrast agent should be used in the careful consideration for nephropathy and needs appropriate prophylaxis [69].
3. Chronic HF Patients with CKD (CRS Type 2)
   (1) Attention needs to be paid to reducing risk factors and optimizing medication.
   (2) Diuresis-associated hypovolemia, RAS inhibitors, and drug-induced hypotension are contributing factors for renal impairment [29].
   (3) In patients with diabetic nephropathy and overt proteinuria, the risk for congestive HF may increase when systolic BP is decreased to less than 120 mmHg [65].
   (4) Peritoneal dialysis may be a therapeutic option for refractory HF patients with severe CKD [70].

Current status of CKD in Japan

Iseki et al. reported that the prevalence of CKD was higher in Japan than in other Asian countries and the USA and that individuals with a low GFR (<60 ml/min/1.73 m^2) were estimated to be 20% of the adult population [71]. According to the Japanese Society for Dialysis Therapy, the prevalence of patients with ESRD was greater than 2000 per million population since 2005. CKD is also a major public health problem in Japan and the Japanese Society of Nephrology published a CKD Practice Guideline in September 2007 [72].

Most patients with CKD are diagnosed by decreased GFR, which is usually estimated from serum creatinine level, age, sex, and ethnicity by using the Modification of Diet

Table 7 The equation for estimated GFR in Japan [72,74].

Estimated GFR ($ml/min/1.73\,m^2$) = $194 \times \text{serum creatinine}^{-1.094} \times \text{age}^{-0.287} \times 0.739$ (if female)

GFR, glomerular filtration rate.

in Renal Disease (MDRD) Study equation. Several studies have revealed that the equation for estimated GFR must be modified properly in non-white individuals, because of the variation in serum creatinine caused by the difference in muscle mass, the calibration difference in serum creatinine assay, or the different method to measure true GFR [73]. Matsuo et al. reported the revised GFR-equation in 2009 to enable more accurate estimation of GFR in the Japanese population (Table 7) [74]. Imai et al. re-evaluated the prevalence of CKD patients using this new equation in 74,024 members of the adult population who participated in a large-scale annual health check-up program in 2005. They concluded that about 13% of Japanese adult population, approximately 13.3 million people, were predicted to have CKD in 2005 [3].

Conclusions

CKD is frequently observed in HF patients and GFR had an inverse graded association with HF severity. CKD is one of the major predictors for admission for worsening HF and cardiovascular/all-cause mortality in such patients. Although a major focus of HF treatment has been on the heart, treatment strategies also should be targeted on the kidney. Evaluation of GFR should be performed in all patients with HF and patients with CKD must be treated carefully considering common pathophysiologic nature between two organs. Given the increased incidence of both diseases which pose significant impact on public health, patients with CKD should be appropriately included in future trials of HF to develop clinical evidence, which will improve the prognosis and quality of life in patients with HF.

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Trend of Westernization of Etiology and Clinical Characteristics of Heart Failure Patients in Japan

– First Report From the CHART-2 Study –

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Background: Hospitalization due to acute heart failure syndrome (AHFS) is an indicator of worsened prognosis for patients with cardiovascular disease (CVD). The Chronic Heart Failure Analysis and Registry in the Tohoku District 2 (CHART-2) Study was designed to elucidate characteristics and prognosis of patients at high risk for CVD progression due to AHFS.

Methods and Results: The CHART-2 Study is a prospective observational multicenter cohort study. Patients with overt HF, structural cardiac disorder but without HF, or with coronary artery disease (CAD) have been consecutively enrolled from October 2006. As of March 2010, a total of 10,219 patients have been recruited, making the Study the largest multicenter prospective cohort of HF patients in Japan. The mean patient age was 68.2± 12.3 years and male patients accounted for 69.8%. Overt HF was observed in 46.3% of patients; and 53.7% did not have HF but were at high risk for AHFS. As HF stage progressed, the prognostic risks (eg, chronic kidney disease, reduced ejection fraction, and increased B-type natriuretic peptide level) became more prominent. Compared with the previous CHART-1 study, the prevalence of ischemic etiology and risk factors (hypertension, diabetes) have increased, as in Western studies.

Conclusions: This first report demonstrates the trend of westernization of ischemic etiology and clinical characteristics of HF patients in Japan, indicating the importance of appropriate management and prevention of CAD to prevent AHFS. (*Circ J* 2011; **75:** 823–833)

Key Words: Coronary artery disease; Heart failure; Prognosis; Risk factors

Cardiovascular disease (CVD) is the leading cause of death in most developed countries.[1] Furthermore, many developing countries are now catching up with regard to this trend.[1] Heart failure (HF) is the end-stage of CVD and is becoming more common all over the world because of the westernization of lifestyle, the rapid aging of the population, and the increased number of survivors of serious cardiovascular illness due to recent advances in medical and surgical treatment.[2,3] We previously performed a multicenter prospective cohort study of HF patients (Chronic Heart Failure Analysis and Registry in the Tohoku District 1 Study: CHART-1) from February 2000 to December 2005 (n=1,278). The CHART-1 Study found that HF patients were also prevalent in Japan and that the prognosis was similarly poor compared with that in Western countries.[4,5] The most prevalent etiology of HF in the CHART-1 Study was non-ischemic cardiomyopathy (28.6%), and coronary artery disease (CAD) accounted for only 25.4% of the total HF patients, which was considerably low compared with a Western HF study.[3] Hospitalization due to the onset of acute heart failure syndrome (AHFS) is a key event in the disease progression of HF and CVD. Thus, it is important to avoid the decompensation of chronic HF and prevent de novo development of congestive HF in CVD patients in order to improve their long-term quality of life.[6,7] Western studies reported that the most frequent etiology of AHFS was ischemic in origin,[8,9] but the characteristics of such patients at high risk in Japan and the type of pathophysiologic derangement that causes decompensation from stable HF remain uncertain. Furthermore, although a large number of studies have shown that most

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