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ORIGINAL ARTICLE
Heart Failure

Body Mass Index Is an Independent Predictor of Long-Term Outcomes in Patients Hospitalized With Heart Failure in Japan

– A Report From the Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD) –

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Background: Obesity is a risk factor for cardiovascular disease (CVD) and is also associated with an increased risk of death in subjects without CVD. However, in heart failure (HF), elevated body mass index (BMI) has been shown to be associated with better prognosis, but it is unknown whether this is the case in unselected HF patients encountered in routine clinical practice in Japan.

Methods and Results: The Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD) studied prospectively the characteristics and treatments in a broad sample of patients hospitalized with worsening HF and the outcomes were followed for 2.1 years. Study cohort (n=2,488) was classified into 3 groups according to baseline BMI: <20.3 kg/m^2 (n=829), 20.3–23.49 kg/m^2 (n=832), and ≥23.5 kg/m^2 (n=827). The mean BMI was 22.3±4.1 kg/m^2. Patients with higher BMI had lower rates of all-cause death, cardiac death, and rehospitalization because of worsening HF. After multivariable adjustment, the risk for all-cause death and cardiac death significantly increased with decreased BMI levels compared with patients with BMI ≥23.5 kg/m^2. However, BMI levels were not associated with rehospitalization for worsening HF.

Conclusions: Lower BMI was independently associated with increased long-term all-cause, as well as cardiac, mortality in patients with HF encountered in routine clinical practice in Japan. (*Circ J* 2010; **74:** 2605–2611)

Key Words: Body mass index; Heart failure; Mortality; Obesity; Prognosis

Obesity is a well-established risk factor of cardiovascular diseases (CVDs)[1] and a higher body mass index (BMI) is associated with an increased risk for cardiovascular events, including new-onset heart failure (HF).[2,3] However, BMI has been also demonstrated to be inversely associated with long-term mortality in HF, the so-called "obesity paradox".[4–8] However, recent studies suggest that this obesity paradox in HF does not persist after matching for indicators of disease severity and cofounders.[9,10] Therefore, although a number of previous studies have demonstrated higher mortality rates in HF patients with lower BMI, better understanding of its relationship to long-term adverse outcomes in unselected HF patients encountered in routine clinical practice, including mortality and hospitalization because of worsening HF, is critically needed. Moreover, most of the previous studies were performed mainly in the United States and Europe, so the association between BMI and outcomes needs to be assessed in HF patients in Japan, because BMI values are much lower in the Japanese general population compared with Western countries.[11]

We analyzed the data from the Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD), a prospec-

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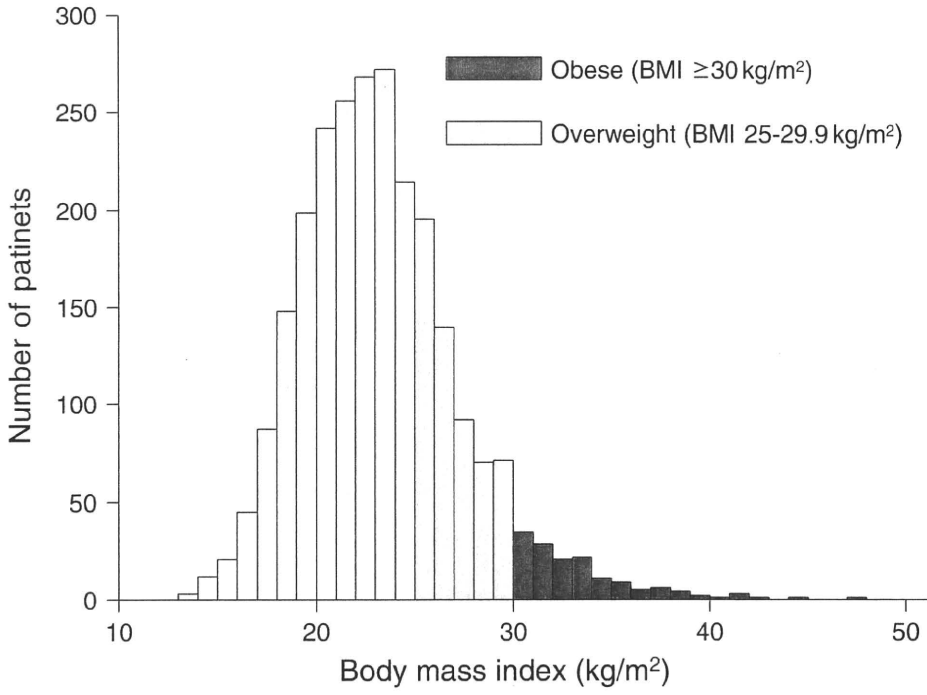

Figure 1. Distribution of baseline body mass index (BMI) among the total cohort of 2,488 patients with heart failure.

tive database of the clinical characteristics, treatments, and outcomes in a broad sample of patients hospitalized with worsening HF in Japan.[12-19] The purpose of the present study was to determine both the prevalence of low BMI in the JCARE-CARD database and whether it is independently associated with long-term outcomes, including mortality and rehospitalization because of worsening HF.

Methods

Study Patients

The details of the JCARE-CARD have been described previously.[12] Briefly, eligible patients were those hospitalized for worsening HF as the primary cause of admission. For each patient, baseline data obtained at discharge included (1) demography; (2) cause of HF; (3) precipitating cause; (4) comorbidities; (5) complications; (6) clinical status; (7) electrocardiographic and echocardiographic findings; (8) plasma brain-type natriuretic peptide (BNP); and (9) treatments, including discharge medications.

The JCARE-CARD enrolled a total of 2,675 patients hospitalized for HF at 164 participating hospitals; 187 patients were excluded because of missing data for height and/or body weight, resulting in 2,488 patients who were divided into 3 groups according to BMI: <20.3 kg/m² (n=829), 20.3–23.49 kg/m² (n=832), and ≥23.5 kg/m² (n=827).

Outcomes

The status of all patients was surveyed after discharge and the following information was obtained: (1) survival, (2) cause of death, and (3) rehospitalization because of an exacerbation of HF that required more than continuation of the usual therapy from the prior admission. Only patients who survived the initial hospitalization were included in the follow-up analysis. Follow-up data were obtained for 2,154 of 2,488 patients (86.6%). Mean post-discharge follow-up was 784±312 days (2.1±0.9 years).

Statistical Analysis

Patient characteristics and treatments were compared using the Pearson chi-square test for categorical variables and 1-way ANOVA for continuous variables. Cumulative event-free rates during the follow-up were derived using the method of Kaplan and Meier. The relationship between BMI and outcome was evaluated with multivariable adjustment. Baseline clinical variables, treatments, and the severity of HF at discharge were used to develop a post-discharge Cox proportional hazard models. $P<0.05$ was used for as the criterion for variables to remain in the model. SPSS version 16.0 J for Windows (Chicago, IL, USA) was used for all statistical analyses.

Results

Patients' Characteristics

Figure 1 shows the distribution of the baseline BMI values among the total cohort (n=2,488). The mean and median BMI values were 22.3±4.1 (mean±SD) and 21.9 kg/m², respectively, ranging from 12.3 to 46.7 kg/m². In total, 409 (15.3%) patients were classified as overweight (BMI 25 to 29.9 kg/m²), and 117 (4.4%) patients as obese (BMI ≥30 kg/m²) using the definition of the World Health Organization (http://www.who.int/mediacentre/factsheets/fs311/en/index.html).

Table 1 provides a comparison of the clinical characteristics of the total cohort and when classified into 3 groups according to BMI. The mean age was 70.5 years and 60.2%

Table 1. Baseline Patients' Characteristics According to BMI

	Total (n=2,488)	BMI (kg/m²)			P value
		<20.3 (n=829)	20.3–23.49 (n=832)	≥23.5 (n=827)	
Demographic					
Age, years (mean±SD)	70.5±13.4	74.2±12.6	71.2±12.6	66.1±13.6	<0.001
Male, %	60.2	50.7	64.7	65.4	<0.001
Cause of heart failure, %					
Ischemic	32.2	29.7	33.3	33.7	0.152
Valvular	27.1	34.7	28.1	18.4	<0.001
Hypertensive	24.7	19.2	23.1	31.9	<0.001
Dilated cardiomyopathy	18.9	17.6	18.6	20.6	0.299
Medical history, %					
Hypertension	52.6	42.6	52.1	63.2	<0.001
Diabetes mellitus	30.3	21.5	31.8	37.5	<0.001
Dyslipidemia	25.4	17.4	24.4	34.5	<0.001
Hyperuricemia	46.9	44.2	45.9	50.7	0.027
Prior stroke	14.8	16.7	14.8	12.7	0.069
COPD	6.3	7.8	6.2	5.0	0.076
Smoking	38.2	32.5	39.1	43.0	<0.001
Prior MI	26.9	25.1	28.5	27.2	0.285
Atrial fibrillation	35.0	37.3	33.8	34.1	0.263
Sustained VT/VF	6.4	7.1	6.8	5.4	0.354
Procedures, %					
PCI	17.8	15.3	18.6	19.6	0.063
CABG	9.5	7.7	10.2	10.6	0.093
Valvular surgery	6.9	9.1	6.4	5.2	0.006
CRT-D	0.2	0.4	0.1	0.1	0.424
Vital signs at discharge					
NYHA functional class	1.77±0.70	1.85±0.76	1.77±0.66	1.70±0.65	<0.001
Heart rate, beats/min	70.3±11.8	70.4±11.3	70.4±12.3	70.3±11.8	0.974
SBP, mmHg	116.9±18.6	114.7±18.2	117.0±18.8	119.0±18.4	<0.001
DBP, mmHg	66.0±11.6	63.5±11.4	65.9±11.7	68.6±11.3	<0.001
Laboratory data at discharge					
Serum creatinine, mg/dl	1.36±1.19	1.32±1.05	1.41±1.20	1.34±1.31	0.356
eGFR, $ml \cdot min^{-1} \cdot 1.73 m^{-2}$	51.4±25.0	50.6±25.6	50.5±25.2	53.2±24.2	0.090
Hemoglobin, g/dl	12.0±2.6	11.3±2.3	12.0±2.6	12.9±2.8	<0.001
Plasma BNP, pg/ml	390±514	494±665	374±428	302±384	<0.001
Echocardiographic parameters at discharge					
LVEDD, mm	55.6±10.2	53.6±10.4	55.9±10.4	57.3±9.6	<0.001
LVESD, mm	43.1±12.2	41.4±12.4	43.0±12.7	44.8±11.1	0.001
LVEF, %	44.2±16.3	44.2±16.5	44.9±16.9	43.3±15.4	0.440

BMI, body mass index; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; VT/VF, ventricular tachycardia/fibrillation; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; CRT-D, cardiac resynchronization therapy with defibrillator; NYHA, New York Heart Association; SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; BNP, B-type natriuretic peptide; LV, left ventricular; EDD, end-diastolic diameter; ESD, end-systolic diameter; EF, ejection fraction.
Values are percent or means±SD.

were men. HF etiology was ischemic in 32.2%, valvular in 27.1%, hypertensive in 24.7%, and dilated cardiomyopathy in 18.9%. The mean left ventricular ejection fraction (LVEF) was 44.2±16.3% at discharge.

Patients with lower BMI values were significantly older and more often women. They had more frequent valvular heart disease as the cause of HF, but less hypertensive heart disease. Higher BMI was associated with higher prevalence of comorbidities, including hypertension, diabetes mellitus, dyslipidemia, hyperuricemia, and smoking. Consistent with the higher prevalence of hypertension among patients with higher BMI, these patients had higher blood pressure values at discharge. The use of cardiac resynchronization therapy with defibrillator was comparable among the 3 groups. New York Heart Association functional classes and plasma BNP levels were significantly higher, and hemoglobin levels lower in patients with lower BMI. LVEF was comparable among the 3 groups, although patients with high BMI had larger LV end-diastolic and end-systolic diameters.

Patients with lower BMI were less frequently prescribed by angiotensin-receptor blockers, β-blockers, calcium-channel-blockers or statins at discharge (Table 2).

Table 2. Medication Use at Hospital Discharge According to BMI

	Total (n=2,488)	BMI (kg/m²) <20.3 (n=829)	20.3–23.49 (n=832)	≥23.5 (n=827)	P value
ACE inhibitor, %	37.9	36.9	39.2	37.4	0.602
ARB, %	44.6	37.3	44.1	52.3	<0.001
ACE inhibitor or ARB, %	77.1	70.2	78.1	82.8	<0.001
β-blocker, %	49.4	45.8	47.7	54.5	0.001
Diuretics, %	87.9	86.1	88.7	89.0	0.162
Digitalis, %	31.4	33.0	32.5	28.7	0.132
Calcium-channel blocker, %	25.3	21.1	25.9	28.9	0.002
Nitrates, %	22.9	21.3	24.5	22.7	0.315
Antiarrhythmic, %	16.5	17.6	16.6	15.5	0.525
Aspirin, %	46.7	45.8	46.0	48.5	0.484
Other antiplatelet, %	11.9	11.3	12.7	11.5	0.652
Warfarin, %	41.2	40.0	41.1	42.6	0.559
Statin, %	20.4	14.4	21.5	25.0	<0.001

ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker. Other abbreviation see in Table 1.

Table 3. HRs for Outcomes According to BMI

Outcome	BMI (kg/m²) <20.3 (n=684)	20.3–23.49 (n=728)	≥23.5 (n=742)	P value
All-cause death (%)	179 (27.2%)	166 (22.8%)	86 (11.6%)	<0.001
Unadjusted HR (95%CI)	2.529 (1.828–3.498)	2.103 (1.514–2.922)	1	
Adjusted HR (95%CI)	1.699 (1.209–2.386)	1.674 (1.199–2.338)		0.004
Cardiac death (%)	115 (16.8%)	103 (14.1%)	54 (7.3%)	<0.001
Unadjusted HR (95%CI)	2.754 (1.824–4.160)	2.127 (1.394–3.244)	1	
Adjusted HR (95%CI)	1.832 (1.193–2.814)	1.708 (1.114–2.619)		0.017
Rehospitalization (%)	271 (39.6%)	268 (36.8%)	229 (30.9%)	<0.001
Unadjusted HR (95%CI)	1.668 (1.335–2.083)	1.461 (1.167–1.828)	1	
Adjusted HR (95%CI)	1.193 (0.940–1.515)	1.206 (0.959–1.516)		0.231
All-cause death or rehospitalization (%)	335 (49.0%)	328 (45.1%)	262 (35.3%)	<0.001
Unadjusted HR (95%CI)	1.704 (1.388–2.092)	1.516 (1.233–1.862)	1	
Adjusted HR (95%CI)	1.182 (0.948–1.473)	1.224 (0.991–1.511)		0.156

The Cox regression model used in the analysis adjusted for the following covariates: demographic (age, sex), cause of heart failure (hypertensive, valvular heart disease), medical history (diabetes mellitus, hyperuricemia, smoking), serum creatinine, hemoglobin concentration, NYHA functional class at discharge, BNP at discharge, and medication use (angiotensin-receptor blocker, β-blocker, calcium-channel blocker, statin). Patients with baseline BMI ≥23.5 kg/m² were the reference group. BNP at discharge entered into the model as categorical variable; ie, BNP at discharge ≥240 pg/ml or <240 pg/ml or unknown.
HR, hazard ratio; CI, confidence interval. Other abbreviations see in Table 1.

Variables Associated With BMI

In the multiple linear regression analysis, higher hemoglobin concentration [standardized partial regression coefficient (β) 0.186, P<0.001], younger age (β 0.185, P<0.001), hypertensive heart disease (β 0.149, P<0.001), diabetes mellitus (β 0.131, P<0.001), lower plasma BNP level (β 0.153, P<0.001), no valvular heart disease (β 0.072, P=0.046) and statin use (β 0.070, P=0.047) were significantly associated with BMI level. High hemoglobin concentration was the most important factor in this model. However, the multiple correlation coefficient (R^2) of the model entered with these 7 variables was 0.199, indicating that the contribution of these variables to BMI level would be limited.

Outcomes

During follow-up of 2.1 years after hospital discharge, the rates of adverse outcomes were as follows: all-cause death 20.0%, cardiac death 12.6%, rehospitalization because of worsening HF 35.7%, and all-cause death or rehospitalization 42.9%. The rate of all-cause death increased with decreased BMI: 27.2% for BMI<20.30 kg/m², 22.8% for 20.30–23.49 kg/m², and 11.6% for ≥23.50 kg/m² (P<0.001; Table 3, Figure 2). The rates of cardiac death, rehospitalization because of HF, and death or rehospitalization increased with decreased baseline BMI level. Even after adjustment for covariates by multivariate analysis, patients with a BMI <20.30 kg/m² had a significantly higher risk for all-cause death (adjusted hazard ratio [HR] 1.699, 95% confidence interval [CI] 1.209–2.386, P=0.004) and cardiac death (adjusted HR 1.832, 95%CI 1.193–2.814, P=0.017). However, BMI values did not associate with rehospitalization because of worsening HF.

The independent predictors associated with all-cause death among those entered into the Cox proportional hazard analysis were hypertension, BMI, serum creatinine, discharge hemoglobin, age, BNP level at discharge, and hyperuricemia

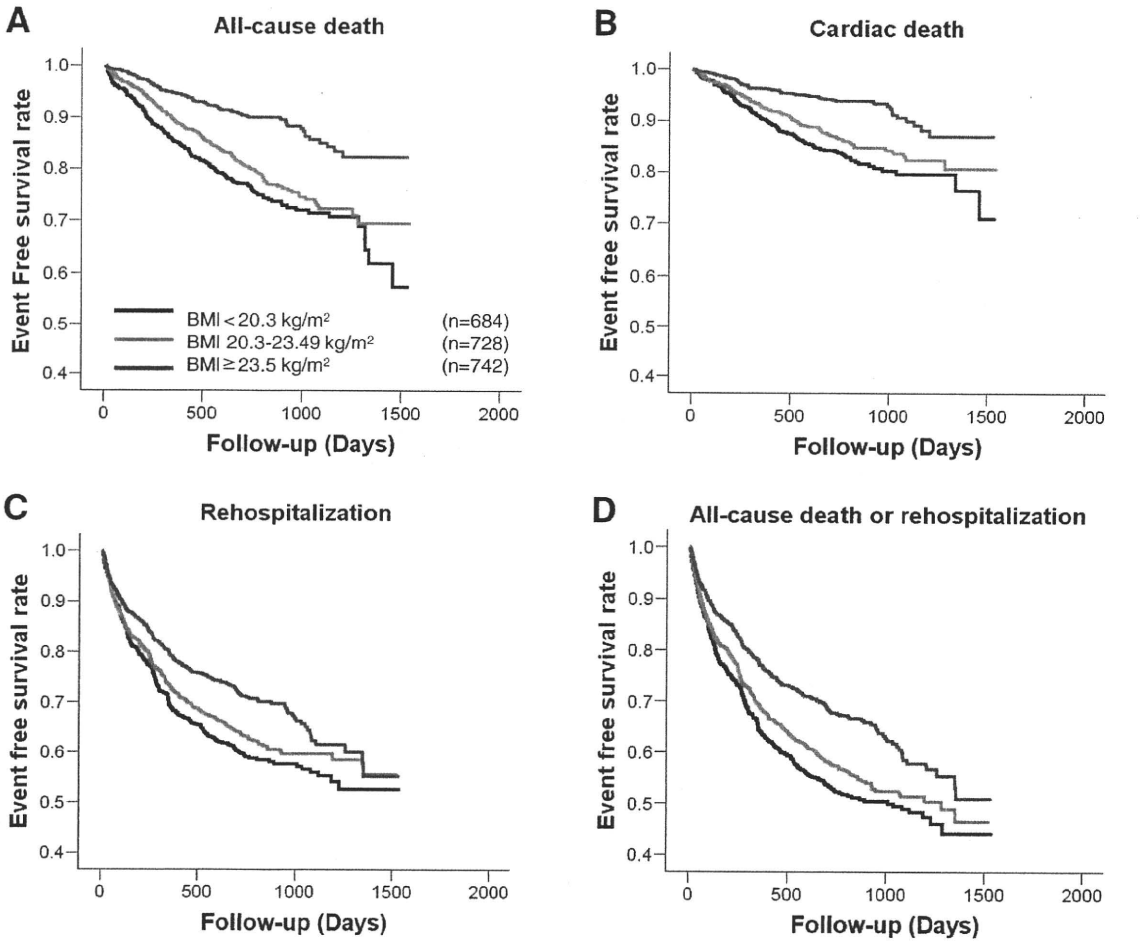

Figure 2. Kaplan-Meier event-free curves for all-cause death (A), cardiac death (B), rehospitalization because of worsening heart failure (C), and all-cause death or rehospitalization (D), according to baseline body mass index (BMI): <20.3 kg/m² (n=829; black lines), 20.3–23.49 kg/m² (n=832; green lines), and ≥23.5 kg/m² (n=827; red lines).

Table 4. Multivariate Predictors of All-Cause Death by Cox Proportional Hazard Model

	HR	95%CI	P value
Hypertension	0.748	0.561–0.998	0.049
Low BMI (per 1 kg/m² decrease)	1.049	1.013–1.087	0.008
Serum creatinine (per 1 mg/dl increase)	1.089	1.016–1.167	0.016
Low hemoglobin (per 1 g/dl decrease)	1.112	1.052–1.175	<0.001
Age (per 10 year increase)	1.368	1.218–1.536	<0.001
BNP ≥240 pg/ml at discharge	1.713	1.193–2.460	0.004
Hyperuricemia	1.858	1.450–2.380	<0.001

Abbreviations see in Tables 1,3.

(Table 4). There was 4.7% increase in all-cause death for each 1-kg/m² decrease in BMI (P=0.008).

Discussion

Using the JCARE-CARD database, the present study demonstrated that, in routine clinical practice in Japan, lower BMI was significantly associated with a higher long-term mortality among patients hospitalized with HF. This relationship was independent of other prognostic risk factors known to be associated with a higher risk for mortality. By weight category, patients with BMI <20.3 kg/m² had a 70% increase in mortality risk. Our findings provide further confirmation of the existence of an "obesity paradox" among HF patients and are the first to demonstrate its existence during long-term follow-up of unselected Japanese HF patients who had lower BMI values than similar patients in US or Europe.

The present study demonstrated that higher BMI values

were significantly associated with decreased risk for all-cause and cardiac death. Previous studies of outpatients with HF also demonstrated that higher BMI was a decreased risk for death and hospitalization compared with normal BMI.[4,5] Horwich et al first reported that overweight and obesity were associated with a lower risk-adjusted mortality in outpatients with HF.[4] Lavie et al also confirmed that event risk was the lowest among the highest quintile of body composition parameters, suggesting the paradoxical association between obesity and HF.[5] The Digitalis Investigation Group (DIG) trial found that overweight and obese BMI subgroups were at significantly decreased risk for all-cause mortality as compared with healthy-weight individuals.[6] There was no heterogeneity of this relationship across the subgroups based on sex, HF etiology, and LVEF.[6] These findings have been also confirmed in the setting of acute decompensated HF,[7] as well as in acute coronary syndromes.[20,21] Therefore, the findings of the present study are consistent with those of other previous studies exploring the relationship between obesity and outcomes among HF patients.

However, there are important and critical differences between our findings and those from other studies. The prevalence of overweight and obese of HF patients (15.3% and 4.4%, respectively) in this study was lower than that reported in previous studies. In the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) study, 40.3% patients were overweight and 31.2% patients were obese.[8] In the DIG trial, 39.7% patients were overweight and 25.9% patients were obese.[6] Moreover, the average BMI values in the present study were as low as 22.3 kg/m^2, which is lower than in previous studies from Europe and the US demonstrating the association between BMI and mortality (26.6 kg/m^2 [median] in DIG and 28.3 kg/m^2 in CHARM[6,8]). The mean BMI values of Japanese middle-aged men and women were 23.7 kg/m^2 and 23.2 kg/m^2, respectively, according to the International Study of Macro-Micro nutrients and Blood Pressure (INTERMAP) study.[11] Those BMI values were much lower than the 29.1 kg/m^2 for men and 28.7 kg/m^2 for women in the US population. More importantly, it would be expected that the present study patients had a lower prevalence of overweight and obesity, because they were more elderly and had more comorbidities, such as hypertension, diabetes, and renal dysfunction, which reflects the "real world" of HF patients in routine clinical practice.

There are several mechanisms for the association of higher BMI and lower mortality among HF patients. First, patients with a higher BMI may present with worsened HF symptoms earlier and at a less severity as compared with those with lower BMI. In addition, they have comorbidities that may be strictly treated. However, in the present study, the significant effect of BMI level on outcome was observed even after adjustment for covariates. Second, HF patients with lower BMI have increased cytokines, such as tumor necrosis factor (TNF)-α. The failing heart produces TNF-α and there is a reported direct relationship between the level of TNF-α expression and the severity of HF.[22] Furthermore, TNF-α may induce cardiac injury, muscle wasting, and cachexia.[22,23] The soluble TNF-α receptor is produced in adipose tissue and its concentrations are significantly correlated with BMI.[24] Therefore, adipose tissue in obese individuals may protect the failing heart through the neutralizing effects of TNF-α. Third, there is a heightened catecholamine response to exercise stress in lean subjects and a decreased catecholamine response in overweight and obese subjects, with no differences in blood pressure.[25] Therefore, obesity may have an inhibitory effect on the neuroendocrine response to physical stress. Given the importance of sympathetic nervous activation in the pathophysiology of HF, the attenuation of this response in overweight and obese patients may contribute to their decreased mortality. Finally, evidence-based HF medications, such as angiotensin-receptor blockers and β-blockers as well as statins, were used more often for patients with higher BMI (Table 2). Those medications might affect the outcomes. However, in the present study high BMI values were associated with better outcomes, even after the adjustment of these covariates. Whatever the possible explanations, further research is clearly needed to elucidate the mechanism between higher BMI and its protective effect on HF. Such studies may indicate a novel therapeutic approach for HF, which has the potential to favorably affect the long-term prognosis. However, the findings in the present study should not be used as a rational against recommending weight reduction in obese patients. It is of particular importance to obtain and maintain a healthy BMI in general, based on the solid evidence that obesity is a strong predictor for developing CVDs such as HF.

Study Limitations

First, the documentation of BMI at hospital discharge might not accurately reflect the change in BMI after discharge. Second, the JCARE-CARD is not a prospective randomized trial and, despite covariate adjustment, other measured and unmeasured factors might have influenced outcomes. We could not completely exclude other unmeasured factors that might also affect outcomes. Third, in the JCARE-CARD database, markers of cytokines, catecholamines, renin–angiotensin–aldosterone system, and biochemical markers, such as plasma total bilirubin, total protein and albumin levels, which might be associated with cardiac cachexia, were not collected. Furthermore, there were no data regarding the use of cardiac rehabilitation programs, which might be expected to improve the long-term outcomes of HF patients. Finally, the data were dependent on the accuracy of documentation and abstraction by the individual medical centers that participated in the program. However, it was not the objective of this survey to restrict enrollment to the narrowly defined population of HF usually included in clinical trials, but rather to include a broad range of HF patients that reflected the current reality of clinical practice.

In conclusion, lower BMI was independently associated with increased long-term all-cause, as well as cardiac mortality, in those patients encountered in routine clinical practice in Japan who are hospitalized with HF. Further study is required to better understand the pathophysiology of the association between body composition and the clinical outcomes of HF.

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References

1. Calle EE, Thun MJ, Petrelli JM, Rodriguez C, Heath CW Jr. Body-mass index and mortality in a prospective cohort of U.S. adults. *N Engl J Med* 1999; **341:** 1097–1105.
2. Levitan EB, Yang AZ, Wolk A, Mittleman MA. Adiposity and incidence of heart failure hospitalization and mortality: A population-based prospective study. *Circ Heart Fail* 2009; **2:** 202–208.
3. Kenchaiah S, Evans JC, Levy D, Wilson PW, Benjamin EJ, Larson MG, et al. Obesity and the risk of heart failure. *N Engl J Med* 2002; **347:** 305–313.
4. Horwich TB, Fonarow GC, Hamilton MA, MacLellan WR, Woo MA, Tillisch JH. The relationship between obesity and mortality in patients with heart failure. *J Am Coll Cardiol* 2001; **38:** 789–795.
5. Lavie CJ, Osman AF, Milani RV, Mehra MR. Body composition and prognosis in chronic systolic heart failure: The obesity paradox. *Am J Cardiol* 2003; **91:** 891–894.
6. Curtis JP, Selter JG, Wang Y, Rathore SS, Jovin IS, Jadbabaie F, et al. The obesity paradox: Body mass index and outcomes in patients with heart failure. *Arch Intern Med* 2005; **165:** 55–61.
7. Fonarow GC, Srikanthan P, Costanzo MR, Cintron GB, Lopatin M. An obesity paradox in acute heart failure: Analysis of body mass index and inhospital mortality for 108,927 patients in the Acute Decompensated Heart Failure National Registry. *Am Heart J* 2007; **153:** 74–81.
8. Kenchaiah S, Pocock SJ, Wang D, Finn PV, Zornoff LA, Skali H, et al. Body mass index and prognosis in patients with chronic heart failure: Insights from the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) program. *Circulation* 2007; **116:** 627–636.
9. Frankenstein L, Zugck C, Nelles M, Schellberg D, Katus HA, Remppis BA. The obesity paradox in stable chronic heart failure does not persist after matching for indicators of disease severity and confounders. *Eur J Heart Fail* 2009; **11:** 1189–1194.
10. Wu AH, Eagle KA, Montgomery DG, Kline-Rogers E, Hu YC, Aaronson KD. Relation of body mass index to mortality after development of heart failure due to acute coronary syndrome. *Am J Cardiol* 2009; **103:** 1736–1740.
11. Zhou BF, Stamler J, Dennis B, Moag-Stahlberg A, Okuda N, Robertson C, et al. Nutrient intakes of middle-aged men and women in China, Japan, United Kingdom, and United States in the late 1990s: The INTERMAP study. *J Hum Hypertens* 2003; **17:** 623–630.
12. Tsutsui H, Tsuchihashi-Makaya M, Kinugawa S, Goto D, Takeshita A. Clinical characteristics and outcome of hospitalized patients with heart failure in Japan. Rationale and Design of Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD). *Circ J* 2006; **70:** 1617–1623.
13. Hamaguchi S, Tsuchihashi-Makaya M, Kinugawa S, Yokota T, Ide T, Takeshita A, et al. Chronic kidney disease as an independent risk for long-term adverse outcomes in patients hospitalized with heart failure in Japan: Report from the Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD). *Circ J* 2009; **73:** 1442–1447.
14. Hamaguchi S, Tsuchihashi-Makaya M, Kinugawa S, Yokota T, Takeshita A, Yokoshiki H, et al. Anemia is an independent predictor of long-term adverse outcomes in patients hospitalized with heart failure in Japan: A Report From the Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD). *Circ J* 2009; **73:** 1901–1908.
15. Hamaguchi S, Yokoshiki H, Kinugawa S, Tsuchihashi-Makaya M, Yokota T, Takeshita A, et al. Effects of atrial fibrillation on long-term outcomes in patients hospitalized for heart failure in Japan. *Circ J* 2009; **73:** 2084–2090.
16. Tsuchihashi-Makaya M, Hamaguchi S, Kinugawa S, Yokota T, Goto D, Yokoshiki H, et al. Characteristics and outcomes of hospitalized patients with heart failure and reduced vs preserved ejection fraction: Report from the Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD). *Circ J* 2009; **73:** 1893–1900.
17. Tsuchihashi-Makaya M, Furumoto T, Kinugawa S, Hamaguchi S, Goto K, Goto D, et al. Discharge use of angiotensin receptor blockers provides comparable effects with angiotensin-converting enzyme inhibitors on outcomes in patients hospitalized for heart failure. *Hypertens Res* 2010; **33:** 197–202.
18. Tsuchihashi-Makaya M, Kinugawa S, Yokoshiki H, Hamaguchi S, Yokota T, Goto D, et al. Beta-blocker use at discharge in patients hospitalized for heart failure is associated with improved survival. *Circ J* 2010; **74:** 1364–1371.
19. Hamaguchi S, Furumoto T, Tsuchihashi-Makaya M, Goto K, Goto D, Yokota T, et al. Hyperuricemia predicts adverse outcomes in patients with heart failure. *Int J Cardiol* 2010 [E-pub ahead of print].
20. Eisenstein EL, McGuire DK, Bhapkar MV, Kristinsson A, Hochman JS, Kong DF, et al. Elevated body mass index and intermediate-term clinical outcomes after acute coronary syndromes. *Am J Med* 2005; **118:** 981–990.
21. Kennedy LM, Dickstein K, Anker SD, Kristianson K, Willenheimer R. The prognostic importance of body mass index after complicated myocardial infarction. *J Am Coll Cardiol* 2005; **45:** 156–158.
22. Feldman AM, Combes A, Wagner D, Kadakomi T, Kubota T, Li YY, et al. The role of tumor necrosis factor in the pathophysiology of heart failure. *J Am Coll Cardiol* 2000; **35:** 537–544.
23. Paulus WJ. Cytokines and heart failure. *Heart Fail Monit* 2000; **1:** 50–56.
24. Mohamed-Ali V, Goodrick S, Bulmer K, Holly JM, Yudkin JS, Coppack SW. Production of soluble tumor necrosis factor receptors by human subcutaneous adipose tissue in vivo. *Am J Physiol* 1999; **277:** E971–E975.
25. Weber MA, Neutel JM, Smith DH. Contrasting clinical properties and exercise responses in obese and lean hypertensive patients. *J Am Coll Cardiol* 2001; **37:** 169–174.

Spironolactone use at discharge was associated with improved survival in hospitalized patients with systolic heart failure

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Background The RALES trial demonstrated that spironolactone improved the prognosis of patients with heart failure (HF). However, it is unknown whether the discharge use of spironolactone is associated with better long-term outcomes among hospitalized systolic HF patients in routine clinical practice. We examined the effects of spironolactone use at discharge on mortality and rehospitalization by comparing with outcomes in patients who did not receive spironolactone.

Methods The JCARE-CARD studied prospectively the characteristics and treatments in a broad sample of patients hospitalized with worsening HF and the outcomes were followed with an average of 2.2 years of follow-up.

Results A total of 946 patients had HF with reduced left ventricular ejection fraction (LVEF) (<40%), among whom spironolactone was prescribed at discharge in 435 patients (46%), but not in 511 patients (54%). The mean age was 66.3 years and 72.2% were male. Etiology was ischemic in 39.7% and mean LVEF was 27.1%. After adjustment for covariates, discharge use of spironolactone was associated with a significant reduction in all-cause death (adjusted hazard ratio 0.612, $P = .020$) and cardiac death (adjusted hazard ratio 0.524, $P = .013$).

Conclusions Among patients with HF hospitalized for systolic dysfunction, spironolactone use at the time of discharge was associated with long-term survival benefit. These findings provide further support for the idea that spironolactone may be useful in patients hospitalized with HF and reduced LVEF. (Am Heart J 2010;160:1156-62.)

Aldosterone plays an important role in the development and progression of chronic heart failure (HF). It induces vascular damage,[1,2] cardiac hypertrophy,[3-5] and fibrosis.[6-9] Higher level of serum aldosterone has been shown to be an independent predictor of increased mortality risk in patients with HF.[10] The RALES demonstrated that spironolactone reduces the risk of mortality and morbidity in patients with HF and systolic dysfunction.[11] Current guidelines from American College of Cardiology/American Heart Association/AHA and European Society of Cardiology recommend the use of spironolactone in HF patients with reduced left ventricular ejection fraction (LVEF) who were symptomatic under the use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) and diuretics.[12,13] However, RALES was performed among carefully selected severe HF patients with current or recent HF of New York Heart Association (NYHA) functional class IV. In addition, it excluded the patients with a serum creatinine concentration of >2.5 mg/dL. Moreover, the use of β-blockers was as low as 10% among the patients enrolled in RALES. Therefore, the patients in the RALES were clearly different from those in the "real world" under current standard practice for HF who are more elderly and have more comorbidities including hypertension, diabetes, and renal dysfunction. However, many patients who received new prescriptions for spironolactone after the publication of RALES have been reported not to have severe HF and about one third had renal dysfunction.[14] These findings indicated that the effect of spironolactone on outcomes needed to be assessed in an unselected population of patients with HF.

The JCARE-CARD studied prospectively the characteristics and treatments in a broad sample of patients hospitalized with HF in Japan from January 2004 to June 2005, and the outcomes including death and

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rehospitalization were followed until 2008.[15-20] The JCARE-CARD enrolled 2,675 patients admitted with HF in a Web-based registry at 164 participating hospitals with an average of follow-up of 2.2 years.

The aim of the present study was to analyze the prognostic value of spironolactone on the mortality and rehospitalization by evaluating the relationship between discharge use of spironolactone and clinical outcomes among patients hospitalized with systolic HF registered in the JCARE-CARD database.

Methods

Patients

The details of the JCARE-CARD have been described previously.[15-20] Briefly, eligible patients were those hospitalized because of worsening HF as the primary cause of admission. The study hospitals were encouraged to register the patients as consecutively as possible. For each patient, baseline data included (1) age, sex, and body mass index (BMI); (2) causes of HF; (3) medical history; (4) prior procedures; (5) vital signs at discharge; (6) laboratory data at discharge; (7) echocardiographic data; and (8) medication use at discharge. The data were entered using a Web-based electronic data capture system licensed by the JCARE-CARD (www.jcare-card.jp).

From the database of a total cohort of 2,675 patients registered in JCARE-CARD, the present analysis used the data of 946 patients who had systolic dysfunction defined as LVEF <40% and did not have valvular heart disease as a cause of HF. They were divided into 2 groups according to the spironolactone use (n = 435; 46%) or no spironolactone use (n = 511; 54%) at the time of discharge from the index hospitalization.

Outcomes

The status of all patients was surveyed by June 2008 and the following information of the outcomes was obtained from the participating cardiologists by using a Web-based electronic data capture system: (1) all-cause death; (2) cardiac death, defined as death due to HF, myocardial infarction, and other causes such as pulmonary embolism; (3) rehospitalization due to an exacerbation of HF that required more than continuation of their usual therapy on prior admission; and (4) the composite end point of all-cause death and rehospitalization due to HF. The end points were adjudicated by the cardiologists in each participating hospital. Of 946 patients, 99 patients (10.5%) missed during the follow-up were excluded from the follow-up analysis. Follow-up data were obtained in 847 (89.5%) of 946 patients. Of 847 patients, 396 patients were in the group of spironolactone use and 451 patients were in that of no spironolactone use. Mean postdischarge follow-up was 801 ± 300 days (2.2 ± 0.8 years).

The hypothesis being tested was whether spironolactone use at hospital discharge would be associated with lower mortality and rehospitalization rates during the follow-up compared with no spironolactone use.

Statistical analysis

Patient characteristics and treatments were compared using Pearson χ^2 test for categorical variables, Student t test for normally distributed continuous variables, and Mann-Whitney U test for continuous variables not normally distributed. Only patients who survived the index hospitalization were included in the follow-up analysis. Cumulative event-free rates during the follow-up were derived using the method of Kaplan and Meier. The relationship between the spironolactone use at discharge and outcomes was evaluated among patients with multivariable adjustment. The covariates, age, BMI, serum creatinine at discharge, systolic blood pressure at discharge, LVEF, and medication use (calcium channel blocker, antiarrhythmic, warfarin), were used in developing the postdischarge Cox proportional hazard models.

The results were reported as hazard ratio (HR), 95% CI, and P value. Hazard ratio for outcomes when spironolactone was used was compared with not used. A P value of <.05 was used as criterion for variables to stay in the model. SPSS version 16.0 J for Windows (SPSS, Chicago, IL) was used for all statistical analyses.

The JCARE-CARD was funded by the Health Sciences Research Grants from the Japanese Ministry of Health, Labor and Welfare (Comprehensive Research on Cardiovascular Diseases), the Japan Heart Foundation, and Japan Arteriosclerosis Prevention Fund. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper, and its final contents.

Results

Patient characteristics

The present study included 946 patients with the mean age of 66.3 ± 13.7 years and 72.2% men (Table I). The causes of HF were ischemic heart disease in 39.6%, dilated cardiomyopathy in 36.3%, and hypertensive heart disease in 21.6%. The mean LVEF was 27.1% ± 7.3%.

Characteristics of patients prescribed spironolactone at discharge and those not receiving it prescription were compared in Table I. Patients discharged with spironolactone had significantly higher BMI. Cause of HF, medical history such as hypertension and diabetes, and treatment procedures such as coronary revascularization did not differ between groups. Systolic blood pressure at discharge was significantly lower in patients with spironolactone use. However, diastolic blood pressure was not different. Estimated glomerular filtration rate was significantly lower and the prevalence of renal dysfunction defined as serum creatinine ≥2.5 mg/dL was greater in patients without spironolactone use. Left ventricular end-diastolic and end-systolic diameters were significantly greater in patients with spironolactone use and LVEF tended to be lower, which, however, did not reach statistical significance.

Use of other medications at hospital discharge was compared between groups in Table II. The use of ACE inhibitor or ARB was as high as 90% in both groups, and that of β-blocker was 65%. Importantly, the use of these guideline-based standard medications was similar between spironolactone use and no spironolactone use groups. However, diuretics, antiarrhythmics, and warfa-

Table I. Patient characteristics

Characteristics	Total (n = 946)	Spironolactone use (n = 435)	No spironolactone use (n = 511)	*P* value
Age (y [mean ± SD])	66.3 ± 13.7	65.2 ± 14.4	67.3 ± 13.1	.052
Male (%)	72.2	73.3	71.2	.472
BMI (kg/m^2)	22.7 ± 4.2	23.0 ± 4.4	22.4 ± 4.0	.043
Causes of HF (%)				
Ischemic	39.6	38.6	40.5	.554
Dilated cardiomyopathy	36.3	39.3	33.7	.072
Hypertensive	21.6	21.1	21.9	.775
Medical history (%)				
Hypertension	50.7	49.1	52.2	.346
Diabetes mellitus	33.1	33.6	32.7	.790
Hyperlipidemia	28.9	28.5	29.2	.826
Hyperuricemia	51.3	49.2	53.0	.245
Prior stroke	13.8	12.9	14.5	.484
COPD	6.0	6.3	5.8	.734
Smoking	46.6	45.1	47.9	.403
Prior myocardial infarction	34.9	35.3	34.5	.797
Atrial fibrillation	24.3	21.7	26.6	.077
Sustained VT/VF	9.2	11.0	7.6	.068
Procedures (%)				
PCI	20.7	20.8	20.6	.950
CABG	11.9	13.3	10.7	.217
ICD	3.8	3.9	3.7	.879
CRT	2.4	3.4	1.6	.061
Vital signs at discharge				
NYHA functional class	1.7 ± 0.6	1.7 ± 0.6	1.7 ± 0.6	.416
NYHA functional class 1or 2 (%)	93.9	94.5	93.3	.468
Heart rate (beat/min)	70.6 ± 12.0	70.6 ± 12.0	70.6 ± 12.0	.988
SBP (mmHg)	113.5 ± 17.1	111.8 ± 17.3	114.9 ± 16.7	.008
DBP (mmHg)	66.2 ± 11.6	65.8 ± 12.1	66.6 ± 11.2	.596
Laboratory data at discharge				
eGFR (mL min^{-1} 1.73 m^{-2})	53.8 ± 24.2	55.9 ± 20.3	52.1 ± 26.9	.017
Serum creatinine ≥2.5 mg/dL	7.9	3.7	11.5	<.001
Hemoglobin (g/dL)	12.9 ± 2.3	13.0 ± 2.1	12.8 ± 2.5	.657
Plasma BNP (pg/mL)	383 ± 534	376 ± 534	388 ± 535	.554
Echocardiographic data				
LV EDD (mm)	61.5 ± 9.4	62.6 ± 9.3	60.6 ± 9.3	.003
LV ESD (mm)	53.0 ± 9.4	54.0 ± 9.4	52.2 ± 9.3	.007
LVEF (%)	27.1 ± 7.3	26.7 ± 7.4	27.5 ± 7.3	.100

Data are shown as percentage or means ± SD.
COPD, Chronic obstructive pulmonary disease; *VT/VF*, ventricular tachycardia/fibrillation; *PCI*, percutaneous coronary intervention; *CABG*, coronary artery bypass grafting; *ICD*, implantable cardioverter defibrillator; *CRT*, cardiac resynchronization therapy; *SBP*, systolic blood pressure; *DBP*, diastolic blood pressure; *eGFR*, estimated glomerular filtration rate; *BNP*, B-type natriuretic peptide; *LV*, left ventricular; *EDD*, end-diastolic diameter; *ESD*, end-systolic diameter; *EF*, ejection fraction.

rin were prescribed more in patients with spironolactone use. On the other hand, calcium channel blocker was used more in patients without spironolactone use.

Postdischarge clinical outcomes according to spironolactone use

During the follow-up of 2.2 years after hospital discharge, the rates of adverse outcomes were as follows: all-cause death 17.8%, cardiac death 11.8%, sudden cardiac death 2.2%, rehospitalization due to the worsening HF 33.4%, and all-cause death or rehospitalization 40.0%. The unadjusted rates of cardiac death were significantly lower in patients with spironolactone use (Table III).

After adjustment for covariates in multivariable Cox proportional hazard models, discharge use of spironolactone, which compared to no spironolactone use, was associated with a reduced risk of all-cause death (HR 0.619, 95% CI 0.413-0.928, P = .020) and cardiac death (HR 0.524, 95% CI 0.315-0.873, P = .013) (Table III and Figure 1). However, spironolactone use was not associated with the risk of rehospitalization due to worsening HF and the combined end point of all-cause death or rehospitalization.

Furthermore, in the subgroup of patients with NYHA functional class I or II, discharge use of spironolactone was associated with a reduced risk of all-cause death (adjusted HR 0.605, 95% CI 0.389-0.940, P = .026) and cardiac death (adjusted HR 0.492, 95% CI 0.276-0.876,

Table II. Medication use at hospital discharge

	Total (N = 946)	Spironolactone use (n = 435)	No spironolactone use (n = 511)	P
ACE inhibitor (%)	44.3	44.6	44.0	.861
ARB (%)	45.6	47.4	44.0	.306
β-Blocker (%)	65.9	66.7	65.2	.628
Diuretics (%)	88.1	100	77.9	<.001
Digitalis (%)	28.8	30.3	27.4	.318
Calcium channel blocker (%)	17.1	11.7	21.7	<.001
Nitrates (%)	22.6	22.3	22.9	.827
Antiarrhythmics (%)	20.9	26.9	15.9	<.001
Aspirin (%)	49.2	48.5	49.7	.713
Warfarin (%)	42.9	46.7	39.7	.032
Statin (%)	23.1	23.7	22.7	.722

Table III. Unadjusted and adjusted HRs for outcomes according to spironolactone use

	Number (%)				
Outcomes	Spironolactone use (n = 396)	No spironolactone use (n = 451)	HR	95% CI	P
All-cause death	59 (14.9%)	92 (20.4%)			
Unadjusted			0.746	0.537-1.035	.078
Adjusted for covariates			0.619	0.413-0.928	.020
Cardiac death	36 (9.1%)	64 (14.2%)			
Unadjusted			0.655	0.435-0.986	.041
Adjusted for covariates			0.524	0.315-0.873	.013
Rehospitalization	125 (31.6%)	158 (35.0%)			
Unadjusted			0.902	0.713-1.141	.389
Adjusted for covariates			0.788	0.592-1.048	.101
All-cause death or rehospitalization	150 (37.9%)	189 (41.9%)			
Unadjusted			0.912	0.735-1.130	.398
Adjusted for covariates			0.820	0.632-1.064	.136

The Cox regression model was used in the analysis adjusted for the following covariates; age, BMI, serum creatinine at discharge, systolic blood pressure at discharge, LVEF, and medication use (calcium channel blocker, antiarrhythmic, warfarin). Patients with no spironolactone use were a reference group.

P = .016) compared to no spironolactone use after adjustment for covariates.

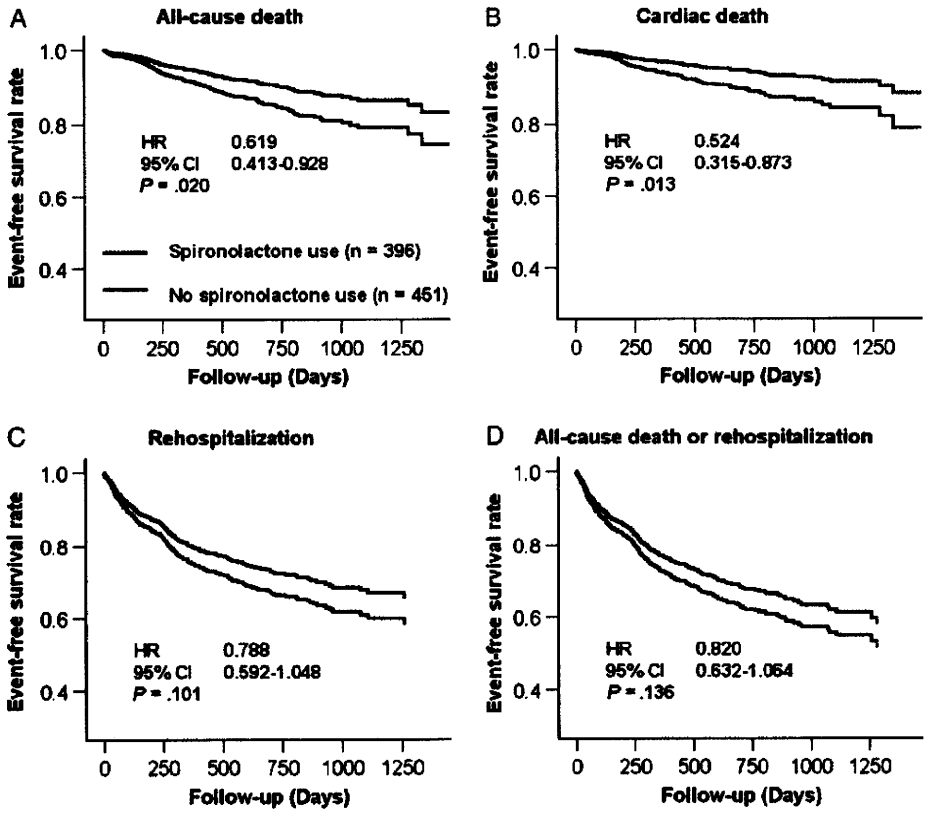
However, in the subgroup patients with serum creatinine ≥2.5 mg/dL (10 patients with spironolactone use and 39 patients with no use), spironolactone use was not significantly associated with the outcomes.

Discussion

The present study suggested that, among patients hospitalized with HF and reduced EF, spironolactone use at discharge was associated with a significant reduction in the risk of cardiac death during the long-term follow-up up to 2.2 years. These findings extended the results of RALES conducted in selected chronic severe HF patients to heterogeneous HF patients with significant survival benefit.

Results from the randomized clinical trial RALES demonstrated that spironolactone significantly improved outcomes in patients with severe HF.[11] RALES enrolled 1,663 patients who had severe HF (NYHA functional class III or IV) and LVEF of no more than 35%. The findings from RALES were further supported by another randomized clinical trial, the EPHESUS, which enrolled 6,632 patients after acute myocardial infarction with LVEF ≤40% and HF.[21] In the EPHESUS, eplerenone, a selective aldosterone antagonist with less adverse effects than spironolactone, reduced the relative risk of death during a mean follow-up of 16 months when added to conventional treatment including ACE inhibitor or ARB and β-blocker. Recent systemic review of 19 randomized clinical trials comprising 10,807 patients demonstrated a 20% reduction in all-cause mortality with the use of aldosterone blockade in clinically heterogeneous groups of patients with LV dysfunction.[22] These studies demonstrated that the addition of aldosterone antagonists in patients with systolic HF and ongoing symptoms despite optimal treatment with ACE inhibition and β-blockers could substantially reduce overall mortality.[23] On the other hand, they found a paucity of evidence on the effects of aldosterone antagonists in patients with diastolic HF or in patients with systolic HF but less severe symptoms.[22]

Figure 1



Kaplan-Meier survival curves free from all-cause death (**A**), cardiac death (**B**), rehospitalization due to worsening HF (**C**), and all-cause death or rehospitalization (**D**) in hospitalized patients with spironolactone use (black lines, n = 396) versus no spironolactone use (red lines, n = 451) at discharge.

More importantly, the patients enrolled in RALES and EPHESUS were recognized as unrepresentative of the general HF population in routine clinical practice. In fact, after the publication of RALES, there was a rapid increase in the rate of prescriptions for spironolactone and in hyperkalemia-associated mortality and morbidity in older patients with HF in Ontario, Canada.[24] This might be explained by the clear difference between the patients in the RALES and those in the "real world" because of the strict inclusion and exclusion criteria that are common to all clinical trials.[25] Furthermore, it may be also due to the recent and rapidly increasing use of β-blockers, which inhibit the release of renin, in patients with HF compared to those enrolled in RALES.[25] Therefore, uncertainty pertaining to the applicability of these findings to the population of patients with HF persists, and it is of critical importance to analyze the registry data of HF patients. The present results extended the previous findings to the "real world" by showing that spironolactone could improve the long-term outcomes in heterogeneous HF patients.

In the present study, >90% of patients had less severe symptom (NYHA functional class I or II) (Table I). The patients with spironolactone use had better renal function and more dilated LV than those with no spironolactone use. According to the European Society of Cardiology and American College of Cardiology/American Heart Association guidelines, the addition of a low-dose aldosterone antagonist should be considered in all patients with a LVEF ≤35% and severe symptomatic HF (NYHA functional class III or IV) unless contraindicated or not tolerated.[12,13] Therefore, in hospitalized patients with severe HF, treatment with an aldosterone antagonist has been recommended to be initiated before discharge.[13] However, published data have suggested that spironolactone was widely used with HF without consideration of their functional class or LVEF and optimization of background treatment with ACE inhibitor and β-blockers.[14] Many patients treated with spironolactone are distinctly dissimilar from those in RALES and the effects of therapy in these patients remain unknown. Therefore, the efficacy of aldosterone

antagonist in patients with reduced LVEF but less severe symptoms needs to be tested by an ongoing large-scale clinical trial, the EMPHASIS-HF trial (ClinicalTrials.gov Identifier NCT00133003), which will enroll 2,584 patients with NYHA functional class II symptoms. The present results suggested that spironolactone use could improve the long-term outcomes in patients with systolic HF and even less severe symptoms (NYHA functional class I or II). These findings should reassure clinicians that the use of spironolactone at discharge can provide an opportunity to improve outcomes for HF patients with severe as well as milder symptoms. Several explanations have been postulated for the beneficial effects of spironolactone in HF. First, spironolactone could induce reverse LV remodeling.[26-28] Spironolactone was demonstrated to improve LV function and decrease plasma BNP levels in patients with chronic HF.[26] In addition, it could also improve exercise tolerance in these patients.[27] Second, spironolactone could decrease cardiac fibrosis.[29] The data from RALES demonstrated that serum procollagen type III amino-terminal peptide (PIIINP) levels, markers of cardiac fibrosis, were significantly higher in HF patients and decreased by the treatment of these patients with spironolactone. Third, spironolactone could improve endothelial function in asymptomatic or mild HF patients when added to optimal treatment including β-blocker.[30]

Study limitations

Several limitations inherent in the design of the registry should be considered. First, the documentation of spironolactone use at hospital discharge might not accurately reflect continuation over time or start after discharge. Moreover, we did not collect the information regarding the dose of spironolactone and whether spironolactone was initiated during or before hospitalization. Second, the information regarding the serum potassium concentration was not obtained in our database. Therefore, we could not assess the impact of hyperkalemia in the outcomes in this study. Third, the present study was not a prospective randomized trial and, despite covariate adjustment, other measured and unmeasured factors may have influenced outcomes. Specifically, severer renal dysfunction, inadequate antiarrhythmic therapy including the use of ICD and antiarrhythmics, and disproportionate use of medications such as calcium channel blockers might affect the outcomes in patients with no spironolactone use, although these confounders were corrected in this study. Fourth, we could not evaluate whether the advantage of spironolactone would persist in the subgroup of renal dysfunction (serum creatinine ≥2.5 mg/dL) because the number of patients was so small for this type of analysis. It thus remained to be assessed exclusively in HF patients associated with renal dysfunction. Finally, data were dependent on the accuracy of documentation and abstraction by individual medical centers that participated in this study. Especially, the end points were adjudicated by the participating cardiologists. Moreover, the present study excluded 10.5% of the overall cohort of patients from the follow-up analysis because end points could not be determined. The patients lost to follow-up might influence the overall outcomes. However, the patient characteristics and medication use at discharge were similar between patients with follow-up and those lost to follow-up except for only 2 variables including history of diabetes (32.8% vs 35.4%, $P = .012$) and diastolic blood pressure (65.9 ± 11.4 vs 68.8 ± 12.8 mmHg, $P = .031$).

Conclusions

Among patients hospitalized for HF and reduced LVEF, treatment with spironolactone at discharge was associated with significantly reduced risk of cardiac death. Widespread use of spironolactone could substantially improve the outcomes in the larger numbers of HF patients in routine clinical practice.

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References

1. Rocha R, Chander PN, Zuckerman A, et al. Role of aldosterone in renal vascular injury in stroke-prone hypertensive rats. Hypertension 1999;33:232-7.
2. Rocha R, Rudolph AE, Frierdich GE, et al. Aldosterone induces a vascular inflammatory phenotype in the rat heart. Am J Physiol Heart Circ Physiol 2002;283:H1802-10.
3. Duprez DA, Bauwens FR, De Buyzere ML, et al. Influence of arterial blood pressure and aldosterone on left ventricular hypertrophy in moderate essential hypertension. Am J Cardiol 1993;71:17A-20A.
4. Navarro-Lopez F, Coca A, Pare JC, et al. Left ventricular hypertrophy in asymptomatic essential hypertension: its relationship with aldosterone and the increase in sodium-proton exchanger activity. Eur Heart J 1993;14(Suppl J):38-41.
5. Schunkert H, Hense HW, Muscholl M, et al. Associations between circulating components of the renin-angiotensin-aldosterone system and left ventricular mass. Heart 1997;77:24-31.

6. Weber KT, Brilla CG. Pathological hypertrophy and cardiac interstitium. Fibrosis and renin-angiotensin-aldosterone system. Circulation 1991;83:1849-65.
7. Young M, Fullerton M, Dilley R, et al. Mineralocorticoids, hypertension, and cardiac fibrosis. J Clin Invest 1994;93:2578-83.
8. Robert V, Van Thiem N, Cheav SL, et al. Increased cardiac types I and III collagen mRNAs in aldosterone-salt hypertension. Hypertension 1994;24:30-6.
9. Campbell SE, Janicki JS, Weber KT. Temporal differences in fibroblast proliferation and phenotype expression in response to chronic administration of angiotensin II or aldosterone. J Mol Cell Cardiol 1995;27:1545-60.
10. Guder G, Bauersachs J, Frantz S, et al. Complementary and incremental mortality risk prediction by cortisol and aldosterone in chronic heart failure. Circulation 2007;115:1754-61.
11. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med 1999;341:709-17.
12. Hunt SA, Abraham WT, Chin MH, et al. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure): developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the Heart Rhythm Society. Circulation 2005;112:e154-235.
13. Dickstein K, Cohen-Solal A, Filippatos G, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur Heart J 2008;29:2388-442.
14. Bozkurt B, Agoston I, Knowlton AA. Complications of inappropriate use of spironolactone in heart failure: when an old medicine spirals out of new guidelines. J Am Coll Cardiol 2003;41:211-4.
15. Tsutsui H, Tsuchihashi-Makaya M, Kinugawa S, et al. Clinical characteristics and outcome of hospitalized patients with heart failure in Japan. Rationale and Design of Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD). Circ J 2006;70:1617-23.
16. Hamaguchi S, Tsuchihashi-Makaya M, Kinugawa S, et al. Chronic kidney disease as an independent risk for long-term adverse outcomes in patients hospitalized with heart failure in Japan. Report from the Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD). Circ J 2009;73:1442-7.
17. Hamaguchi S, Tsuchihashi-Makaya M, Kinugawa S, et al. Anemia is an independent predictor of long-term adverse outcomes in patients hospitalized with heart failure in Japan. A Report From the Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD). Circ J 2009;73:1901-8.
18. Hamaguchi S, Yokoshiki H, Kinugawa S, et al. Effects of atrial fibrillation on long-term outcomes in patients hospitalized for heart failure in Japan. Circ J 2009;73:2084-90.
19. Tsuchihashi-Makaya M, Hamaguchi S, Kinugawa S, et al. Characteristics and outcomes of hospitalized patients with heart failure and reduced vs preserved ejection fraction. Report From the Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD). Circ J 2009;73:1893-900.
20. Tsuchihashi-Makaya M, Furumoto T, Kinugawa S, et al. Discharge use of angiotensin receptor blockers provides comparable effects with angiotensin-converting enzyme inhibitors on outcomes in patients hospitalized for heart failure. Hypertens Res 2010;33:197-202.
21. Pitt B, Remme W, Zannad F, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med 2003;348:1309-21.
22. Ezekowitz JA, McAlister FA. Aldosterone blockade and left ventricular dysfunction: a systematic review of randomized clinical trials. Eur Heart J 2009;30:469-77.
23. Jessup M. Aldosterone blockade and heart failure. N Engl J Med 2003;348:1380-2.
24. Juurlink DN, Mamdani MM, Lee DS, et al. Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. N Engl J Med 2004;351:543-51.
25. McMurray JJ, O'Meara E. Treatment of heart failure with spironolactone—trial and tribulations. N Engl J Med 2004;351:526-8.
26. Tsutamoto T, Wada A, Maeda K, et al. Effect of spironolactone on plasma brain natriuretic peptide and left ventricular remodeling in patients with congestive heart failure. J Am Coll Cardiol 2001;37:1228-33.
27. Cicoira M, Zanolla L, Rossi A, et al. Long-term, dose-dependent effects of spironolactone on left ventricular function and exercise tolerance in patients with chronic heart failure. J Am Coll Cardiol 2002;40:304-10.
28. Chan AK, Sanderson JE, Wang T, et al. Aldosterone receptor antagonism induces reverse remodeling when added to angiotensin receptor blockade in chronic heart failure. J Am Coll Cardiol 2007;50:591-6.
29. Zannad F, Alla F, Dousset B, et al. Limitation of excessive extracellular matrix turnover may contribute to survival benefit of spironolactone therapy in patients with congestive heart failure: insights from the randomized aldactone evaluation study (RALES). RALES Investigators. Circulation 2000;102:2700-6.
30. Macdonald JE, Kennedy N, Struthers AD. Effects of spironolactone on endothelial function, vascular angiotensin converting enzyme activity, and other prognostic markers in patients with mild heart failure already taking optimal treatment. Heart 2004;90:765-70.

Clinical Investigations

Increased Left Atrial Volume Index Predicts a Poor Prognosis in Patients With Heart Failure

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ABSTRACT

Background: Left atrial volume index (LAVI) is known to reflect the duration and severity of increased left atrial pressure caused by left ventricular (LV) diastolic dysfunction. However, the prognostic value of LAVI in patients with heart failure (HF) has not been fully investigated.

Methods and Results: Transthoracic echocardiography was performed in 146 consecutive patients (78 men, 68 women; mean age 72 ± 12 y) who were hospitalized for HF. There were 45 cardiac events (32%) during a median follow-up period of 448 days. There were no significant differences in LV end-diastolic dimensions or ejection fraction between patients who did or did not have cardiac events. However, LAVI was markedly higher in patients with, than those without, cardiac events (56 ± 26 vs 44 ± 22 mL/m^2; $P < .01$). Kaplan-Meier analysis showed that there was a stepwise increase in risk of cardiac events with each increment of LAVI category, and LAVI >53.3 mL/m^2 correlated with the highest risk of cardiac events (log-rank test; $P < .01$). Multivariate Cox proportional hazard analysis showed that high LAVI was an independent predictor for cardiac events (hazard ratio 1.427; 95% confidence interval 1.024–1.934; $P < .05$).

Conclusion: LAVI may be useful for stratification of risk in patients with HF. (*J Cardiac Fail 2011;17:210–216*)

Key Words: Diastolic dysfunction, left atrial volume, risk stratification, prognostic factor.

Heart failure (HF) is a major cause of death, and it has a poor prognosis despite the significant reduction in mortality achieved in clinical trials.[1–3] Therefore, the prognostic evaluation and stratification of risk in patients with HF continue to be important, involving complex assessments of multiple interacting variables. Numerous studies have shown that left ventricular (LV) systolic dysfunction and diastolic dysfunction are prognostic factors for HF.[4,5]

Because the left atrium (LA) is directly exposed to LV diastolic pressure through the mitral valve, the size of the LA reflects the duration and severity of increased LA pressure following increased LV diastolic pressure. Therefore, LA volume is reported to be a sensitive marker of LV diastolic dysfunction.[6–8] Recently, the LA volume index (LAVI) was suggested as a new marker for cardiac function. It was also reported that a high LAVI was a powerful predictor of poor prognosis after acute myocardial infarction.[9] However, the prognostic value of LAVI in patients with HF has not been fully investigated.

The aim of the present study was to examine the clinical significance of LAVI in patients with HF. We hypothesized that LAVI increases with increasing severity of HF, and that LAVI provides important prognostic information.

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Methods

Study Design

Out of 166 consecutive patients with HF, we prospectively studied 146 patients (78 men, 68 women; mean age 72 ± 12 y) who were admitted to Yamagata University Hospital, Yamagata, Japan, for treatment of worsening HF or therapeutic evaluation of HF. The diagnosis of HF was made by 2 senior cardiologists using the generally accepted Framingham criteria[10] and other relevant information, including a history of dyspnea and symptomatic exercise intolerance with signs of pulmonary congestion or peripheral edema, the presence of moist rales on auscultation, or documentation of left ventricular enlargement or dysfunction by chest X-ray or echocardiography.[11]

The functional severity of HF at admission was assessed as New York Heart Association (NYHA) functional class II in 34 patients, class III in 73 patients, and class IV in 39 patients. The etiology of HF was dilated cardiomyopathy in 40 patients (27%), ischemic heart disease in 37 (25%), valvular heart disease in 19 (13%), hypertensive heart disease in 17 (12%), and other causes in 33 (23%). Diagnoses of hypertension, diabetes, and hyperlipidemia were obtained from medical records or patient histories of current or previous medical therapy. Patients with no history of atrial fibrillation (AF), and who did not show AF on continuous electrocardiographic monitoring during hospitalization, were defined as patients with sinus rhythm, and patients with transient and chronic AF were defined as AF patients. The exclusion criteria were renal insufficiency characterized by a serum creatinine concentration >2.0 mg/dL (n = 10), severe mitral regurgitation (MR; n = 4) or previous mitral valve surgery (n = 4), mitral stenosis (n = 1), and atrioventricular block (n = 1). Informed consent was given by each of the patients before participation in the study, and the protocol was approved by the institution's Human Investigations Committee.

Blood samples were obtained at admission and discharge for measurement of plasma B-type natriuretic peptide (BNP), creatinine, uric acid, and sodium. Plasma BNP levels were measured by using a commercially available specific radioimmunoassay (Shiono RIA BNP assay kit; Shionogi Co, Tokyo, Japan).[11] Clinical data, including age, gender, and NYHA functional class at admission, were obtained from hospital medical records and patient interviews. Diuretics were administered in flexible doses on the basis of body weight and daily diuresis. The time of discharge was decided by 2 senior cardiologists.

Echocardiography

Transthoracic echocardiography was performed 3–7 days before discharge, on a Hewlett-Packard Sonos 7500 ultrasound instrument, equipped with a sector transducer (carrier frequency of 2.5 or 3.75 MHz). Therefore, all echocardiographic data were measured at the chronic compensation phase of HF.

LA volume was assessed at LV end-systole by using the biplanar area-length method from 4- and 2-chamber views.[7] Measurements of LA volume were indexed by body surface area (LA volume index; LAVI). The normal range for LAVI has been reported to be 14–26 mL/m^2.[12,13] An LAVI value ≥32 mL/m^2 is considered to indicate significant enlargement,[7] and an LAVI value ≥40 mL/m^2 is considered to indicate severe enlargement.[14]

Left atrial dimension (LAD) was measured at end-systole in the 2-dimensional parasternal long-axis view. LV internal diameter and wall thickness were measured at end-diastole and end-systole in the 2-dimensional parasternal long-axis view.[14] LV end-diastolic dimension (LVDd) was used to calculate LV mass index (LVMI), using an anatomically validated formula.[15] LV ejection fraction (LVEF) was calculated using the biplanar method of disks (modified Simpson rule).[14] The Tei index was measured as previously described.[16] All patients underwent pulsed-wave Doppler examination of mitral inflow. Peak transmitral-flow E-wave and A-wave velocities, E-wave deceleration time (DCT), and the ratio of E-wave to A-wave were measured from the apical 4-chamber view. The apical 4-chamber view was used to obtain tissue Doppler imaging (TDI) of the mitral annulus. A sample volume of the pulsed-wave Doppler was positioned at the lateral side of the mitral annulus, and the spectral signal of the mitral annular velocity was recorded. The peak early (E′) mitral annular velocity was measured and the ratio of the E-wave to E′ (E/E′) calculated. All echocardiographic measurements were calculated as mean values from 5 consecutive cardiac cycles.

Endpoints and Follow-up of Patients

Patients were prospectively followed until the occurrence of cardiac events, and no patients were lost to follow-up after discharge (median follow-up period of 502 days). The endpoints were: 1) cardiac death, defined as death due to worsening HF or sudden cardiac death; and 2) worsening HF requiring readmission to hospital.[11,17] Sudden cardiac death was defined as death without definite preceding symptoms or signs and was confirmed by the attending physician.

Statistical Analysis

Results are expressed as mean ± SD for continuous variables and as percentages of the total number of patients for categoric variables. Skewed variables are presented as median and interquartile range. The *t* test and chi-square test were used for comparison of continuous and categoric variables, respectively. When the data was not normally distributed, the Mann-Whitney test was used. A Cox proportional hazard analysis was performed to determine independent predictors of cardiac events for the entire population. Variables that were significant in the univariate analysis were entered into the multivariate model which adjusted for age, LVDd, and AF. The cardiac event–free curve was analyzed by the Kaplan-Meier method and compared by the log-rank test. The optimum LAVI for predicting cardiac events was determined as that giving the largest sum of sensitivity plus specificity on the receiver operating characteristic (ROC) curve. ROC curves were constructed to evaluate the area under the curves (AUC). Statistical significance was defined as $P < .05$. Statistical analyses were performed using a standard statistics computer program. The intraobserver and interobserver reliability of LAVI measurements were assessed by 2 echocardiologists in 20 patients, each repeated once. Based on the intraclass correlation coefficient, the mean intraobserver reliability of LAVI measurements was 98.0% and the mean interobserver reliability was 95.6%.

Results

Clinical Characteristics of the Study Subjects

The mean age of the study subjects was 72 ± 12 years, 53% of the patients were men, 36% were classified as AF patients, and 77% were in NYHA functional classes III or

Table 1. Comparison of Clinical Characteristics Between Patients With and Without Cardiac Events

	Event Free (n = 101)	Cardiac Event (n = 45)	*P* Value
Age (y)	72 ± 12	73 ± 11	.4915
Gender (M/F)	49/52	29/16	.0748
NYHA functional class I-II/III-IV (at admission)	28/73	6/39	.0485
NYHA functional class I-II/III-IV (at discharge)	101/0	44/1	.1027
AF	35 (35%)	18 (40%)	.5350
Heart rate (beats/min)	66 ± 12	69 ± 13	.3177
Hypertension	63 (62%)	27 (60%)	.7851
Diabetes mellitus	36 (36%)	17 (38%)	.8044
Hyperlipidemia	36 (36%)	16 (36%)	.9918
Current smoking	47 (47%)	22 (49%)	.7925
Etiology of heart failure			.6859
DCM	31 (31%)	9 (20%)	
ICM	23 (23%)	14 (31%)	
VHD	13 (13%)	6 (13%)	
HHD	12 (12%)	5 (11%)	
Others	22 (22%)	11 (24%)	
Echocardiography			
LAD (mm)	42 ± 8	46 ± 8	.0106
LVDd (mm)	56 ± 21	53 ± 9	.4614
LVEF (%)	47 ± 15	43 ± 16	.1701
E/A (sinus rhythm)	0.85 ± 0.45	0.99 ± 0.73	.2231
Deceleration time (ms)	190 ± 57	182 ± 69	.4538
Tei index	0.56 ± 0.33	0.64 ± 0.37	.3884
MR moderate	13 (13%)	12 (27%)	.0361
LVMI (g/m^2)	201 ± 69	225 ± 81	.1098
E/E′	11.0 ± 6.2	13.8 ± 7.9	.0184
LAVI (mL/m^2)	44 ± 22	56 ± 26	.0037
Blood marker at admission			
BNP (pg/mL)	516 (266–1100)	765 (401–1375)	.0823
Log_{10} BNP	2.75 ± 0.44	2.86 ± 0.35	.1633
Serum creatinine (mg/dL)	0.92 ± 0.39	0.97 ± 0.38	.0244
Uric acid (mg/dL)	6.6 ± 1.9	6.8 ± 1.9	.0424
Sodium (mEq/L)	141 ± 4	140 ± 4	.3289
Blood marker at discharge			
BNP (pg/mL)	216 (88–399)	259 (129–447)	.0027
Log_{10} BNP	2.29 ± 0.47	2.56 ± 0.38	.0010
Medication			
ACE inhibitors or ARBs	88 (87%)	37 (82%)	.2871
β-blockers	67 (66%)	24 (53%)	.1039
Ca-channel blockers	26 (26%)	7 (16%)	.1401
Diuretics	90 (89%)	41 (91%)	.7129
Digitalis	20 (20%)	6 (13%)	.2182

AF, atrial fibrillation; DCM, dilated cardiomyopathy; ICM, ischemic cardiomyopathy; VHD, valvular heart disease; HHD, hypertensive heart disease; LAD, left atrial dimension; LVDd, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; LAVI, left atrial volume index; BNP, B-type natriuretic peptide; ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker. Results are presented as mean ± SD, n (%), or median (interquartile range).

IV at admission. The etiology of HF was ischemic heart disease in 25% and nonischemic heart disease in 75%. The mean LVDd, LVEF, and LAVI were 56 mm, 46%, and 48 mL/m^2, respectively. The median plasma BNP level at admission was 583 pg/mL.

Follow-up was completed for all patients. There were 45 cardiac events (31%) during the follow-up period, and these comprised 7 cardiac deaths and 38 rehospitalizations for worsening HF.

The clinical characteristics of patients with or without cardiac events were compared (Table 1). NYHA functional class was worse in patients with cardiac events than in those without cardiac events. There were no significant differences in age, gender, prevalence of AF, hypertension, diabetes mellitus, hyperlipidemia, or etiology of HF between patients with or without cardiac events (Table 1).

Echocardiographic Parameters

LAD, E/E′, and LAVI were greater and MR more severe in patients with than in those without cardiac events (Table 1). There were no significant differences in other echocardiographic parameters between patients with and without cardiac events (Table 1).

Medication Use and Blood Markers at Admission

Serum creatinine and uric acid levels were significantly higher in patients with than without cardiac events (Table 1). Although there was no significant difference in plasma BNP levels at admission between patients with or without cardiac events, plasma BNP levels at discharge were significantly higher in patients with than without cardiac events. There were no significant differences in

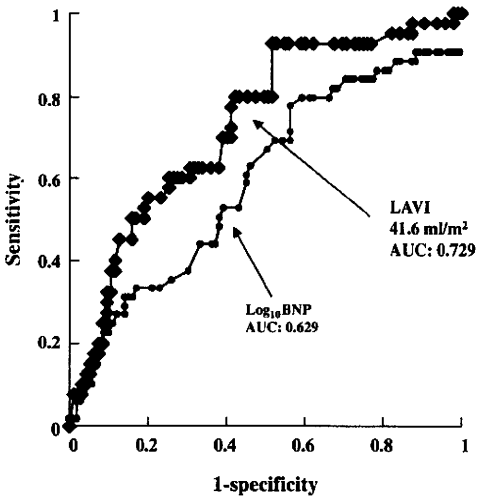

Fig. 1. Receiver operating characteristic (ROC) curve analyses of left atrial volume index (LAVI) and $\log_{10}$ B-type natriuretic peptide (BNP) for predicting cardiac events. The area under the ROC curve (AUC) for LAVI was 0.729. LAVI >41.6 mL/m^2 had a sensitivity of 80% and a specificity of 58%. The AUC for LAVI was greater than that for $\log_{10}$ BNP.

medication use between patients with and without cardiac events.

Risk Stratification by LAVI and Clinical Outcome

LAVI increased with worsening NYHA functional class. The ROC curve for LAVI as a predictor of cardiac events is shown in Figure 1. The AUC for LAVI was 0.729. LAVI >41.6 mL/m^2 had a sensitivity of 80% and a specificity of 58% for cardiac events. In addition, the AUC for LAVI as a predictor of cardiac events was 0.758 in patients with sinus rhythm, which was larger than that in all patients, including patients with AF.

The ROC curves obtained for LAVI and $\log_{10}$ BNP at discharge were compared (Fig. 1). The sensitivity and specificity of $\log_{10}$ BNP for detecting cardiac events were 67% and 54%, respectively. The AUC for LAVI (0.729) was greater than that for $\log_{10}$ BNP (0.629), suggesting that LAVI was superior to $\log_{10}$ BNP for predicting adverse outcomes.

Table 2. Results of Univariate Cox Proportional Hazard Analysis

Variable	Hazard Ratio	95% CI	*P* Value
Age (per 1 y increase)	1.006	0.981–1.032	.6564
NYHA functional class III-IV (at admission)	2.702	1.063–6.897	.0368
AF	1.325	0.719–2.443	.3671
LVDd (per 1 SD increase)	0.992	0.968–1.016	.5063
LVEF (per 1 SD increase)	0.985	0.965–1.004	.1273
MR moderate	2.024	1.037–3.953	.0385
E/E′ (per 1 SD increase)	1.316	1.028–1.670	.0281
LAVI (per 1 SD increase)	1.461	1.154–1.803	.0010
Creatinine (per 1 SD increase)	1.251	1.025–1.526	.0276
$\log_{10}$ BNP at admission (per 1 SD increase)	1.512	0.771–2.967	.2290
$\log_{10}$ BNP at discharge (per 1 SD increase)	2.957	1.487–5.883	.0020

CI, confidence interval; MR, mitral regurgitation; other abbreviations as in Table 1.

Table 3. Results of Multivariate Cox Proportional Hazard Analysis

Variable	Hazard Ratio	95% CI	*P* Value
Age (per 1 y increase)	0.987	0.959–1.015	.3563
NYHA functional class III-IV (at admission)	3.205	1.103–9.346	.0324
AF	1.046	0.467–2.343	.9133
LVDd (per 1 SD increase)	0.547	0.266–1.113	.0966
MR moderate	0.466	0.217–1.002	.0605
E/E′ (per 1 SD increase)	1.175	0.878–1.574	.2827
LAVI (per 1 SD increase)	1.427	1.024–1.934	.0317
Creatinine (per 1 SD increase)	1.158	0.923–1.453	.2035
$\log_{10}$ BNP at discharge (per 1 SD increase)	1.471	1.019–2.123	.0395

Abbreviations as in Tables 1 and 2.

Simple linear regression analysis showed that LAVI was correlated with E/E′ (r = 0.284; P = .0006).

The univariate Cox proportional hazard analysis revealed that LAVI was a significant prognostic factor for cardiac events (Table 2). $\log_{10}$ BNP at discharge, prevalence of NYHA functional class III-IV at admission, moderate MR, an increase in E/E′ of 1 SD, and serum creatinine levels were also related to cardiac events. In the multivariate Cox proportional hazard analysis, LAVI was an independent predictor of cardiac events after adjusting for age, NYHA functional class, AF, LVDd, and moderate MR (Table 3).

All patients were stratified into 3 groups according to tertiles for LAVI: <35.4 mL/m^2 (n = 49), 35.4–53.3 mL/m^2 (n = 49); and >53.3 mL/m^2 (n = 48). Kaplan-Meier analysis showed that there was a stepwise increase in risk of cardiac events with each increment of LAVI category, and LAVI >53.3 mL/m^2 was associated with the highest risk of cardiac events (log-rank test: P < .01; Fig. 2). As shown in Figure. 3, the relative risk of cardiac events was 4.9 times greater in the highest tertile compared with the lowest tertile.

Changes in LAVI Between Admission and Discharge

In 36 patients, LAVI was measured at both admission and discharge (Fig. 4). LAVI was greater at admission and tended to decrease at discharge after 22 ± 17 days in patients without cardiac events (51 ± 4 vs 44 ± 2 mL/m^2; P = .081). However, LAVI was high at both admission and discharge in patients with cardiac events (58 ± 7 vs 56 ± 4 mL/m^2; P = .4255).

Discussion

The present study demonstrated that LAVI was an independent predictor of adverse cardiac events in patients with HF.

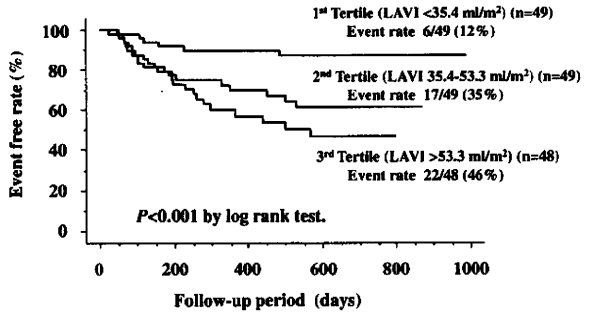

Fig. 2. Kaplan-Meier analysis showed that there was a stepwise increase in risk of cardiac events with each increment of left atrial volume index (LAVI) category, and LAVI >53.3 mL/m^2 was associated with the highest risk of cardiac events (log-rank test: $P < .01$).

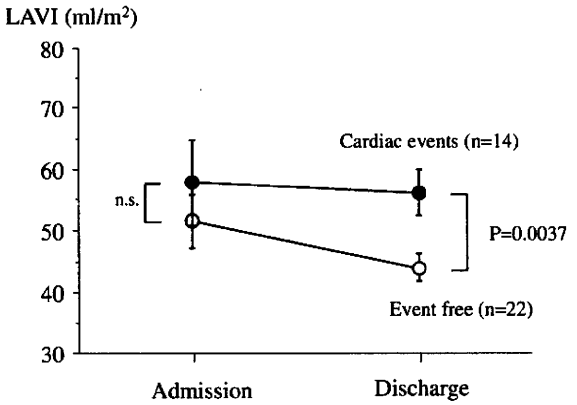

Fig. 4. Changes in left atrial volume index (LAVI) between admission and discharge. Results are expressed as mean ± SE.

Abnormal LV relaxation and decreased LV compliance may occur as a consequence of altered actin-myosin interactions and increased collagen deposition or cross-linking, with changes in cardiac viscoelastic properties.[18] Because the LA is directly exposed to LV filling pressure during the diastolic phase, a persistent increase in LA filling pressure leads to dilatation of the chamber and stretching of the atrial myocardium.[6,8] Therefore, LA volume may be a marker of the burden of LV diastolic dysfunction, which increases LA filling pressure[8] and LV end-diastolic pressure (LVEDP).[19] It is well known that LV systolic dysfunction is an important prognostic factor in HF. However, the incidence of HF with preserved ejection fraction has increased and now comprises nearly 50% of patients with HF,[19–22] suggesting that LV diastolic dysfunction may play an important role in the onset of HF. Tsang et al[23] reported that LAVI indicated the severity of diastolic dysfunction and provided an index of the burden of cardiovascular risk in patients without a history of AF or valvular heart disease. However, the prognostic value of LAVI in patients with HF has not been fully determined.

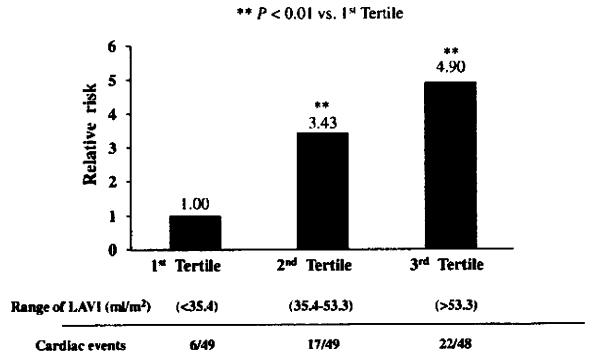

Fig. 3. Relative risk of cardiac events by tertiles of left atrial volume index (LAVI). The relative risk of cardiac events was greatest for patients in the third tertile of LAVI (**$P < .01$ versus first tertile).

LAVI was greater in patients with cardiac events than in those without cardiac events (Table 1). E/E′, which is a well known marker of LV diastolic dysfunction,[24] was also greater in patients with cardiac events. These results suggest that LAVI reflects increasing LVEDP and LA pressure caused by LV diastolic dysfunction. However, simple linear regression analysis showed a weak correlation ($r = 0.284$) between LAVI and E/E′, suggesting that these 2 parameters may have different prognostic significance. Furthermore, as shown in Table 3, LAVI was superior to E/E′ as a predictor of prognosis.

Whereas markers of LV diastolic dysfunction predicted a poor prognosis, LVEF was not a significant prognostic factor in the present study (Table 2). This may be attributed to the fact that in 51% of the enrolled patients LVEF was preserved (>45%). LAVI has been reported to be a powerful predictor of mortality and has remained an independent predictor after adjustment for clinical factors and LV systolic function in patients with acute myocardial infarction.[9] It was suggested that LA volume is less influenced by acute changes and reflects subacute or chronic function, whereas Doppler variables are affected by multiple factors and change rapidly. In the present study, patients with reduced LVEF (<45%) and a high LAVI (>41.6 mL/m^2) had a greater incidence of cardiac events (15/43 patients) compared with patients with reduced LVEF but a normal LAVI (5/28 patients). This result suggested that increased LAVI is a powerful predictor of cardiac events in patients with HF, and provides additional prognostic information to that provided by conventional parameters of LV function.

Plasma BNP levels at discharge are reportedly a better reflection of prognosis compared with levels measured at admission.[25] This is consistent with the results presented here (Table 2). Plasma BNP levels at discharge were significantly higher in patients with cardiac events than in those without cardiac events. Elevated plasma BNP levels at discharge may reflect the chronic increase in LA pressure, which causes dilatation of the LA chamber and stretching of the atrial myocardium. In 36 patients, LAVI was

measured at both admission and discharge, and the results suggested that a persistent increase in LAVI may be associated with adverse outcomes (Fig. 4).

Some earlier reports have suggested a relationship between LAVI and prognosis in patients with HF. Popescu et al[26] reported that LAVI was a better prognostic predictor than plasma BNP levels in 46 elderly patients with HF. Although that study population was small, the results are consistent with those from the present study. Lim et al[27] also reported that LAVI was an independent predictor of mortality in patients with suspected HF who were referred from the community. The LAVI cutoff value in that study was quite different from the present study and that of Popescu et al, probably because the study population was different.

Several earlier studies demonstrated that advanced diastolic dysfunction, characterized by an increased E/A ratio and shortening of the E-deceleration time, was strongly associated with increased mortality.[28–30] However, E/A ratio cannot be calculated in patients with AF, whose numbers continue to increase because of the aging population. In the present study, 36% of patients had AF; however, LAVI remained an independent predictor of cardiac events after adjustment for the prevalence of AF and moderate MR (Table 3). The multivariate Cox proportional hazard analysis and the ROC curve analysis revealed that LAVI was a more powerful prognostic predictor than plasma BNP level at discharge.

The present study has several limitations. First, the number of subjects studied was relatively small. Second, because echocardiography was not performed during follow-up, it was not possible to determine whether the long-term prognosis was affected by improvement in the LAVI.

In conclusion, LAVI is an independent prognostic factor for cardiac events and may be useful for risk stratification in patients with HF.

Disclosures

None.

References

1. Funk M, Krumholz HM. Epidemiologic and economic impact of advanced heart failure. J Cardiovasc Nurs 1996;10:1–10.
2. CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med 1987;316:1429–35.
3. SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med 1991;325:293–302.
4. Vasan RS, Levy D. Defining diastolic heart failure: a call for standardized diagnostic criteria. Circulation 2000;101:2118–21.
5. Zile MR, Gaasch WH, Carroll JD, Feldman MD, Aurigemma GP, Schaer GL, et al. Heart failure with a normal ejection fraction: is measurement of diastolic function necessary to make the diagnosis of diastolic heart failure? Circulation 2001;104:779–82.
6. Appleton CP, Galloway JM, Gonzalez MS, Gaballa M, Basnight MA. Estimation of left ventricular filling pressures using two-dimensional and Doppler echocardiography in adult patients with cardiac disease. Additional value of analyzing left atrial size, left atrial ejection fraction and the difference in duration of pulmonary venous and mitral flow velocity at atrial contraction. J Am Coll Cardiol 1993;22:1972–82.
7. Basnight MA, Gonzalez MS. Kershenovich SC, Appleton CP. Pulmonary venous flow velocity: relation to hemodynamics, mitral flow velocity and left atrial volume, and ejection fraction. J Am Soc Echocardiogr 1991;4:547–58.
8. Simek CL, Feldman MD, Haber HL, Wu CC, Jayaweera AR, Kaul S. Relationship between left ventricular wall thickness and left atrial size: comparison with other measures of diastolic function. J Am Soc Echocardiogr 1995;8:37–47.
9. Moller JE, Hillis GS, Oh JK, Seward JB, Reeder GS, Wright RS, et al. Left atrial volume: a powerful predictor of survival after acute myocardial infarction. Circulation 2003;107:2207–12.
10. McKee P, Castelli W, McNamara PM, Kannel WB. The natural history of congestive heart failure: the Framingham Study. N Engl J Med 1971;285:1441–6.
11. Arimoto T, Takeishi Y, Shiga R, Fukui A, Tachibana H, Nozaki N, et al. Prognostic value of elevated circulating heart-type fatty acid binding protein in patients with congestive heart failure. J Card Fail 2005;11:56–60.
12. Wang Y, Gutman JM, Heilbron D, Wahr D, Schiller NB. Atrial volume in a normal adult population by two-dimensional echocardiography. Chest 1984;86:595–601.
13. Abhayaratna WP, Seward JB, Appleton CP, Douglas PS, Oh JK, Tajik AJ, et al. Left atrial size: physiologic determinants and clinical applications. J Am Coll Cardiol 2006;47:2357–63.
14. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al, American Society of Echocardiography's Guidelines and Standards Committee, European Association of Echocardiography. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005;18:1440–63.
15. Devereux RB, Alonso DR, Lutas EM, Gottlieb GJ, Campo E, Sachs I, et al. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. Am J Cardiol 1986;57:450–8.
16. Tei C. New noninvasive index for combined systolic and diastolic ventricular function. J Cardiol 1995;26:135–6.
17. Niizeki T, Takeishi Y, Arimoto T, Takabatake N, Nozaki N, Hirono O, et al. Heart-type fatty acid–binding protein is more sensitive than troponin T to detect the ongoing myocardial damage in chronic heart failure patients. J Card Fail 2007;13:120–7.
18. Dent CL, Bowman AW, Scott MJ, Allen JS, Lisauskas JB, Janif M, et al. Echocardiographic characterization of fundamental mechanisms of abnormal diastolic filling in diabetic rats with a parameterized diastolic filling formalism. J Am Soc Echocardiogr 2001;14:1166–72.
19. Vasan RS, Larson MG, Benjamin EJ, Evans JC, Reiss CK, Levy D. Congestive heart failure in subjects with normal versus reduced left ventricular ejection fraction: prevalence and mortality in a population-based cohort. J Am Coll Cardiol 1999;33:1948–55.
20. Devereux RB, Roman MJ, Liu JE, Welty TK, Lee ET, Rodeheffer R, et al. Congestive heart failure despite normal left ventricular systolic function in a population-based sample: the Strong Heart Study. Am J Cardiol 2000;86:1090–6.
21. Kitzman DW, Gardin JM, Gottdiener JS, Arnold A, Boineau R, Aurigemma G, et al, CHS Research Group. Importance of heart failure with preserved systolic function in patients ≥65 years of age. Cardiovascular Health Study. Am J Cardiol 2001;87:413–9.
22. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. N Engl J Med 2006;355:251–9.