Effects of Weight Loss in Outpatients With Mild Chronic Heart Failure: Findings From the J-MELODIC Study

YOSHITAKA OKUHARA, MD, PhD,[1] MASANORI ASAKURA, MD, PhD,[1] YOSHIYUKI ORIHARA, MD,[1] YOSHIRO NAITO, MD, PhD,[1] TAKESHI TSUJINO, MD, PhD,[2] MASAHARU ISHIHARA, MD, PhD,[1] AND TOHRU MASUYAMA, MD, PhD[1], ON BEHALF OF THE J-MELODIC STUDY INVESTIGATORS

Hyogo, and Kobe, Japan

ABSTRACT

Background: Weight loss is a strong prognostic factor in chronic heart failure (CHF); however, little is known about its effects in patients with mild CHF. Therefore, we investigated the effects of weight loss in patients with mild CHF.

Methods and Results: We analyzed a total of 242 outpatients with mild CHF from the J-MELODIC study cohort. Weight loss was defined as ≥5% weight loss in 1 year. Twenty-seven patients (11.2%) lost ≥5% weight in 1 year. Weight loss was associated with higher rates of underweight and worsening renal function in 1 year compared with the absence of ≥5% weight loss. The predictors of weight loss included edema, B-type natriuretic peptide, and diabetes mellitus at baseline. Although weight loss was significantly associated with subsequent cardiovascular death or hospitalization for HF (log-rank $P = .002$) and subsequent death from any cause (log-rank $P = .002$), underweight was not associated with these outcomes (log-rank $P = .356$ and $P = .168$, respectively). Even after adjusting for covariates, weight loss was a significant and independent risk factor for subsequent cardiovascular death or hospitalization for HF (hazard ratio 3.22, 95% confidence interval 1.10−8.41; $P = .034$).

Conclusions: In patients with mild CHF, ≥5% weight loss was a significant predictor for subsequent cardiovascular death or hospitalization for HF. (*J Cardiac Fail 2019;25:44−50*)

Key Words: Weight loss, obesity paradox, chronic heart failure, cardiac cachexia.

Obesity promotes cardiovascular disease, hypertension, diabetes mellitus (DM), and cancer. However, in several diseases, including chronic heart failure (CHF), patients with obesity have a better prognosis than those without obesity; this is known as the "obesity paradox."[1,2] Conversely, low body weight (BW) and low body mass index (BMI) are reportedly strong predictors of heart failure (HF) exacerbation and death. Takiguchi et al reported BMI as an independent predictor of cardiac and all-cause mortality in hospitalized patients with HF, with the risk progressively increasing from obese to overweight, and normal to underweight patients,[3] although being markedly underweight is probably an indication of cardiac cachexia. Weight loss is also reportedly a prognostic factor in CHF. Based on the data from the SOLVD and V-FeFT II trials, Anker et al reported that ≥6% weight loss during the follow-up period (9 months of follow-up in the V-FeFT II trial) was a strong predictor of impaired survival.[4] It was reported that ≥5% weight loss was an important predictor of poor prognosis in patients with CHF and should be considered as cardiac cachexia in a subanalysis of data from the CHARM trial.[5] However, because these studies included many patients with severe symptoms, there is little information about the effects of weight loss in outpatients with mild CHF, and further investigations are warranted. The aim of the present study was therefore to investigate the effect of weight loss on prognosis in outpatients with mild CHF.

From the [1]Cardiovascular Division, Department of Internal Medicine, Hyogo College of Medicine, Hyogo, Japan and [2]Department of Pharmacy, School of Pharmacy, Hyogo University of Health Sciences, Kobe, Japan.

Manuscript received August 3, 2018; revised manuscript received November 1, 2018; revised manuscript accepted November 10, 2018.

Reprint requests: Yoshitaka Okuhara, MD, PhD, Cardiovascular Division, Department of Internal Medicine, Hyogo College of Medicine, 1-1 Mukogawa-cho, Nishinomiya, Hyogo 663-8501, Japan. Tel: +81-798-45-6553; Fax: +81-798-45-6551. E-mail: okuhara@hyo-med.ac.jp

Funding: This work was supported by a grant from the Japan Heart Foundation.

See page 49 for disclosure information.

1071-9164/$ - see front matter

https://doi.org/10.1016/j.cardfail.2018.11.003

Methods

Study Population

The J-MELODIC study was a multicenter, prospective, randomized, open, blinded end point design study that compared the effects of long-term administration of furosemide and azosemide treatment in outpatients with CHF classified in New York Heart Association (NYHA) functional class II or III. The design and primary results have been described previously.[6] In brief, the inclusion criteria were as follows: age ≥20 years; clinical diagnosis of HF based on a slight modification of the Framingham criteria within 6 months before inclusion; CHF outpatients with NYHA functional class II or III; no change in baseline therapy or HF symptoms within 1 month before enrollment; and receiving standard therapy and oral loop diuretics. The exclusion criteria were as follows: uncontrolled DM or hypertension; acute coronary syndrome; underwent percutaneous coronary intervention or an open heart surgery within the past 3 months; implantable cardiac defibrillator; hemodynamically significant left ventricular outflow tract obstruction; serum creatinine ≥2.5 mg/dL; required intravenous inotropes; and any serious noncardiovascular disease (malignancy). Consequently, 320 outpatients who met the inclusion criteria were randomized to receive azosemide or furosemide. The dose of each diuretic was appropriately adjusted within 8 weeks according to the symptoms of each patient, and standard and diuretic therapy for CHF was maintained for the patients for the rest of the study. The trial was approved by the Ethics Committees of each center, and all patients provided written informed consents.

Study Design

We analyzed patients with mild CHF who were not hospitalized for HF or did not die from any cause for 1 year and had weight measurements at baseline and 1 year. As shown in Fig. 1, 242 patients were eligible for this study after excluding patients who were lost to follow-up for 1 year (n = 26), were hospitalized for HF or died from any cause for 1 year (n = 26), were in NYHA functional class III at baseline (n = 21), and had missing data for BW at 1 year (n = 5). The eligible patients were divided into 2 groups: patients with and without weight loss. Weight loss was defined as ≥5% weight loss at 1 year based on the report on cardiac cachexia,[5,7] underweight as BMI <18.5 kg/m^2, and worsening renal function (WRF) as ≥25% decrease in estimated glomerular filtration rate (eGFR) at 1 year compared with baseline. We assessed a composite of cardiovascular death or unplanned admission to hospital for acute decompensated HF and all-cause mortality as in the J-MELODIC study.

Statistical Analysis

All continuous variables are expressed as mean ± standard deviation (SD) if they fit a normal distribution; alternatively, values are expressed as median and interquartile range (IQR). Parameters that fit normal distribution were analyzed with the use of paired/unpaired *t* tests. When the data did not fit a normal distribution, the Wilcoxon signed-rank/Mann-Whitney test was used. Categoric variables were analyzed by means of the chi-square, Fisher exact test, or McNemar test as appropriate. Univariable analyses were used to determine factors predictive of ≥5% weight loss and were performed based on demographic and clinical factors. Factors from the univariable analyses with $P \leq .1$ were further evaluated in the multivariable logistic model. We investigated subsequent outcomes to assess the effects of ≥5% weight loss at 1 year or underweight in patients with mild CHF. Kaplan-Meier analysis was used for the analysis of outcomes, with *P* values calculated by means of the log-rank test. Multivariable Cox proportional hazards regression analysis was performed to adjust for covariates which were known from previous reports (age, sex, baseline weight, and left ventricular ejection fraction [LVEF]).[4,8] Results are expressed as odds ratio (OR) and hazard ratio (HR) with 95% confidence interval (95% CI). A *P* value of <.05 was considered to be statistically significant. All statistical

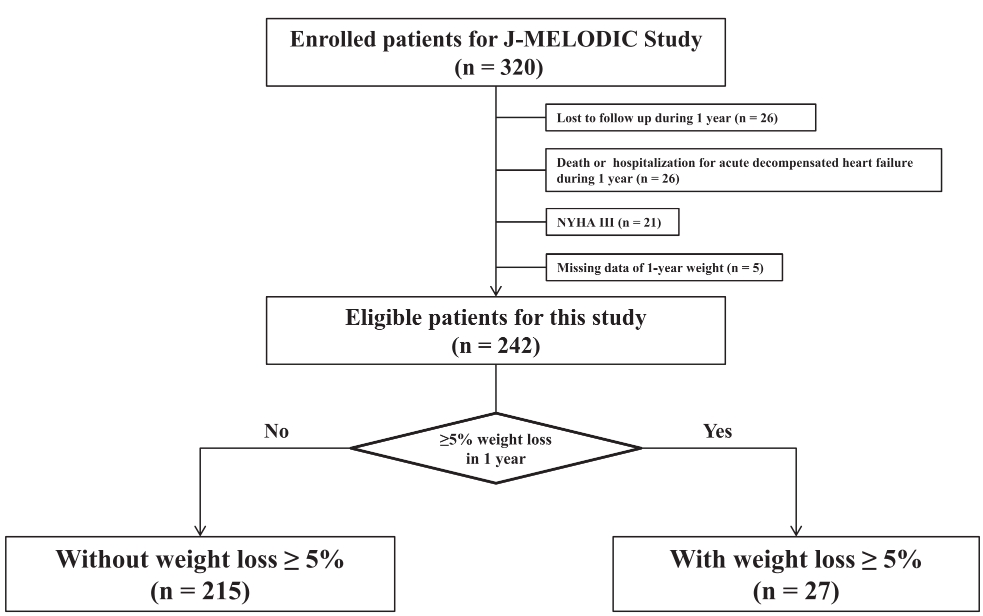

Fig. 1. Study flowchart.

analyses were performed with the use of JMP version 11.2 software (SAS Institute, Cary, North Carolina).

Results

Patient Population

As presented in Table 1, 11.2% of the 242 patients lost ≥5% weight in 1 year. Weight loss of ≥5% was associated with being older, presence of edema, and not having DM at baseline. In addition, weight loss of ≥5% was linked to lower hemoglobin level and higher rate of underweight at 1 year compared with those without ≥5% weight loss. The higher rate of NYHA functional class and lower eGFR at 1 year were found as a statistical tendency in patients with ≥5% weight loss compared with those without ≥5% weight loss ($P = .066$ and $P = .072$, respectively). A comparison between baseline and 1-year values showed that edema improved only in the patients with ≥5% weight loss. Patients without ≥5% weight loss showed a significant increase in BMI and BW. eGFR was significantly decreased only in patients with ≥5% weight loss. A decrease in B-type natriuretic peptide (BNP) and increase in LVEF were observed only in the patients without ≥5% weight loss. As shown in Fig. 2, there were significant differences between the 2 groups in the percentage changes between measurements taken at baseline and 1 year in median BW (0% vs −7.4%; $P < .001$) and median eGFR (−0.87% vs −5.07%; $P = .028$). The incidence of WRF was greater in patients with ≥5% weight loss than in those without ≥5% weight loss (19.2% vs 4.2%; $P = .010$).

Predictors of Weight Loss

Table 2 presents the predictors of ≥5% weight loss in patients with CHF. Multivariable analysis showed that the independent factors for ≥5% weight loss included edema (OR 5.18, 95% CI 2.06−13.99; $P < .001$), BNP (OR 1.02 per 10 pg/mL increase, 95% CI 1.00−1.05; $P = .041$), and DM (OR 0.25, 95% CI 0.06−0.80; $P = .016$) at baseline.

Weight Loss and Subsequent Outcomes

The subsequent median follow-up period was 694 (range 488−865) days after weight loss. Based on Kaplan-Meier analysis, we investigated the effects of ≥5% weight loss on

Table 1. Baseline Characteristics

Characteristic	Total(n = 242)	Patients Without ≥5% Weight Loss(n = 215)		Patients With ≥5% Weight Loss(n = 27)	
	Baseline	Baseline	1 Year	Baseline	1 Year
Age, median (IQR), y	72 (65−78)	72 (64−77)		74 (69−81)*	
Male, n (%)	147 (60.7)	130 (60.5)		17 (63.0)	
NYHA functional class, n (%)					
I	–	–	42 (19.5)	–	1 (3.7)
II	242 (100)	215 (100)	167 (77.7)	27 (100)	23 (85.2)
III	–	–	6 (2.8)	–	3 (11.1)
IV	–	–	0 (0)	–	0 (0)
Edema, n (%)	75 (31.0)	57 (26.5)	52 (24.2)	18 (66.7)*	10 (37.0)†
BW, median (IQR), kg	59.0 (52.0−67.0)	59.2 (52.0−67.0)	59.5 (53.0−68.0)†	58.0 (53.0−62.0)	51.5 (49.5−58.0)*,†
BMI, median (IQR), kg/m^2	23.6 (20.8−26.2)	23.7 (20.9−26.0)	24.0 (21.3−26.2)†	22.0 (19.9−26.3)	20.7 (18.4−23.8)*,†
Underweight, n (%)	21 (8.7)	17 (7.9)	17 (7.9)	4 (14.8)	7 (25.9)*,†
SBP, mean (SD), mm Hg	126 (16)	126 (17)	125 (17)	124 (14)	126 (18)
HR, median (IQR), beats/min	72 (63−80)	71 (63−80)	72 (64−79)	72 (65−79)	68 (63−78)
Hemoglobin, mean (SD), g/dL	12.9 (1.9)	13.0 (1.8)	13.0 (1.9)	12.3 (2.0)	12.2 (2.4)*
BUN, median (IQR), mg/dL	20 (16−24)	20 (15−2)4	18 (15−24)	20 (17−25)	21 (17−25)
eGFR, median (IQR), mL·min^{-1}·1.73 m^{-2}	55.1 (43.4−66.4)	55.7 (43.3−66.9)	52.1 (42.9−71.1)	54.0 (44.8−60.3)	47.7 (36.0−54.7)†
WRF, n (%)			9 (4.2)		5 (19.2)*
BNP, median (IQR), pg/mL	103 (43−215)	92.1 (42.6−202.0)	80.9 (38.6−152.0)†	123 (54.9−342.0)	90.2 (57.8−181.0)
LVEF, median (IQR), %	52 (40−64)	51 (40−64)	53 (41−65)†	57 (44−61)	53 (45−62)
LVEF ≤40%, n (%)	64 (26.4)	59 (27.4)	48 (22.3)	5 (18.5)	5 (18.5)
E/e′, median (IQR)	11.7 (8.7−15.6)	11.6 (8.4−15.6)	10.8 (8.6−15.0)	12.9 (9.3−16.4)	11.2 (7.2−19.8)
AF or AFL, n (%)	91 (37.6)	77 (35.8)		14 (51.9)	
Ischemic etiology, n (%)	83 (34.3)	74 (34.4)		9 (33.3)	
Hypertention, n (%)	154 (63.6)	137 (63.7)		17 (63.0)	
Diabetes mellitus, n (%)	72 (29.8)	69 (32.1)		3 (11.1)*	
Oral medications, n (%)					
Loop diuretics	242 (100)	215 (100)		27 (100)	
Furosemide equivalent, median (IQR), mg	30 (20−60)	30 (30−60)		30 (20−60)	
Aldosterone antagonists	101 (41.7)	91 (42.3)		10 (37.0)	
ACE inhibitors or ARBs	171 (70.7)	153 (71.2)		18 (66.7)	
β-Blockers	122 (50.4)	112 (52.1)		10 (37.0)	

IQR, interquartile range; NYHA, New York Heart Association; BW, body weight; BMI, body mass index; SBP, systolic blood pressure; HR, heart rate; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; WRF, worsening renal function; BNP, brain natriuretic peptide; LVEF, left ventricular ejection fraction; AF, atrial fibrillation; AFL, atrial flutter; DM, diabetes mellitus; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

*$P < .05$ versus same period in patients without ≥ 5% weight loss.

†$P < .05$ versus baseline.

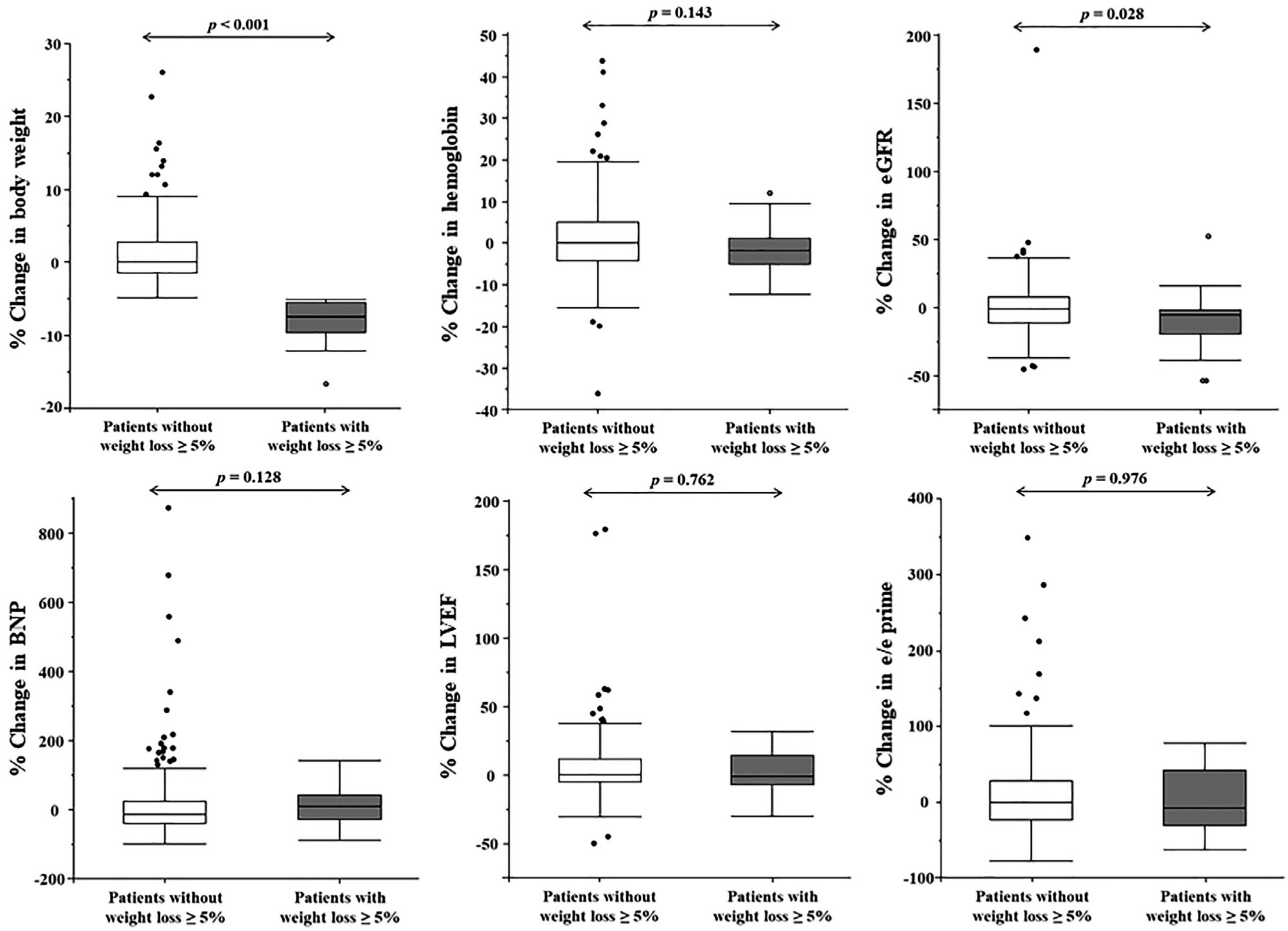

Fig. 2. Comparison of the percentage change in various parameters between patients with and without ≥5% weight loss in 1 year. eGFR, estimated glomerular filtration rate; BNP, B-type natriuretic peptide; LVEF, left ventricular ejection fraction.

subsequent outcomes. The rates of cardiovascular death or hospitalization for HF were 8.0% in patients without ≥5% weight loss and 39.4% in those with ≥5% weight loss (log-rank $P = .002$; Fig. 3a), and the rates of death from any cause were 3.5% in patients without ≥5% weight loss and 23.0% in those with ≥5% weight loss (log-rank $P = .002$; Fig. 3b). In multivariable Cox proportional hazards regression analysis, ≥5% weight loss was significantly associated with subsequent cardiovascular death or hospitalization for heart failure (HR 3.22, 95% CI 1.10–8.41; $P = .034$) after

Table 2. Univariable and Multivariable Analyses of Factors Related to >5% Weight Loss

	Univariable Analysis		Multivariable Analysis	
	Odds Ratio (95% CI)	*P* Value	Odds Ratio (95% CI)	*P* Value
Age	1.05 (1.01–1.10)	.035	1.00 (0.96–1.06)	.889
Male	1.11 (0.49–2.63)	.802	–	–
Edema	5.54 (2.41–13.6)	<.001	5.18 (2.06–13.99)	<.001
BMI	0.94 (0.84–1.05)	.256	–	–
SBP	0.99 (0.97–1.02)	.534	–	–
Hb	0.83 (0.66–1.03)	.093	0.94 (0.71–1.23)	.630
BUN	1.03 (0.98–1.07)	.245	–	–
eGFR	0.99 (0.96–1.01)	.263	–	–
BNP per 10 pg/mL increase	1.02 (1.01–1.05)	.026	1.02 (1.00–1.05)	.041
LVEF	1.01 (0.98–1.04)	.597	–	–
E/e′	1.02 (0.96–1.08)	.469	–	–
DM	0.26 (0.06–0.79)	.015	0.25 (0.06–0.80)	.016
Ischemic etiology	0.95 (0.39–2.18)	.911	–	–
Oral furosemide dose	1.01 (0.98–1.04)	.471	–	–

CI, confidence interval; BMI, body mass index; SBP, systolic blood pressure; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; BNP, brain natriuretic peptide; LVEF, left ventricular ejection fraction; DM, diabetes mellitus.

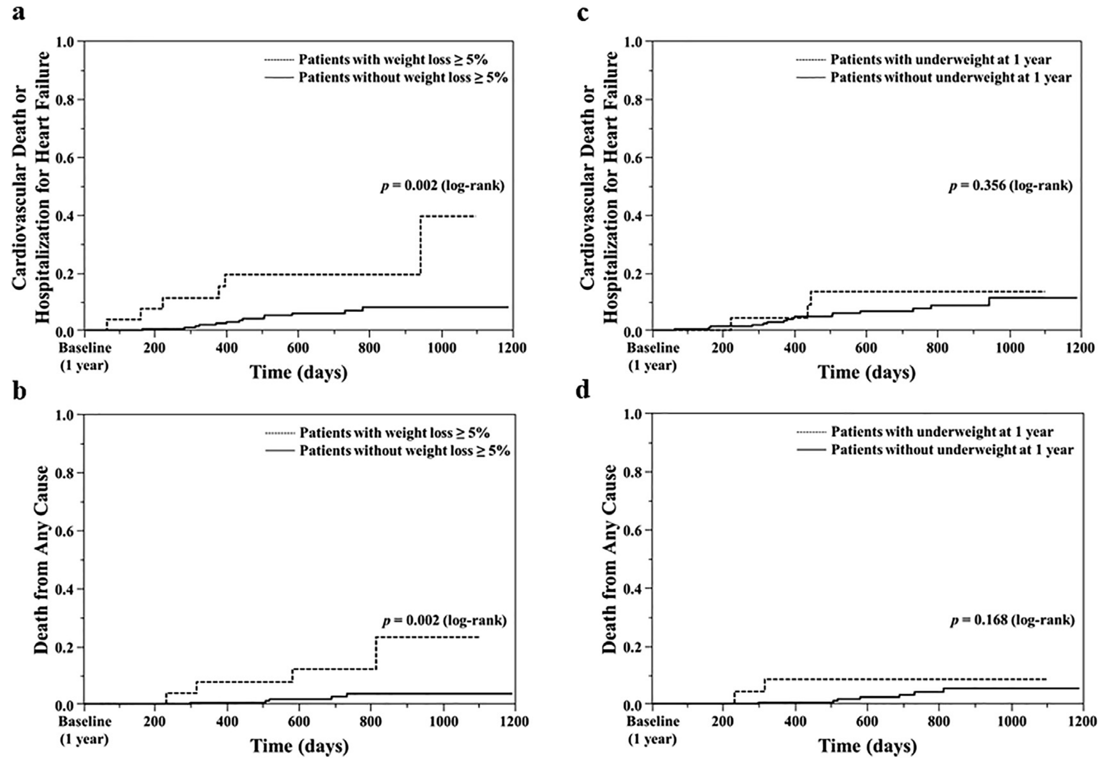

Fig. 3. Subsequent outcomes and ≥5% weight loss in 1 year or underweight in patients with mild chronic heart failure.

adjusting for age, sex, baseline weight, and LVEF. On the other hand, subsequent death from any cause failed to reach statistical significance (HR 2.51, 95% CI 0.57−10.37; $P = .212$). Conversely, the rate of cardiovascular death or hospitalization for HF was 11.2% in patients without underweight and 13.3% in those with underweight (log-rank $P = .356$; Fig. 3c). In contrast, rates of death from any cause were 5.2% in patients without underweight and 8.3% in those with underweight (log-rank $P = .168$; Fig. 3d). In multivariable Cox proportional hazards regression analysis, underweight was not associated with subsequent cardiovascular death or hospitalization for heart failure (HR 2.90, 95% CI 0.56−12.02; $P = .187$) nor death from any cause (HR 3.45, 95% CI 0.39−23.43; $P = .240$) after adjusting for covariates.

Discussion

This study evaluated the clinical effects of ≥5% weight loss at 1 year in patients with mild CHF. Our results showed that 11.2% (27/242) had lost ≥5% weight at 1 year. The predictors of ≥5% weight loss were edema, high BNP, and not having DM at baseline. Underweight and WRF were advanced in patients with weight loss of ≥5% in 1 year. In multivariable Cox proportional hazards regression analysis, weight loss was a significant and independent risk factor for subsequent cardiovascular death or hospitalization for HF in patients with mild CHF.

There have been no studies to investigate the effects of weight loss in patients with mild CHF. In a CHARM subanalysis that investigated the effect of weight loss in 6 months on subsequent mortality, the percentage of patients in NYHA functional class II was 45.7% (3171/6933) at baseline.[5] In the RICA registry, which assessed the impact of weight loss on mortality in patients with CHF, 56.9% of the patients were in NYHA functional class I or II and the median BNP level was 644 pg/mL at baseline.[9] In our study, all patients were in NYHA functional class II and their median BNP level was 103 pg/mL at baseline, excluding those who were hospitalized for worsening HF or who died from any cause in 1 year. Thus, we examined the effects of weight loss occurring in mild stable patients with CHF. In addition, the proportion of patients with LVEF ≤40% was only 26.4% overall in our study and did not differ between the 2 groups. Most studies on weight loss have included many more patients with LVEF ≤40%. In a CHARM subanalysis, the percentage of patients with LVEF ≤40% was 51.4% (3563/6933) at baseline.[5] In a SOLVD subanalysis, all of the patients had LVEF ≤40%.[4] Thus, our study included a large number of patients with preserved LVEF.

Weight loss was more commonly observed in patients with older age and edema and without DM at baseline. On the basis of multivariable analysis in our study, the predictors of weight loss were edema and BNP levels at baseline. Consistently with our result, weight loss was associated with edema in the CHARM subanalysis.[5] Therefore, weight loss may be at least in part explained by an improvement of edema in patients with CHF. This improvement generally indicates decongestion in HF treatment. However, the patients with ≥5% weight loss showed poor outcomes. Because residual edema and NYHA functional class of III or higher at 1 year were more frequently found in patients with >5% weight loss despite losing weight, incomplete decongestion may be related to poor outcomes. However, more importantly, a slight but significant weight gain and decreased BNP were found in patients without ≥5% weight loss. This phenomenon is the "obesity paradox," which may occur as a result of improved nutritional status and increased skeletal muscle.[10–12] We did not adjust for the presence of edema in our study, which can cause an overestimation of nonfluid weight in patients with ≥5% weight loss. Further studies are needed to assess the effects of weight loss in the setting of mild CHF without edema.

Interestingly, weight loss was less common in patients with CHF and DM in this study. The obesity paradox was not observed in patients with DM and HF in a large cohort of patients with HF.[13] Conversely, the obesity paradox was observed in hospitalized patients with DM and acute HF.[14] Samanta et al reported that normal weight had higher mortality than overweight or obesity in patients with myocardial infarction and left ventricular dysfunction despite the fact that overweight and obese patients were more likely to have DM.[15] Therefore, the effects of weight loss should be carefully assessed in patients with DM and CHF.

Although many researchers have focused on the characteristics of patients with CHF before weight loss, little is known about changes associated with the weight loss. We therefore investigated physiologic changes accompanying weight loss. We showed that ≥5% weight loss at 1 year was associated with anemia, WRF, and higher rate of underweight. Anemia and renal insufficiency are associated with cardiac cachexia and are strong prognostic factors in patients with HF.[16–18] Remarkably, although NYHA functional class III or higher was included in patients with ≥5% weight loss in 1 year, there was no significant deterioration in the severity of HF as assessed by edema, LVEF, BNP, and E/e′. Reportedly, exercise capacity links to skeletal muscle mass independently from LVEF, cardiac output, and left ventricular end-diastolic volume in patients with CHF.[10–12] In the present study, weight loss may represent decreased skeletal muscle mass. Overall, these results suggest that weight loss in HF is a complicated pathology involving extracardiac factors such as anemia, renal insufficiency, and reduction of skeletal muscle mass.

The patients included in this study were older than those included in the SOLVD and CHARM trials, in which weight loss was related to impaired survival.[4,5] In the RICA registry, which included patients older than those in our study, weight loss did not increase mortality.[9] Thus, the effects of weight loss are not homogeneous across different studies and should be evaluated in various settings. Our study showed that ≥5% weight loss at 1 year but not underweight was significantly associated with subsequent cardiovascular death or hospitalization for HF, suggesting that weight loss rather than underweight affects prognosis in patients with mild CHF.

Study Limitations

The results of this study should be interpreted in the context of the following limitations. First, the sample size was small, and considering its retrospective nature, inadequate validity of comparisons may lead to incorrect interpretation. We can not exclude the possibility that residual measured and/or unmeasured confounders may have influenced our observations. The results may be subject to residual confounding that can not be fully corrected for. Second, BW was compared with baseline only after 1 year, and detailed weight change was not investigated during the year. Third, we could not distinguish if weight variation was a planned weight reduction or not (eg, diet, overeating, and muscle training). Moreover, we could not distinguish whether weight loss was due to fat or muscle reduction. Fourth, although patients with any serious cancer were not included in the J-MELODIC study, we could not recognize weight loss due to potential malignant disorders and other wasting disorders (eg, thyroid disease and depression) which progressed for 1 year after baseline. Finally, renal function was assessed by eGFR calculated from serum creatinine level and age. The serum creatinine level depends on muscle mass and diet intake, which may cause underestimation of renal function in patients with ≥5% weight loss.

Conclusion

In patients with mild CHF, ≥5% weight loss was a significant predictor for subsequent cardiovascular death or hospitalization for HF. Further research is warranted to clarify the effects of weight loss in patients with CHF.

Acknowledgments: The authors thank the J-MELODIC investigators, coordinators, and participating institutions for the data.

Disclosures: None.

References

1. Carbone S, Lavie CJ, Arena R. Obesity and heart failure: focus on the obesity paradox. May Clin Proc 2017;92:266–79.
2. Zhang X, Liu Y, Shao H, Zheng X. Obesity paradox in lung cancer prognosis: evolving biological insights and clinical implications. J Thorac Oncol 2017;12:1478–88.
3. Takiguchi M, Yoshihisa A, Miura S, Shimizu T, Nakamura Y, Yamauchi H, et al. Impact of body mass index on mortality in heart failure patients. Eur J Clin Invest 2014;44:1197–205.
4. Anker SD, Negassa A, Coats AJ, Afzal R, Poole-Wilson PA, Cohn JN, et al. Prognostic importance of weight loss in chronic heart failure and the effect of treatment with angiotensin-converting-enzyme inhibitors: an observational study. Lancet 2003;361(9363):1077–83.
5. Pocock SJ, McMurray JJ, Dobson J, Yusuf S, Granger CB, Michelson EL, et al. Weight loss and mortality risk in patients with chronic heart failure in the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) programme. Eur Heart J 2008;29:2641–50.
6. Masuyama T, Tsujino T, Origasa H, Yamamoto K, Akasaka T, Hirano Y, et al. Superiority of long-acting to short-acting

loop diuretics in the treatment of congestive heart failure. Circ J 2012;76:833–42.

7. Evans WJ, Morley JE, Argiles J, Bales C, Baracos V, Guttridge D, et al. Cachexia: a new definition. Clin Nutr 2008;27:793–9.
8. Nishikido T, Oyama JI, Nagatomo D, Node K. A reduction of BMI predicts the risk of rehospitalization and cardiac death in nonobese patients with heart failure. Int J Cardiol Published online August 18, 2018.
9. Trullas JC, Formiga F, Montero M, Carrera-Izquierdo M, Grau-Amoros J, Chivite-Guillen D, et al. Impact of weight loss on mortality in chronic heart failure: findings from the RICA registry. Int J Cardiol 2013;168:306–11.
10. Lang CC, Chomsky DB, Rayos G, Yeoh TK, Wilson JR. Skeletal muscle mass and exercise performance in stable ambulatory patients with heart failure. J Appl Physiol 1997;82:257–61.
11. Cicoira M, Zanolla L, Franceschini L, Rossi A, Golia G, Zamboni M, et al. Skeletal muscle mass independently predicts peak oxygen consumption and ventilatory response during exercise in noncachectic patients with chronic heart failure. J Am Coll Cardiol 2001;37:2080–5.
12. Franciosa JA, Park M, Barry Levine T. Lack of correlation between exercise capacity and indexes of resting left ventricular performance in heart failure. Am J Cardol 1981;47:33–9.
13. Zamora E, Lupon J, Enjuanes C, Pascual-Figal D, de Antonio M, Domingo M, et al. No benefit from the obesity paradox for diabetic patients with heart failure. Eur J Heart Fail 2016;18:851–8.
14. Abi Khalil C, Sulaiman K, Singh R, Jayyousi A, Asaad N, AlHabib KF, et al. BMI is inversely correlated to the risk of mortality in patients with type 2 diabetes hospitalized for acute heart failure: findings from the Gulf Acute Heart Failure (Gulf-CARE) registry. Int J Cardiol 2017;241:262–9.
15. Samanta R, Pouliopoulos J, Kumar S, Narayan A, Nadri F, Qian P, et al. Influence of BMI on inducible ventricular tachycardia and mortality in patients with myocardial infarction and left ventricular dysfunction: the obesity paradox. Int J Cardiol 2018;265:148–54.
16. Ezekowitz JA, McAlister FA, Armstrong PW. Anemia is common in heart failure and is associated with poor outcomes. Insights from a cohort of 12 065 patients with new-onset heart failure. Circulation 2003;107:223–5.
17. Cicoira M, Anker SD, Ronco C. Cardio-renal cachexia syndromes (CRCS): pathophysiological foundations of a vicious pathological circle. J Cachexia Sarcopenia Muscle 2011;2:135.
18. Tanaka S, Kamiya K, Hamazaki N, Matsuzawa R, Nozaki K, Maekawa E, et al. Incremental value of objective frailty assessment to predict mortality in elderly patients hospitalized for heart failure. J Card Fail Published online August 16, 2018.