Published in final edited form as:

J Cardiovasc Nurs. 2014 ; 29(5): 439–447. doi:10.1097/JCN.0b013e3182a46ba8.

The link of unintentional weight loss to cardiac event-free survival in patients with heart failure Brief title: Weight loss, depressive symptoms, and hsCRP

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Abstract

Background—Patients with heart failure (HF) commonly have unintentional weight loss, depressive symptoms, and elevated levels of high-sensitivity C-reactive protein (hsCRP). Each of these variables has been independently associated with shorter cardiac event-free survival. However, little data exist on the relationships of unintentional weight loss, hsCRP, and depressive symptoms to cardiac event-free survival.

Objective—To determine 1) whether depressive symptoms and elevated hsCRP predicted unintentional weight loss and 2) whether unintentional weight loss predicted shorter cardiac event-free survival.

Methods—This was a prospective study of 243 consecutive HF patients (61% male, 61 ± 14 years) enrolled during an index hospitalization for HF exacerbation. Patients provided blood samples to measure hsCRP and completed the Beck Depression Inventory to assess depressive symptoms at discharge. Body weight was measured at discharge and 6 months later. Unintentional weight loss was defined as weight loss of greater than 6% of body weight since discharge. Cardiac event-free survival was followed for one-year after the second measurement of body weight through monthly telephone interviews. Hierarchical logistic regression was used to determine whether depressive symptoms and elevated hsCRP predicted unintentional weight loss. Cox hazard regression was used to determine whether unintentional weight loss predicted cardiac event-free survival.

Results—Thirty-five patients (14.4%) experienced unintentional weight loss at 6-months after discharge. Hierarchical Cox hazard regression revealed that patients with unintentional weight loss had 3.2 times higher risk for cardiac events, adjusting for other clinical factors ($p < 0.001$). In

hierarchical logistic regression, elevated hsCRP (odds ratio [OR] = 1.49, 95% confidence interval [CI] = 1.15-1.92) and depressive symptoms (OR = 1.07, 95% CI = 1.02-1.12) independently predicted unintentional weight loss.

Conclusions—Unintentional weight loss was an independent predictor of poor outcomes. HF patients with depressive symptoms and elevated hsCRP are at a higher risk for unintentional weight loss.

INTRODUCTION

Patients with heart failure (HF) are likely to experience progressive unintentional weight loss.¹⁻³ It is estimated that the prevalence of unintentional weight loss, defined as a loss of 6% or more of body weight over 6 months, ranges from 12 to 16% in stable outpatients with HF^{4,5} to as high as 50% in patients with severe HF.⁶ Unintentional weight loss was consistently shown to be associated with shortened survival in prior studies.^{2,4,5} Multiple factors have been identified as causes of unintentional weight loss in HF patients including malnutrition, inadequate food intake due to loss of appetite, dietary salt restriction, and malabsorption or loss of nutrients due to gastro-intestinal congestion.⁷⁻¹² However, additional biobehavioral factors associated with unintentional weight loss and their relationships to health outcomes in patients with HF have not been examined.

Depressive symptoms, which are prevalent in patients with HF, may be associated with higher risk for unintentional weight loss. A recent meta-analysis¹³ demonstrated that up to 48% of patients with HF have clinically significant depressive symptoms. Prior investigators^{14,15} have reported that depressive symptoms are more prevalent in elderly people who have inadequate food intake. We previously reported that depressive symptoms were associated with poor nutritional intake in HF patients.¹⁶ Little attention has been paid to the relationship of depressive symptoms to unintentional weight loss. Furthermore, the association of depressive symptoms and unintentional weight loss with cardiac events has not been explored in patients with HF.

Increased serum levels of C-reactive protein (CRP), which has been included in diagnostic criteria for cachexia,^{9,17} were reported in HF patients with unintentional weight loss.¹⁸ Elevated serum CRP has been proposed to be an inflammatory marker of an important biological pathway linking depressive symptoms with cardiac events in patients with HF.¹⁹ Although increased serum CRP and depressive symptoms have been shown to be independent predictors of hospitalization and cardiac mortality in HF patients,²⁰⁻²² little data exist on the relationships among depressive symptoms, high-sensitivity CRP (hsCRP) and unintentional weight loss.

Therefore, the purposes of this study were 1) to determine whether depressive symptoms and elevated hsCRP predicted unintentional weight loss after controlling for other clinical variables and 2) to determine whether unintentional weight loss was independently associated with shorter cardiac event-free survival in patients with HF after controlling for same clinical variables, depressive symptoms, and hsCRP. The following 2 hypotheses were tested.

Hypothesis 1: Unintentional weight loss will be greater in patients with depressive symptoms and elevated hsCRP after controlling for age, gender, HF etiology, body mass index, New York Heart Association functional class, left ventricular ejection fraction, total comorbidity score, use of angiotensin-converting enzyme inhibitors, diuretics, and beta blockers.

Hypothesis 2: Unintentional weight loss will be an independent predictor of time to first cardiac event after controlling for the same clinical variables, depressive symptoms, and hsCRP.

METHOD

Design and settings

This was a prospective cohort study with an 18-month follow-up to evaluate the relationships among depressive symptoms, hsCRP, unintentional weight loss, and cardiac event-free survival in patients with HF. Patients with HF were recruited during an index hospitalization due to exacerbation of HF in two tertiary medical centers located in Seoul, Korea.

Sample

Eligibility criteria for participation were: (1) diagnosed with chronic HF by a cardiologist and confirmed using the Framingham criteria²³ with impaired or preserved left ventricular systolic function; (2) taking same doses of prescribed HF medications for at least one month; (3) able to read and speak Korean. Exclusion criteria were: (1) referred for heart transplantation; (2) valvular heart disease or myocarditis as the primary HF etiology; (3) history of myocardial infarction within the past three months; (4) any cognitive impairment defined by a diagnosis of cerebrovascular accident, dementia, or head injury; (5) current history of cancer, severe thyroid disease, hepatic, or renal failure; and (6) involvement in a weight control program.

The required sample size for this study was estimated using a power analysis suggested by Erdfelder and colleagues.^{24,25} Effect size was estimated from a previous study⁴ in which weight loss of 6% or more over 6 months was the strongest predictor of shortened survival with adjusted hazard ratio (HR) of 2.10. Considering α of 0.05, with up to 13 independent variables in the model, and 80% power ($1 - \beta$) a multiple logistic regression to detect a medium effect size ($f^2 = 0.15$) would require a sample size of 217 patients.²⁵

A total of 266 patients were eligible to participate in this study. Nine patients declined to participate, 3 withdrew, 6 were lost during follow-up, and 5 were determined to have incomplete questionnaires. Consequently, a total of 243 patients were included in this study.

Measurements of variables

Unintentional weight loss—Body weight was measured to the nearest 0.1 kg by a trained research assistant at hospital discharge and 6-months later using the same electronic scale (Dong Sahn Jenix, Seoul, Korea). Unintentional weight loss was defined as weight loss greater than 6% of discharge body weight within 6 months in the absence of dieting or other

primary causes such as certain infectious diseases (e.g. tuberculosis) or chronic illness such as obstructive lung disease and cancer.⁴ The 6% cut-off was chosen because prior research has shown that this level of weight loss is associated with increased risk of death and has been used to define clinically significant unintentional weight loss in patients with HF.⁴ Patients were divided into two groups: those with unintentional weight loss and those without unintentional weight loss.

Depressive symptoms—Depressive symptoms were measured using the Korean version of the Beck Depression Inventory (K-BDI),²⁶ a 21-item questionnaire to assess the presence and severity of depressive symptoms. The presence of each symptom was rated on a 0 (not at all) to 3 (very much) scale, and a total score was obtained by adding the ratings of the 21 items. The possible range of scores is 0 to 63, with higher scores indicating more severe depressive symptoms. The validity and reliability of the K-BDI has been previously established in Korean patients.²⁶ All patients were categorized into two groups: those with depressive symptoms, or those without depressive symptoms, based on the published cut-point score of 16.²⁷ The Cronbach's alpha of 0.90 in this study was comparable to the initial K-BDI of 0.86.²⁶

High-sensitivity C-reactive protein (hsCRP)—Patients fasted overnight and blood was drawn to measure serum levels of hsCRP the morning of discharge before breakfast. Serum samples were stored at -70°C prior to assay. The latex-enhanced immunoturbidimetric assay (ADVIA 1650 Chemistry System, Siemens, Tarrytown, NY) was used to determine serum levels of hsCRP. The sensitivity of the hsCRP assay was less than 0.05 mg/L. Inter-assay and intra-assay coefficient of variation were within 5%. The personnel who performed these assays were blinded to patient status. The current recommended cut-points for defining risk for cardiac events are: low risk = < 1.0 mg/L, average risk = 1.0 to 3.0 mg/L, high risk = > 3.0 mg/L.²⁸⁻³⁰

Cardiac event-free survival—The primary end point was the composite of time to first event of rehospitalization or cardiac-related death. We conducted monthly telephone follow-up interviews for 12-months to obtain hospitalization data. If a patient reported that he/she was hospitalized or visited any hospital in the past 1 month, he/she was asked the reason for readmission, the date of readmission and discharge, and hospital name. Discharge diagnosis and hospitalization were confirmed by medical record review by a nurse with expertise in HF. Date and cause of death were obtained from family members, physicians, medical record, or death certificates.

Other clinical variables—We included covariates of age, gender, HF etiology, New York Heart Association (NYHA) functional class, left ventricular ejection fraction, total comorbidity score from the Charlson comorbidity index,³¹ and prescribed medications at discharge. Patients were assigned to one of four NYHA functional classes based on patient interviews: I (no dyspnea with ordinary physical activity), II (dyspnea occurs with ordinary physical activity), III (dyspnea occurs with less than ordinary physical activity), or IV (dyspnea occurs at rest).³² Height was measured by a trained research assistant before

discharge, and body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared.³³

Procedures

Approval from the Institutional Review Boards at each enrollment site was obtained prior to beginning the study. Eligible patients were referred by cardiologists to the primary investigator and a trained research assistant. Patients were screened for involvement in any individual or organized weight control program over the past six months. Written informed consent was received from each patient. Body weight and height were measured in light clothes without shoes the morning of discharge before breakfast and before taking prescribed medications including diuretics. In addition, physical examinations were performed by a trained research assistant with expertise in care of patients with HF to determine that no patient had peripheral or pulmonary edema, significantly increased jugular venous pressure, or ascites at the time of discharge according to the Framingham criteria.²³ Patients completed questionnaires with the trained research assistant if needed to measure depressive symptoms and blood was drawn to measure serum levels of hsCRP.

Six months later, body weight in light clothes without shoes was again measured by a trained research assistant using the same scale before breakfast and before taking prescribed medications in the each HF clinic. The hospital administrative databases were reviewed to determine medication changes, especially in relation to weight and a history of weight change was carefully evaluated to determine unintentional weight loss. Edematous status was determined by physical assessment for jugular vein distension, rales, S₃ gallop, bilateral ankle edema and X-ray report for hepatomegaly, cardiomegaly, pleural effusion or pulmonary edema by a trained research assistant. The health status of all patients was followed by monthly telephone contact with patient or family member for a 12-month period after the second measurement of body weight to obtain data on hospitalization and death by asking the following question: "For the past 1 month, have you been readmitted or visited any hospital?"

Data analysis

SPSS version 18.0 was used for data analyses; *p* values less than 0.05 were considered significant. Patient characteristics were shown using means with standard deviations or frequency with percent. The distribution of hsCRP values was markedly skewed; consequently values were natural log-transformed for analyses. Skewness and kurtosis of hsCRP were 3.90 and 16.02, respectively; whereas skewness and kurtosis of log-transformed hsCRP were 0.03 and -0.31, respectively. Chi-square tests and independent *t*-tests were used to determine differences between patients with and without unintentional weight loss.

Hierarchical logistic regression was used to determine whether depressive symptoms and increased hsCRP independently predicted unintentional weight loss after controlling for age, gender, HF etiology, BMI, NYHA functional class, left ventricular ejection fraction, total comorbidity score, use of ACE inhibitors, diuretics, and beta blockers. Hierarchical Cox proportional hazard regression was used to determine the association of unintentional weight

loss with cardiac event-free survival after controlling for the same clinical variables, depressive symptoms, log-transformed hsCRP.

The proportional hazard assumption of invariant HR over the follow-up period was examined by using log-minus-log survival function and determined to be valid. The time-dependent covariate analysis was not statistically significant ($p = 0.658$), suggesting that the assumption of proportionality was reasonable. The HR for cardiac event-free survival and odds ratio (OR) for unintentional weight loss were obtained for all independent variables along with 95% confidence intervals (CIs).

RESULTS

Patient characteristics

Patient characteristics are shown in Table 1. Average age was 61 with a range of 22 to 88 years. Less than half of the patients were female and more than half were overweight or obese. The majority of patients were in NYHA class II and III. Although about one third of the total sample of patients had depressive symptoms, two thirds of patients with unintentional weight loss had depressive symptoms. The median value (25th, 75th quartile) of hsCRP was 1.82 mg/L (0.56 mg/L, 7.53 mg/L) with a range from 0.03 mg/L to 182.0 mg/L. Most patients were prescribed ACE inhibitors, beta blockers, or diuretics.

In addition to depressive symptoms, patients who experienced unintentional weight loss were significantly older, had greater number of comorbidities, higher serum levels of hsCRP, and more were female compared to patients without unintentional weight loss (Table 1).

Unintentional weight loss over 6-month

Figure 1 shows the distribution weight changes over the six month follow-up period. At six months after discharge, 35 patients (14.4%) experienced unintentional weight loss of greater than 6% while more than 50% of patients had stable or increased body weight.

Depressive symptoms, hsCRP, and unintentional weight loss

Table 2 presents the results from hierarchical logistic regression analysis predicting the unintentional weight loss in HF patients. After controlling for age, gender, HF etiology, BMI, NYHA functional class, left ventricular ejection fraction, total comorbidity score, and use of ACE inhibitors, diuretics, and beta blockers in the initial step, log-transformed hsCRP and depressive symptoms as continuous variables were added in the second step. Total comorbidity score was the only control variable to independently predict unintentional weight loss (OR = 1.84, 95% CI = 1.30 - 2.59). Elevated log-transformed hsCRP (OR = 1.49, 95% CI = 1.15-1.92) and more severe depressive symptoms (OR = 1.07, 95% CI = 1.02-1.12) independently predicted unintentional weight loss in patient with HF. The risk of unintentional weight loss increased by approximately 50% for each one unit increase in log-transformed hsCRP ($p = 0.002$) and by 7% for each one unit increase in depressive symptom scores ($p = 0.007$).

Cardiac event-free survival

During the 12-month follow-up period, eight patients (3.3%) died due to HF exacerbation and 12 (4.9%) died from other cardiac problems. Thirty-four patients (14.0%) were rehospitalized due to HF exacerbation and 40 (16.5%) were readmitted due to other cardiac cause. Thirteen patients (5.3%) who initially visited the emergency department for worsening HF symptoms during the course of this study were admitted to the hospital and included in the survival analyses.

Unintentional weight loss and cardiac event-free survival

Figure 2 shows the unadjusted hazard ratio for percentage weight change over the six month follow-up period. Patients who experienced unintentional weight loss of greater than 6% had a 2.5 times higher risk for cardiac events compared to those with weight loss or weight gain within 1% ($p = 0.001$).

Table 3 presents the results from hierarchical Cox proportional hazard regression analysis predicting cardiac event-free survival in HF patients. Initially, other clinical variables including age, gender, HF etiology, BMI, NYHA functional class, left ventricular ejection fraction, total comorbidity score, use of ACE inhibitors, diuretics, and beta blockers were included in the first step. After depressive symptoms and log-transformed hsCRP as continuous variables were added in the second step, unintentional weight loss was added in the final step. Decreased LVEF was the only control variable to independently predict cardiac event-free survival (HR = 0.98, 95% CI = 0.97 - 0.99). In hierarchical Cox proportional hazard regression, unintentional weight loss predicted cardiac event-free survival (HR = 3.17, 95% CI = 1.84 - 5.45) after controlling for other clinical variables, depressive symptoms and log-transformed hsCRP. Patients with unintentional weight loss had a 3.2 times higher risk for cardiac events compared to those without unintentional weight loss ($p < 0.001$).

DISCUSSION

This is one of a few studies to demonstrate a relationship between unintentional weight loss and cardiac event-free survival in patients with HF.^{2,4,5} Our results suggest that depressive symptoms and elevated hsCRP as a marker of inflammation independently predict unintentional weight loss. However, longitudinal studies will be needed to determine if depressive symptoms and inflammation are causally linked to unintentional weight loss.

A notable finding from our study was that depressive symptoms were a significant predictor of unintentional weight loss, which independently predicted shorter cardiac event-free survival in HF patients. It is not possible to determine the specific mechanisms responsible for the impact of depressive symptoms on unintentional weight loss based on our data. However, one hypothesis that can be proposed is that loss of appetite induced by depressive symptoms may decrease food intake resulting in unintentional weight loss. Depressed people tend to choose foods more for emotional reasons,^{34,35} and those with severe and chronic depressive symptoms may be especially vulnerable to poor nutritional intake.³⁶⁻³⁸

Therefore, assessment and treatment of depressive symptoms may be a component of interventions to prevent unintentional weight loss.

We proposed that elevated levels of hsCRP contributed to unintentional weight loss, which independently predicted shorter cardiac event-free survival. This relationship can be understood from the framework in which increased levels of hsCRP as a marker of inflammation is associated with cardiac cachexia. Enhanced systemic inflammation decreases food intake and increases tissue catabolism resulting in unintentional weight loss.^{3,9-11} Thus, monitoring serum levels of hsCRP would be helpful for the detection of inflammation that may be associated with unintentional weight loss in patients with HF.

In this study, 14% of patients had unintentional weight loss of greater than 6% within past 6 months. The prevalence of unintentional weight loss seen in our study is similar to that reported in previous studies.^{2,4-6} Of particular note, patients with HF in our study who had unintentional weight loss were 3.2 times more likely to be rehospitalized or die due to cardiac problems than those without unintentional weight loss. This finding is consistent with results from previous studies.^{2,4,5} Several investigators^{4,11,39} have considered that ACE inhibitors or beta blockers play a role in preventing unintentional weight loss, while diuretics decrease absorption of nutrients resulting in unintentional weight loss. We controlled for those medications, and other clinical variables associated with unintentional weight loss as well as baseline BMI demonstrating that unintentional weight loss independently predicted cardiac rehospitalization as well as cardiac mortality. Furthermore, after controlling for depressive symptoms as a psychological factor and hsCRP as an inflammatory biomarker, unintentional weight loss independently predicted shorter cardiac event-free survival in patients with HF. Given the importance of unintentional weight loss in the prognosis of HF patients, it is clinically relevant to monitor weight changes over time to detect progressive weight loss.

Both elevated hsCRP levels and depressive symptoms accounted for unintentional weight loss in this study. Depressive symptoms and elevated inflammatory mediators have previously been observed together in patients with HF.^{40,41} Higher circulating levels of inflammation can be seen in patients with depressive symptoms who often do not eat enough food to meet energy demands, which can lead to progressive weight loss.^{11,12,42} Additionally, total comorbidity score was associated with an increased risk of unintentional weight loss. It was previously observed that the frequency of comorbidities is similar between patients with and without depressive symptoms.⁴³ However, it is possible that comorbidities play an interactive role in the relationships among hsCRP, depressive symptoms, and weight loss. Patients with comorbidities typically have increased inflammation and a greater percentage of patients with comorbidities have depressive symptoms. Future studies are needed to elucidate the potential biobehavioral mechanisms underlying these relationships.

Limitations

Our measure of body weight did not distinguish among muscle, fat, fluid, and bone mass loss. Therefore, we cannot determine which components of body mass loss contributed to event-free survival outcomes. Regardless, our results and those of others^{4,5} show that

monitoring changes in body weight is sufficient in a clinical setting to identify patients at risk. Thus, from a clinical perspective, measurement of the components of body mass lost is not essential. No generalization to cardiac cachexia can be made as it is unknown if unintentional weight loss in this study was different from cachexia characterized by muscle wasting and increased lipolysis that is not reversible with adequate food intake. We also did not measure food intake or other biomarkers of nutritional status. Although patients who stated their intention to lose weight were excluded from our study, our data provide no objective means of differentiating unintentional weight loss from intentional weight loss. Therefore, future research should consider measurements of nutritional intake and body composition to further clarify their respective roles of depressive symptoms and hsCRP on health outcomes of patients with HF.

CONCLUSIONS AND RECOMMENDATIONS

This study supported previous reports that unintentional weight loss is an independent predictor of cardiac event-free survival in patients with HF. To our knowledge, this is the first prospective cohort study to determine possible links between unintentional weight loss and event-free survival adjusting for depressive symptoms and inflammation. Our findings demonstrated that increased depressive symptoms and elevated hsCRP independently predicted unintentional weight loss and that weight loss was associated with shorter cardiac event-free survival. Future prospective longitudinal studies should explore the potential moderating or mediating effect of unintentional weight loss as a link between depressive symptoms and health outcomes. In the meantime, it is important for clinicians to regularly monitor depressive symptoms and serum levels of hsCRP to identify when intervention is needed to prevent unintentional weight loss. Randomized controlled trials to reduce inflammation and depressive symptoms would be applicable to delay the progressive weight loss and warrant preventable cardiac events. Mild to moderate exercise could be one of potential interventions for HF patients with high levels of hsCRP, because mild to moderate exercise plays a role in reversing muscle wasting and increasing plasma high-density lipoprotein that reduce proinflammatory activity.^{3,10,44} Appetite stimulants have been recommended to increase food intake to meet the required body energy and inhibit proinflammatory activity.¹¹ Dietary supplements including fish oil, anti-oxidants (e.g., vitamins C and E), or omega-3 fatty acids have also been suggested to delay the progressive weight loss.¹⁰

Acknowledgments

This research was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (2011-0024857), and by the National Institutes of Health, National Institute of Nursing Research (K23 NR013480).

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What's new and important?

More severe depressive symptoms and increased serum levels of hsCRP were independently associated with unintentional weight loss, which subsequently predicted rehospitalization or death due to cardiac problems. Accordingly, to prevent unintentional weight loss in patients with HF, health care providers may need to follow these steps:

- Pay attention to patients who tend to have decreased food intake
- Close assessment for weight change, especially for progressive weight loss
- Regularly monitor depressive symptoms and serum levels of hsCRP
- Implement some interventions such as mild to moderate exercise programs, use of appetite stimulants, or dietary supplements in care of HF patients with depressive symptoms and high level of hsCRP to delay the progressive weight loss.

Figure 1.
Weight changes over six months

Figure 2.
Unadjusted hazard ratio for percentage weight changes over six months

Table 1

Patient characteristics N = 243

Characteristics		N (%) or Mean $\pm$ SD			P
		Total (N = 243)	Patients with unintentional weight loss (n = 35)	Patients without unintentional weight loss (n = 208)	
Age [*] (years)		61($\pm$ 14)	68 ($\pm$ 7)	59 ($\pm$ 15)	0.001
Gender [*]	Male	148 (60.9)	14 (40.0)	134 (64.4)	0.006
	Female	95 (39.1)	21 (60.0)	74 (35.6)	
Body mass index (kg/m ²)		24.0 ($\pm$ 3.6)	23.5 ($\pm$ 4.6)	24.1 ($\pm$ 3.4)	0.293
	Underweight (< 18.5)	7 (2.9)	3 (8.6)	4 (1.9)	0.019
	Normal weight (18.5 to 22.99)	95 (39.1)	19 (54.3)	76 (36.5)	
	Overweight (23.0 to 27.59)	98 (40.3)	6(17.1)	92 (44.2)	
	Obese ($\geq$ 27.60)	43 (17.7)	7 (20.0)	36 (17.3)	
NYHA	Class I	45 (18.5)	1 (2.8)	44 (21.0)	0.019
	Class II	84 (34.6)	11 (31.4)	73 (35.1)	
	Class III	84 (34.6)	15 (42.9)	69 (33.2)	
	Class IV	30 (12.3)	8 (22.9)	22 (10.6)	
HF etiology	Non-ischemic heart disease	122 (50.2)	15 (42.9)	107 (51.4)	0.347
	Ischemic heart disease	121 (49.8)	20 (57.1)	101 (48.6)	
Left ventricular ejection fraction (%)		36.5 ($\pm$ 17.9)	36.7 ($\pm$ 15.5)	36.5 ($\pm$ 18.3)	0.930
Total comorbidity score [*]		2.6 ($\pm$ 1.5)	3.5 ($\pm$ 1.2)	2.4 ($\pm$ 1.5)	< 0.001
Depressive symptoms [*] (in total K-BDI score)		14.7 ($\pm$ 9.5)	20.3 ($\pm$ 9.7)	13.8 ($\pm$ 9.2)	< 0.001
	No depressive symptoms ($\leq$ 16)	154 (63.4)	13 (37.1)	141 (67.8)	0.001
	Depressive symptoms (> 16)	89 (36.6)	22 (62.9)	67 (32.2)	
High-sensitivity C-reactive protein [*] (mg/L)		11.2 ($\pm$ 27.8)	31.1 ($\pm$ 46.4)	7.9 ($\pm$ 21.7)	< 0.001
	< 1.0 mg/L	87 (35.8)	4 (11.4)	83 (39.9)	0.001
	1.0 to 3.0 mg/L	58 (23.9)	10 (28.6)	48 (23.1)	
	> 3.0 mg/L	98 (40.3)	21 (60.0)	77 (37.0)	
Medication	ACE inhibitors	168 (69.1)	28 (80.0)	140 (67.3)	0.133
	Angiotension II receptor blocker	38 (15.6)	3 (8.6)	35 (16.8)	0.499
	Digoxin	54 (22.2)	8 (22.9)	46 (22.1)	0.922
	β blocker	217 (89.3)	30 (85.7)	187 (89.9)	0.458
	Diuretics	193 (79.4)	24 (68.6)	169 (81.3)	0.112
	Aldosterone antagonist	58 (23.9)	10 (28.6)	48 (23.1)	0.480

ACE; angiotensin-converting enzyme, HF; heart failure, K-BDI; the Korean version of Beck

Depression Inventory, NYHA; New York Heart Association

*

; $p < 0.05$ in the independent *t*-test or Chi-square test

Table 2

Independent predictors of unintentional weight loss in patients with heart failure by hierarchical logistic regression N = 243

Characteristics		Adjusted odds ratio	95% CI	P
Age (year)		1.04	1.00 – 1.09	0.077
Female gender		1.60	0.64–4.00	0.317
Body mass index (kg/m ²)		0.93	0.83 – 1.04	0.209
NYHA functional class	II	2.90	0.31 – 27.57	0.354
	III	2.38	0.25 – 22.49	0.451
	IV	1.36	0.12 – 16.17	0.807
Ischemic heart disease as HF etiology		1.42	0.57–3.55	0.450
Left ventricular ejection fraction (%)		0.99	0.96 – 1.02	0.533
Total comorbidity		1.84	1.30–2.59	0.001
ACE inhibitors		2.45	0.65 – 9.24	0.187
Diuretics		0.57	0.21 – 1.54	0.269
β blockers		0.97	0.25 – 3.77	0.959
Log-transformed hsCRP		1.49	1.15 – 1.92	0.002
Depressive symptoms (in total score of K-BDI)		1.07	1.02–1.12	0.007

ACE; angiotensin-converting enzyme, hsCRP; high-sensitivity C-reactive protein, HF; heart failure, K-BDI; the Korean version of Beck Depression Inventory, NYHA; New York Heart Association

Table 3

Independent predictors of cardiac event-free survival in patients with heart failure by hierarchical Cox hazard regression N = 243

Characteristics		Adjusted hazard ratio	95% CI	P
Age (year)		0.99	0.97 – 1.01	0.398
Female gender		1.02	0.66 – 1.57	0.924
Body mass index (kg/m ²)		0.97	0.92 – 1.02	0.260
NYHA functional class	II	0.83	0.42 – 1.63	0.586
	III	0.86	0.42 – 1.75	0.672
	IV	0.55	0.23 – 1.27	0.159
Ischemic heart disease as HF etiology		0.94	0.62 – 1.43	0.764
Left ventricular ejection fraction (%)		0.98	0.97–0.99	0.002
Total comorbidity		0.95	0.81 – 1.12	0.536
ACE inhibitors		0.91	0.57 – 1.44	0.687
Diuretics		1.21	0.74 – 1.98	0.442
β blockers		1.66	0.85 – 3.25	0.137
Log-transformed hsCRP		1.54	1.02 – 2.33	0.044
Depressive symptoms (in total score of K-BDI)		1.06	1.04 – 1.08	<0.001
The presence of unintentional weight loss		3.17	1.84 – 5.45	<0.001

ACE; angiotensin-converting enzyme, hsCRP; high-sensitivity C-reactive protein, HF; heart failure, K-BDI; the Korean version of Beck Depression Inventory, NYHA; New York Heart Association