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Association of Weight Change With Subsequent Outcomes in Patients Hospitalized with Acute Decompensated Heart Failure

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Abstract

Association of weight loss achieved through various decongestive strategies with clinical outcomes in acute decompensated heart failure (HF) patients is not well described. Our goal was to determine the relationship between weight change during hospitalization and subsequent clinical events in decompensated HF patients. We evaluated data on 433 patients hospitalized with advanced HF enrolled in the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial. The influence of change in weight during hospitalization to clinical outcomes (days alive out of hospital in the first 6 months; death; death or rehospitalization; and death, rehospitalization or cardiac transplantation) was evaluated. On average patients lost approximately 3.6 Kg during hospitalization. When categorized into 3 weight loss tertiles, those in highest tertile were more likely to be older, females, smokers, with higher body weight, prior percutaneous coronary intervention(s), baseline heart rate, and BNP and blood urea nitrogen values, but lower ejection fraction and peak oxygen consumptions. No significant differences were observed between weight change and any in-hospital or follow-up events (days well HR 0.995 [95% CI 0.975–1.016]; 180 days death HR 1.012 [95% CI 0.969–1.057]; death/rehospitalization-180 days HR 1.014 [95% CI 0.990–1.038]). In conclusions, weight loss in patients with acute decompensated HF during hospitalization was not related to clinical end-points. This data challenges the merit of using weight as a surrogate endpoint for more important clinical events i.e. death and/or rehospitalization in patients with heart failure in the design of treatment strategies for novel therapeutic agents in randomized controlled clinical trials.

Keywords

heart failure; weight; outcomes

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Whether the ubiquitous use of weight change as a surrogate end-point in clinical HF trials is associated with important clinical adverse events (i.e. death and/or rehospitalization) remains uncertain. The relationship between weight loss and subsequent clinical outcomes in the EVEREST and UNLOAD trials was divergent [1–3]. The EVEREST investigators demonstrated that a 1 kg difference in weight loss at time of discharge was not associated with a reduction in rehospitalization for HF or cardiovascular death [1,2]. In contrast, the UNLOAD investigators in showed that the greater decrease in weight in the ultrafiltration group was associated with a greater reduction in rehospitalization days in the ultrafiltration group compared with the diuretic treated cohort (1.4 days versus 4.2 days) [3]. Accordingly, the purpose of this investigation was to determine the relationship between weight change during the index hospitalization and subsequent clinical events, specifically death and/or rehospitalization in patients with acute decompensate HF patients who were enrolled in the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial [4]. We hypothesized that weight loss would significantly and positively influence subsequent clinical outcomes including re-hospitalization following discharge.

METHODS

The ESCAPE trial enrolled 433 patients hospitalized with advanced HF at 26 sites in North America between January 18, 2000 and November 17, 2003. The design, primary endpoints, and results of the ESCAPE trial have been previously published [4]. Briefly, patients hospitalized with severe symptomatic HF despite recommended therapies were randomly assigned to receive clinical assessment or pulmonary artery catheter -guided therapy. Patients met the following inclusion criteria within the prior year: 1) an urgent visit to the emergency department, 2) treatment during the proceeding month with more than 160 mg of furosemide daily, 3) therapy with an angiotensin-converting enzyme (ACE) inhibitor and diuretic for at least 3 months, 4) left ventricular ejection fraction of ≤0.30, 5) systolic blood pressure of ≤125 mm Hg, and 6) at least 1 sign and 1 symptom of congestion. The exclusion criteria included: 1) serum creatinine >3.5 mg/dL, 2) prior use of dobutamine or dopamine >3 μg/kg/min, or 3) any prior use of milrinone during the current hospitalization. The target in both groups was resolution of clinical symptoms and signs of congestion (orthopnea, edema, and jugular venous pressure elevation) with the additional therapeutic goals in the pulmonary artery catheter group of achieving a pulmonary capillary wedge pressure of ≤15 mm Hg and a right atrial pressure of ≤8 mm Hg. Medication use was not specified, but intravenous inotropic agents were discouraged. ACE inhibitor and beta-blocker doses were titrated in the outpatient HF programs at these selected centers during the 6 months after randomization according to patient tolerability and current guidelines [5]. Diuretics were adjusted both during and after hospitalization to optimize fluid balance without progressive deterioration in renal function. For the purpose of this analysis, we included all patients in whom hospitalization weight change data was available.

Selected demographics, baseline characteristics, laboratory values, quality of life indices, and physiologic parameters were collected at baseline and throughout the hospitalization as well as at several time periods during follow-up using standard data collection forms. Weights were carefully measured throughout the hospitalization as were electrolytes, renal

function, and biological markers. In hospital weight change was used as a surrogate for fluid loss. It was defined as the difference in baseline weight (in kg) and discharge weight. If the patient's discharge weight was missing, then the hospital day 7 weight, day 5 weight, or day 3 weight was used in the calculation in that order. If the weight data was missing at all three time points, the patient was excluded from the analysis. Patients were followed for a total of 180 days. Data on quality of life, recurrent hospitalizations, and death were carefully collected. The all-cause mortality and recurrent hospitalization data were ascertained by the site investigators.

For descriptive purpose, patients were categorized in to 3 tertiles of their weight loss. Continuous variables were described using median (interquartile) values and categorical variables as percentages. The Kruskal Wallis test was used to test for differences in continuous variables, and the chi-square test was used to detect global differences in categorical variables. Multiple linear regression analysis was used to identify baseline predictors of observed weight loss. Baseline weight, age, presence of diabetes, blood urea nitrogen, serum creatinine, gender, length of initial hospitalization (from randomization), brain natriuretic peptide, sodium, baseline diuretic use, left ventricular ejection fraction, diuretic dose, V02, systolic blood pressure, treatment, and ischemic etiology were used as candidate variables. The relationship of observed weight loss to diuretic dose was also examined using the Pearson's coefficient correlation.

Next we looked at the ability of weight loss to predict endpoints, including the primary endpoint (days well), death, and death/rehospitalization using Cox proportional hazard models to adjust for baseline confounders. A p-value of <0.05 was considered to indicate a significant difference. All analyses were performed using SAS software (version 8.2, SAS Institute, Cary, NC).

RESULTS

Of 433 patients enrolled in ESCAPE, information on change in weight during hospitalization was available in 383 (88.5%). The distribution of weight loss during the hospitalization is shown in Figure 1. On average there was a 3.6 Kg loss of weight during hospitalization with patients managed with a PAC having more weight loss than those in the clinical assessment arm (3.39 vs. 3.89; p=0.3327). Table 1 outlines the clinical features, laboratory data and medication use at baseline among patients in the 3 weight change categories. Compared with patients in the lowest weight change tertile, those in the highest tertile were more likely to be older, female, smokers, have higher baseline body weight and a history of prior percutaneous coronary intervention(s). Patients in the highest tertile of weight change also had the highest baseline heart rate and diastolic blood pressure, whereas left ventricular ejection fraction was lowest in this cohort. Laboratory values of blood urea nitrogen and brain natriuretic peptide were highest and that for peak oxygen consumption lowest among this cohort. At discharge, the orthopnea scale and jugular venous distention was significantly lower among patients in the highest weight change tertile (Table 2). Discharge serum sodium was lowest and blood urea nitrogen and serum creatinine highest in this cohort. Use of beta-blockers and ACE inhibitors or angiotensin receptor blockers

decreased marginally (4.8% and 4.5%, respectively) whereas the use of digoxin and spironolactone increased (4.4% and 10%, respectively) from admission to discharge.

Results of multiple linear regression analysis to identify baseline predictors of observed in-hospital weight loss are shown in Table 3. This analysis identified baseline weight, age, baseline serum creatinine, and baseline brain natriuretic peptide as independently associated with weight loss. Diuretic dose was not a significant predictor after adjusting for other factors (Table 3). The relationship of weight loss to diuretic dose is shown in Figure 2. Although a statistically significant relationship was observed between weight loss and maximal diuretic dose ($t=3.15$, $p=0.0018$), this association was not clinically meaningful as suggested by a very low Pearson's correlation coefficient value ($R=0.028$).

Table 4 shows the clinical events in patients in various weight change tertiles. No significant differences were observed between weight change and any in-hospital or follow-up events. The primary end-point of the ESCAPE study, days alive out of hospital in the first 6 months, as well as other end-points (i.e. death; death or rehospitalization; and a combination of death, rehospitalization or cardiac transplantation) were all not significantly different amongst the 3 groups.

Cox Proportional Hazard analysis was performed to evaluate whether weight loss was significantly linked to the endpoints of days alive out of hospital in the first 6 months; death; and death or rehospitalization (table 5). This analysis failed to demonstrate a significant relationship between weight loss and any of these endpoints. We also modeled effective weight loss on the measures of quality of life, but were unable to demonstrate a relationship at one month, three months, and six months (data not shown).

DISCUSSION

The most relevant observation from this analysis is that therapies used to reduce volume overload during a HF hospitalization result in significant weight loss, but that weight reduction between admission and discharge is not associated with a reduction in clinical events including days alive out of hospital, death and rehospitalization, even after adjustment for confounders. Furthermore, quality of life at 6 months was not significantly influenced by weight loss. In fact, an average of approximately 3.6 kg reduction in weight was achieved with therapies targeted to reduce volume overload and further enhanced by the use of pulmonary artery catheter in severe acute decompensated HF patients. But this decrease in weight from admission to discharge failed to influence clinical events of rehospitalization or death when adjusted for other confounders.

Two prior studies have reported the impact of weight change during a HF hospitalization and subsequent clinical outcomes. The EVEREST investigators randomly assigned patients admitted with heart failure to receive 30 mg daily of oral tolvaptan (n=2072) or placebo for 60 days on the background of standard therapies [1,2]. Tolvaptan resulted in significant reduction in mean body weight compared with placebo (1.76 ± 1.91 kg vs. 0.97 ± 1.84 kg; $p<0.001$). However, the end points of death and cardiovascular death or rehospitalization did not differ between the 2 groups (death HR 0.98, 95% CI 0.87–1.11; $p=0.68$; and

cardiovascular death or rehospitalization HR 1.04, 95% CI 0.95–1.14 [referent placebo group]). In contrast, the UNLOAD investigators randomized patients with decompensated HF to veno-venous ultrafiltration (n=100) or standard intravenous diuretic therapy (n=100) [3]. At 48 h, ultrafiltration was associated with a greater reduction of weight (5.0 ±3.1 kg vs. 3.1±3.5 kg; p <0.001) and net fluid (4.6±2.6 liters vs. 3.3±2.6 liters; p = 0.001). However, at 90 days the ultrafiltration group had fewer patients rehospitalized for HF (18% versus 32%; p=0.037), HF rehospitalizations (0.22±0.54 vs. 0.46+0.76; p=0.022), rehospitalization days per patient (1.4±4.2 versus 3.8±8.5; p=0.022), and unscheduled office and emergency room visits (21% versus 44%; p=0.009). Mortality was similar in the 2 groups (9.6% versus 11.6%). Thus, our study findings concur with that of the much larger EVEREST trial [1,2], but contradicts the results of the smaller UNLOAD study [3]. While it is possible that the difference in findings observed in the above studies including ours may be related to differences in the sample size, the possibility that different strategies used to achieve the volume loss in above studies may have accounted for this disparate results cannot be excluded. The UNLOAD investigators hypothesized that the removal of isotonic rather than hypotonic fluid may account for the prolonged impact of ultrafiltration on recurrent hospitalizations. Preliminary evidence also suggests that the effects of hemofiltration are superior to the effect of diuretic therapy [6–9]. Particularly, following similar amount of fluid loss achieved with ultrafiltration and diuretics, there was a greater decline in norepinephrine, renin and aldosterone levels with the former strategy compared with diuretics [8].

Clinicians use daily weights as a way to evaluate therapeutic response of strategies to reduce volume overload during the hospital course for decompensated HF. It is assumed that reducing weight in these patients improves not only patients' symptoms of congestion, but also post-discharge clinical outcomes. In fact, clinical trials have argued to use weight change as a component of composite endpoints or as an isolated primary endpoint to evaluate the advantage of novel therapeutic agents. Weight loss was the primary end-point of the UNLOAD trial. However, in this analysis, we are unable to demonstrate that a change in weight reflected improved clinical outcomes in the subsequent six months, a finding consistent with the larger EVEREST study. These results were contrary to our hypothesis and suggest that weight change as a surrogate of alteration of the volume status and prolonged improvement in clinical outcomes is inappropriate.

Despite the results of this study, weight change does have a role in the management of patients hospitalized with HF. Clearly weight loss has been shown to correlate closely with changes in volume in patients with HF. Specifically, symptoms (orthopnea scale) and signs of congestion (i.e. jugular venous distention) improved in our patients at the time of discharge with maximum improvement in those with the greatest change in weight. Similarly, the EVEREST investigators showed that composite global clinical status and dyspnea improved in the tolvaptan group that had more weight loss [2]. Most clinicians would agree with the clinical observation that there is a correlation between improvement in congestion and exercise tolerance. Conversely, it is well recognized that gain in weight precedes manifestation of volume overload and predates rehospitalization for decompesated HF. Chaudhry et al, in a nested case-control study, demonstrated that increases in body weight are associated with hospitalization for HF and begin at least 1 week before admission

[10]. Furthermore, they demonstrated that the rates of HF hospitalization progressively increased with greater weight gain relative to baseline (mean increases of >2 and ≤5 pounds, >5 and ≤10 pounds, and >10 pounds associated with adjusted ORs for HF hospitalization of 2.77 [95% CI 1.13–6.80], 4.46 [95% CI 1.45–13.75], and 7.65 [95% CI 2.22–26.39], respectively [referent ≤2 pounds]). Thus, our data when interpreted in conjunction with all information that relates weight to outcomes in patients with HF, suggests that change in weight more than likely reflects change in volume status and symptoms over short-term in these patients, but correlates poorly with short- and long-term clinical outcomes.

Our analysis was retrospective and is subject to missing information and other confounding due to lack of information collected. Specifically, we did not have any information on compliance with medications, diet, fluid restriction, modification of diuretic dose in accordance with changes in weight and other life style changes factors that are significantly linked to HF outcomes. Inference regarding causation should also be made with caution. Our study sample consisted of only class IV HF patients and its findings need to be validated among patients with lesser degree of HF. We also did not have information on the proportion of weight loss relative to the gain from dry body weight/baseline weight. A greater weight loss is targeted and/or expected for patients with highest weight gain relative to their baseline weight. Whether this parameter is a better surrogate than that used currently (weight at admission minus weight at discharge) for subsequent outcomes in patients with HF need to be evaluated in future studies.

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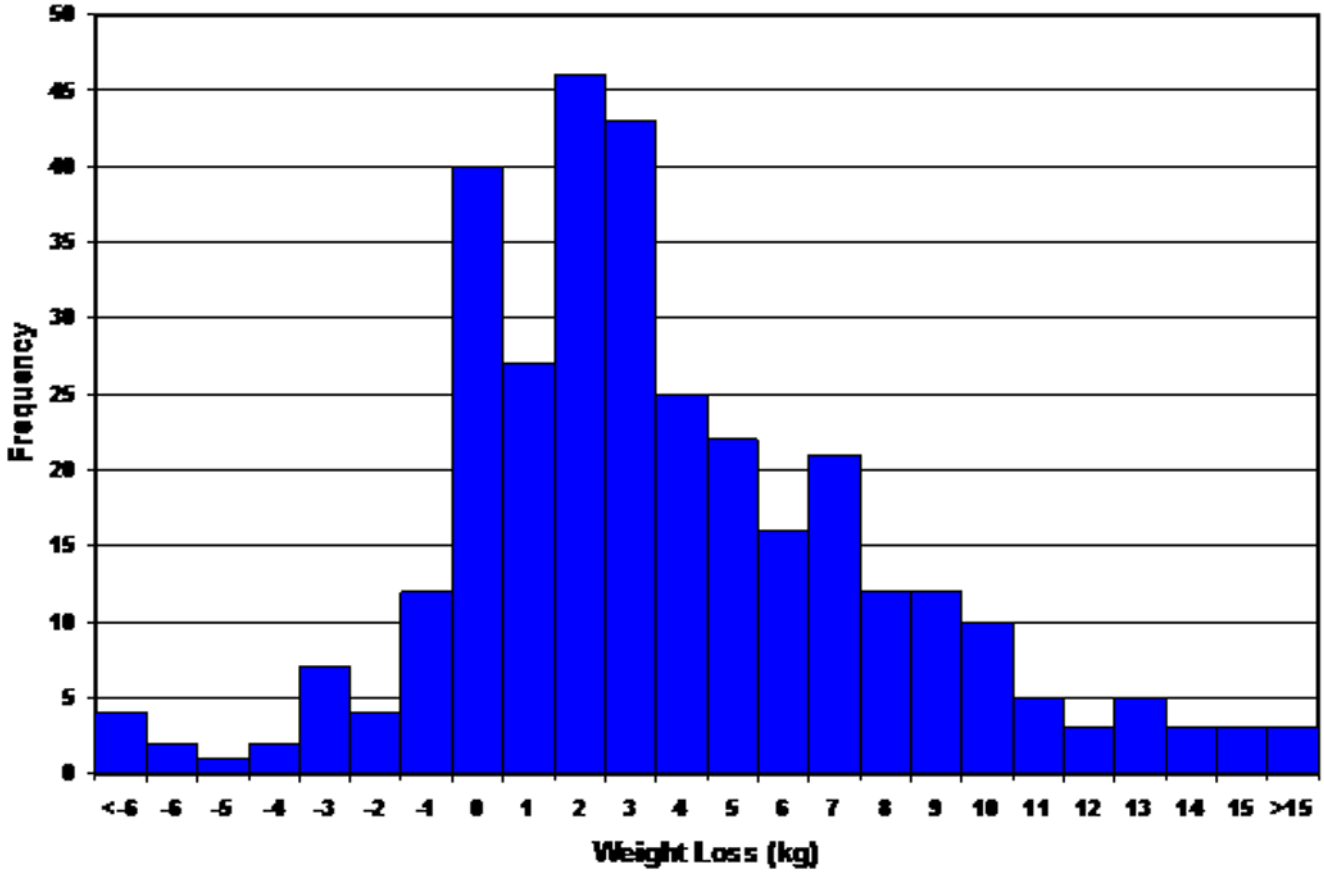

Figure 1.
Distribution of Weight Changes during initial hospitalization

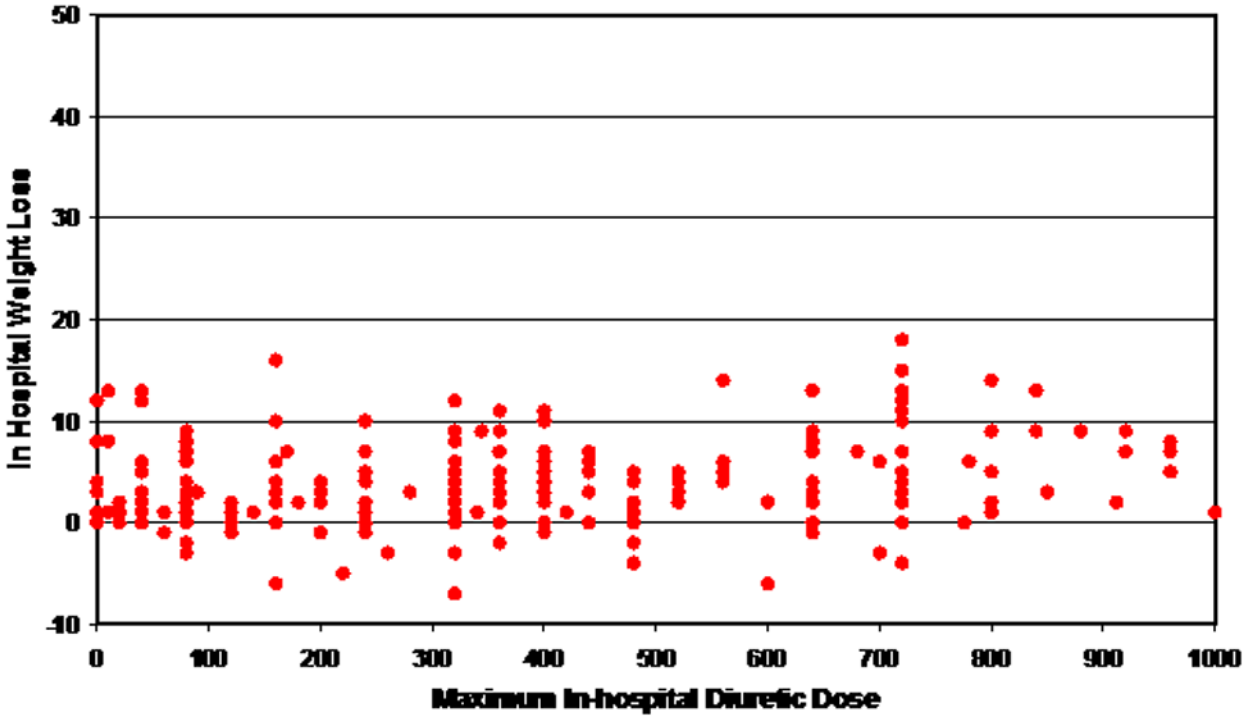

Figure 2.
Diuretic dose (mg) and weight loss (kg)

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Table 1

Baseline Clinical Characteristics

	Weight Change			
Variable	**Lowest Tertile (n=128)**	**Middle Tertile (n=128)**	**Highest tertile (n=127)**	**P value**
Age, (yrs), (median IQR)	56 (46–67)	55 (47–64)	58 (46–66)	0.645
Women	38%	25%	19%	0.003
Nonwhite	41%	37%	44%	0.486
Baseline weight, (kg) (median, IQR)	78 (62–96)	85 (73–97)	87 (76–106)	<0.001
Etiology of the heart failure				
Ischemic	43%	50%	54%	0.209
Non-ischemic	56%	50%	46%	
Hypertension	49%	43%	48%	0.654
Diabetes mellitus	30%	30%	37%	0.386
Current smoker	7.1%	10%	21%	0.047
Prior stroke	0%	0.8%	0%	1.000
Prior percutaneous coronary intervention	16%	23%	29%	0.035
Prior coronary artery bypass graft surgery	27	32	31	0.608
Heart rate, (bpm) (median, IQR)	80 (70–89)	80 (70–93)	84 (72–96)	0.029
Blood pressure, (mm Hg) (median, IQR)				
Systolic	102 (90–116)	105 (94–117)	106 (95–117)	0.389
Diastolic	63 (58–70)	68 (60–73)	70 (60–76)	0.001
Orthopnea scale (0–4)	3 (3–4)	3 (3–4)	3 (3–4)	0.207
Jugular venous pressure >/=12 mm Hg	46%	46%	67%	0.001
Symptom score (global)	42 (30–60)	40 (30–60)	40 (20–60)	0.468
Left ventricular ejection fraction, (%) (median, IQR)	20 (15–25)	20 (15–23)	17 (15–20)	0.017
Serum sodium, (mEq/L) (median, IQR)	137 (135–139)	137 (136–140)	137 (134–140)	0.100
Blood Urea Nitrogen, (mg/dL) (median, IQR)	29 (20–49)	26 (17–35)	29 (19–41)	0.034
Serum creatinine, (mg/dL) (median, IQR)	1.4	1.3	1.3	0.107
Baseline Brain Natriuretic Peptide, (pg/mmol) (median, IQR)	428 (131–869)	463 (168–1132)	890 (389–1500)	<0.001
Peak VO2 (median, IQR)	9.9	10	7.9	<0.001
Six-minute walk, (ft) (median, IQR)	360 (0–700)	343 (0–830)	300 (0–632)	0.770

	Weight Change			
Variable	**Lowest Tertile (n=128)**	**Middle Tertile (n=128)**	**Highest tertile (n=127)**	**P value**
Beta-blocker prior to admission	70%	66%	51%	0.005
Angiotensin Converting Enzyme inhibitors or Angiotensin Receptor Blockers prior to admission	97%	98%	94%	0.183
Digoxin prior to admission	75%	77%	70%	0.401
Spironolactone prior to admission	48%	46%	40%	0.446

Table 2

Discharge Status and Medications

Characteristics	Weight Change			
	Lowest Tertile (n=128)	Middle Tertile (n=128)	Highest tertile (n=127)	P value
Weight, Kg, (median, IQR)	78 (62–97)	83 (70–94)	79 (68–94)	0.379
Systolic Blood Pressure, (mm Hg)	100 (92–113)	100 (90–110)	99 (90–110)	0.329
Orthopnea (0–4 scale)	2 (1–3)	2 (1–3)	1 (1–3)	0.05
Estimated Jugular Venous Pressure >=12 mm Hg	9.%	5%	5%	0.264
Creatinine, mg/dl, (median, IQR)	1.4	1.3	1.5	0.015
Blood Urea Nitrogen, mg/dl, (median, IQR)	28 (20–44)	32 (20–43)	34 (25–49)	0.056
Serum sodium, mEq/L, (median, IQR)	136 (133–138)	136 (134–138)	135 (132–138)	0.061
Symptom score (global)	70 (50–83)	70 (50–80)	70 (50–80)	0.637
Beta-blockers at discharge	65%	64%	44%	0.001
Angiotensin Converting Enzyme inhibitors or Angiotensin Receptor Blockers at discharge	88%	95%	88%	0.002
Digoxin at discharge	77%	81%	79%	0.747
Spironolactone at discharge	52%	61%	51%	0.207

Table 3

Predictors of Weight Loss

Parameter	Estimate	Std Error	t Value	Pr > |t|
Treatment (Pulmonary artery catheter versus clinical assessment group)	0.906	0.560	1.62	0.1070
Baseline weight (per 10 kg)	0.829	0.144	5.77	<0.0001
Age (per 10 years)	0.686	0.254	2.71	0.0072
Blood Urea Nitrogen (per 10 mg/dL)	0.131	0.201	0.65	0.5134
Creatinine (per mg/dL)	−1.826	0.775	2.35	0.0192
Female	−1.131	0.695	1.63	0.1048
Length initial hospitalization (days)	0.019	0.028	0.68	0.4946
Brain Natriuretic Peptide (logarithm) (pcg/mmol)	0.901	0.212	4.25	<0.0001
Serum sodium (mEq/dl)	−0.099	0.069	−1.43	0.1549
Baseline diuretic use	1.514	1.089	1.39	0.1658
Left Ventricular Ejection Fraction (%)	−0.030	0.044	−0.69	0.4905
Diuretic dose (logarithm) (mg/day)	0.037	0.228	0.16	0.8757
Low systolic blood pressure (amount < 120 mm Hg)	−0.011	0.023	−0.49	0.6214
Ischemic etiology versus non-ishemic	−0.562	0.630	−0.89	0.3732

Table 4

In-hospital and Follow-up Adverse Events

Characteristics	Weight Change			
	Lowest Tertile (n=128)	Middle Tertile (n=128)	Highest tertile (n=127)	P value
Implantable cardioverter-defibrillator firing	0%	0%	1.6%	0.109
Cardiogenic shock	0.8%	0.8%	2.4%	0.460
Ischemia/angina	2.3%	2.1%	2.4%	1.000
Pulmonary artery catheter infection	1.4%	2.4%	0%	0.197
Stroke or transient ischemic attack	0%	0%	0%	-
Cardiac arrest	1.6%	1.6%	4.7%	0.212
Infection	8.6%	6.3%	14%	0.089
Mortality and Hospitalization				
Days alive and well, median, IQR-Left ventricular assist device and transplant coded dead	165 (120–174)	167 (119–175)	162 (68–172)	0.140
Days alive and well, median, IQR- Left ventricular assist device and transplant coded well	166 (141–174)	167 (143–175)	163 (101–172)	0.098
180-day mortality	19%	14%	21%	0.316
Total days-Randomization to discharge, median, IQR	5%	5%	6%	<0.001
Composite endpoint (Death/rehospitalization/cardiac transplant (%)	67%	62%	66%	0.623

Table 5

Effect of Weight Loss on Endpoints

Endpoint	Hazard Ratio	95% Confidence Interval	Chi-square	P-Value
Primary (days well)	0.995	0.975, 1.016	0.21	0.6461
Death-180 days	1.012	0.969, 1.057	0.28	0.5942
Death/rehospitalization-180 days	1.014	0.990, 1.038	1.26	0.2613