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## **Weight changes in Heart Failure with Preserved Ejection Fraction: findings from TOPCAT**

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## **Abstract**

*Background:* Weight loss has been associated with poor outcomes in patients with heart failure (HF). However, few data are available for patients with heart failure with preserved ejection fraction (HFpEF). The impact of weight gain on outcomes has not been frequently reported either.

*Aims:* To study post-randomization weight changes and how these could impact outcomes and the effect of spironolactone in patients with HFpEF enrolled in the TOPCAT-Americas trial (N =1767).

*Methods:* Mixed-effects regressions and time-updated Cox models to assess the factors associated with weight changes and their impact on subsequent outcomes.

*Results:* Over a median follow-up of 3 years, 824 (47%) patients experienced weight loss  $\geq 5\%$  and 390 (22%) experienced weight loss  $\geq 10\%$ . Patients experiencing weight loss were older and more frequently women with severe HF symptoms.

Spironolactone slightly reduced body weight before 12 months of follow-up:  $\beta = -0.55$  (-0.82 to -0.29) Kg, without effect on weight afterwards:  $\beta = 0.01$  (-0.66 to 0.68) Kg; treatment-by-time interaction  $P=0.0015$ . Spironolactone did not increase the odds of weight loss but reduced the odds of weight gain. Weight loss  $\geq 5\%$  was associated with a higher risk of cardiovascular and all-cause death irrespective of baseline body mass index: HR=1.47, 95%CI=1.07-2.01 and HR=1.84, 95%CI=1.46-2.31, respectively. Weight gain was not associated with an increased risk of any outcome.

*Conclusion:* Weight loss  $\geq 5\%$  was frequent and independently associated with an increased risk of subsequent mortality. Spironolactone induced only slight body weight reductions early after its introduction and up to a maximum of 8-12 months of follow-up.

*Key-words:* Heart failure with preserved ejection fraction; spironolactone; weight loss; cachexia.

### **Condensed abstract**

We studied the post-randomization weight changes and how these could impact outcomes and the effect of spironolactone in patients with heart failure with preserved ejection fraction enrolled in the TOPCAT-Americas trial (N =1767). Over a median follow-up of 3 years, 824 (47%) patients experienced weight loss  $\geq 5\%$  and 390 (22%) experienced weight loss  $\geq 10\%$ . Weight loss  $\geq 5\%$  was associated with a higher risk of cardiovascular and all-cause death irrespective of baseline body mass index: HR=1.47, 95%CI=1.07-2.01 and HR=1.84, 95%CI=1.46-2.31, respectively. Weight gain was not associated with an increased risk of any outcome.

## Introduction

Obesity increases the risk of developing heart failure with preserved ejection fraction (HFpEF);<sup>1</sup> however, patients with established heart failure (HF) and overweight or mild to moderate obesity might have a better prognosis than those with normal or below normal weight, a phenomenon called the “obesity paradox”.<sup>2-4</sup> However, the “obesity paradox” has been described in observational studies, which are prone to reverse causation i.e., leaner HF patients are usually older, present at a more advanced stage of the disease, and with more frailty and cachexia features than overweight patients.<sup>5</sup>

An important, but often missing, piece of information is weight loss over time, particularly unintentional weight loss which may indicate wasting and cachexia, and has been associated with a poor prognosis.<sup>6, 7</sup> Moreover, many HF patients presenting with normal or below normal weight might have been losing weight before their presentation, thus contributing to the association between low weight and poor outcomes. On the other hand, intentional weight loss in obese patients (e.g., after bariatric surgery) improves cardiovascular outcomes and reduces incident HF.<sup>8, 9</sup> However, data on patients with established HF are lacking.<sup>10</sup>

While weight loss has been associated with poor outcomes in HF, few data are available regarding weight gain. Common advice, tells patients to identify rapid weight gain as an early sign of cardiac decompensation; however, weight gains (>2.3 Kg or 5lb) have not been associated with HF decompensation.<sup>11</sup>

The above-mentioned data have been described mostly in patients with heart failure with reduced ejection fraction (HFrEF), with less evidence available for HFpEF.

Furthermore, obesity patterns have been suggested as potential modifiers of the effect of mineralocorticoid receptor antagonists (MRAs). In HF<sub>r</sub>EF patients participating in the Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms (EMPAHSIS-HF) trial, abdominal obesity was associated with a better response to eplerenone.<sup>12</sup> However, in HF<sub>p</sub>EF patients randomized in “the Americas” in the Aldosterone Antagonist Therapy for Adults With Heart Failure and Preserved Systolic Function (TOPCAT) trial, the effect of spironolactone was not modified by obesity.<sup>13</sup> Still, the impact of weight loss and gain on outcomes and the effect of spironolactone in HF<sub>p</sub>EF patients have not been described yet. In the present report, we aim to study post-randomization weight changes and how these could impact outcomes and the effect of spironolactone in patients with HF<sub>p</sub>EF enrolled in the TOPCAT-Americas trial.

## **Methods**

### **Patient population**

TOPCAT was a multinational, double-blind, randomized, placebo-controlled, parallel-group study that investigated the effects of spironolactone versus placebo on clinical outcomes in patients with HF<sub>p</sub>EF. The rationale and design of the study have been previously published.<sup>14</sup> In short, the trial included 3445 patients >50 years of age with symptomatic HF and preserved ejection fraction (defined as a left ventricular ejection fraction  $\geq 45\%$ ), who were followed for a median of 3 years. Eligible patients had to have systolic blood pressure <140 mmHg, serum potassium <5.0 mmol/L, and either a prior HF hospitalization within 12 months or elevated natriuretic peptide levels (B-type natriuretic peptide  $\geq 100$  pg/mL or N-terminal pro-B-type natriuretic peptide  $\geq 360$  pg/mL). Key exclusion criteria were severe renal dysfunction (defined



as estimated glomerular function rate  $<30$  ml/ min/ $1.73$  m<sup>2</sup> or serum creatinine  $\geq 2.4$  mg/dl), severe systemic illness with life expectancy of  $<3$  years from randomization and use of an aldosterone antagonist or potassium sparing diuretic agent within 14 days before randomization.

Due to previously reported differences in patient demographics, event rates, adherence to study medication, responses to treatment, and outcomes among TOPCAT subjects enrolled in Russia and the Republic of Georgia, we restricted our analyses to the subset of TOPCAT subjects enrolled in the Americas (United States, Canada, Argentina, Brazil; N =1767).<sup>15-17</sup> Two patients did not have post-randomization body weight available, therefore our analysis includes 1765 patients with available body weight at randomization and post-randomization.

All patients provided informed consent. The protocol was approved by the Institutional Review Board at each of the participating centers prior to enrollment of the first patient. The study was overseen by the Institutional Review Board.

### **Body weight changes**

Body weight changes were calculated at each study visit as percentage (%) of weight change from randomization. Patients were categorized by weight loss and gain during the follow-up ( $\geq 5\%$  and  $\geq 10\%$ ). Weight change was also studied as a continuous covariate.

### **Study outcomes**

The outcomes analyzed were the primary (a composite of HF hospitalization, aborted cardiac arrest or cardiovascular death), cardiovascular and all-cause mortality.

### **Statistical analysis**

For descriptive statistics, TOPCAT-Americas patients were divided in those experiencing any weight loss or gain  $\geq 5\%$  and  $\geq 10\%$  vs. those not experiencing such weight loss or gain. Patients' characteristics are presented as mean  $\pm$  standard deviation, median (percentile<sub>25-75</sub>), or numbers and percentages, as appropriate. The groups were compared using parametric or non-parametric tests for continuous variables and chi-square tests for categorical variables. To study the effect of spironolactone (vs. placebo) on weight over time, mixed effects linear regression models were used with continuous weight as outcome variable, and treatment (spironolactone or placebo), age, sex, race, NYHA class, systolic blood pressure, diabetes, atrial fibrillation, previous myocardial infarction, previous heart failure hospitalization, estimated glomerular filtration rate (eGFR), diuretic use, study visit, treatment-by-study visit interaction, and baseline weight as dependent variables, with random effects at the patient level, and unstructured covariance matrix to allow for correlation between measures. Mixed effects logistic regression models were performed to study the effect of spironolactone on weight loss or gain ( $\geq 5\%$  and  $\geq 10\%$ ) throughout the follow-up. The impact of weight changes (loss or gain) on outcomes was studied with time-updated Cox models, adjusting for age, sex, race, NYHA class, systolic blood pressure, diabetes, atrial fibrillation, previous myocardial infarction, previous heart failure hospitalization, estimated glomerular filtration rate, diuretic use, baseline weight, treatment (spironolactone or placebo), and treatment-by-weight change interaction. Whenever interactions were significant, the respective subgroup analyses are presented. In addition, we prespecified a subgroup analysis based on body mass index (BMI) to test if weight changes had different impact in patients with a BMI  $< 30$  and  $\geq 30$  Kg/m<sup>2</sup>. A landmark sensitivity analysis (using the 1-year landmark) was performed to test the associations between weight changes and

subsequent mortality. The adjustment variables were selected their prognostic importance and differences found in Table 1. Two-tailed p values <0.05 were considered statistically significant. Statistical analyses were performed using STATA® Statistical Software version 17.0 (STATA Corp, College Station, Texas).

## **Results**

### **Patients' characteristics**

Over a median follow-up of 3 years, 824 (46.7%) patients experienced at least one episode of weight loss  $\geq 5\%$  and 390 (22.0%) experienced at least one episode of weight loss  $\geq 10\%$ . Patients experiencing a weight loss  $\geq 5\%$  were older (72.3 vs. 70.8 years), with worse NYHA class (38.6% vs. 32.1% in NYHA III), and more frequent chronic obstructive pulmonary disease (18.6% vs. 14.7%). *Table 1*. Patients with  $\geq 10\%$  weight loss were more frequently women (54.6% vs. 48.7%), with higher baseline body weight and body mass index (97.4 Kg vs. 93.3 Kg and 34.8 Kg/m<sup>2</sup> vs. 33.6 Kg/m<sup>2</sup>, respectively) and worse NYHA class (45.9% vs. 32.1% in NYHA III).

*Supplemental Table 1.*

During the follow-up 567 (32.1%) of the patients experienced at least one episode of weight gain  $\geq 5\%$  and 208 (11.8%) experienced at least one episode of weight gain  $\geq 10\%$ . Patients with a weight gain  $\geq 10\%$  were younger (68 years vs. 72 years), more frequently with type 2 diabetes (52.4% vs. 43.6%), and a previous HF hospitalization (69.2% vs. 57.6%). *Supplemental Table 2.*

### **Spirolactone effect on body weight**

Spirolactone slightly reduced body weight before 12 months of follow-up:  $\beta = -0.55$  (-0.82 to -0.29) Kg, without effect on weight at 12 months and after:  $\beta = 0.01$  (-0.66 to 0.68) Kg; treatment-by-time interaction  $P = 0.0015$ . *Figure 1*. Spirolactone did

not increase the odds of weight loss (neither  $\geq 5\%$  nor  $\geq 10\%$ ) at any time point but reduced the odds of weight gain  $\geq 5\%$  before 12 months of follow-up: OR 0.58, 95%CI 0.36-0.93, without impact on weight gain at 12 months and after. The odds of gaining weight  $\geq 10\%$  also tended to be decreased with spironolactone treatment before month 12, but did not reach statistical significance: OR 0.39, 95%CI 0.14-1.10. *Table 2.*

### **Association between body weight changes and subsequent outcomes**

A weight loss  $\geq 5\%$  was not independently associated with a higher risk of a subsequent primary outcome event, but a weight loss  $\geq 10\%$  was: HR 1.37, 95%CI 1.07-1.76. Weight losses  $\geq 5\%$  and  $\geq 10\%$  were associated with a higher risk of cardiovascular death: HR 1.47, 95%CI 1.07-2.01 for a weight loss  $\geq 5\%$  and HR 1.73, 95%CI 1.18-2.54 for a weight loss  $\geq 10\%$ , a higher risk of death from non-cardiovascular causes: HR 2.42, 95%CI 1.71-3.41 for a weight loss  $\geq 5\%$  and HR 2.57, 95%CI 1.73-3.82 for a weight loss  $\geq 10\%$ , and a higher risk of all-cause death: HR 1.84, 95%CI 1.46-2.31 for a weight loss  $\geq 5\%$  and HR 2.08, 95%CI 1.58-2.74 for a weight loss  $\geq 10\%$ . Weight gains were not associated with an increased risk of any outcome. *Table 3.* The representation of the association of continuous body weight with subsequent mortality is depicted in the *Graphical Abstract* and (consistently with the categorical analysis) shows an increased risk of death with body weight losses  $\geq 5\%$ .

### **Interaction between body weight loss and spironolactone effect**

Patients without a  $\geq 10\%$  weight loss during the follow-up might have experienced more benefit from spironolactone treatment for reducing all-cause mortality than patients with weight losses  $\geq 10\%$ : all-cause death spironolactone vs. placebo HR 1.40, 95%CI 0.86-2.28 for patients with a  $\geq 10\%$  weight loss vs. HR 0.79, 95%CI

0.63-0.99 for patients with weight variations within 10% of body weight vs. HR 0.81, 95%CI 0.33-2.00 for patients with  $\geq 10\%$  weight gain; treatment-by-weight changes interaction  $P = 0.045$ . Concordantly, a weight loss  $\geq 10\%$  of body weight was associated with a higher risk of death regardless of the treatment group, but with a slightly higher risk of death from any cause among patients treated with spironolactone than among placebo-treated patients: weight loss  $\geq 10\%$  HR 2.85, 95%CI 1.98-4.09 in spironolactone group vs. HR 1.54, 95%CI 1.01-2.33 in placebo group; treatment-by-weight changes interaction  $P = 0.045$ . *Supplemental Table 3.*

### **Influence of baseline body mass index on the prognostic impact of weight loss**

Baseline BMI did not influence the prognostic impact of weight loss; BMI-by-weight loss interaction  $P > 0.1$  for weight losses  $\geq 5\%$  and  $\geq 10\%$ . *Supplemental Table 4.*

### **Landmark sensitivity analysis**

Using a 12-month landmark where 1649 patients (out of 1745) still were in the trial, the associations between weight changes and subsequent mortality remained similar to those above described, with an increased risk associated with weight loss, but no risk associated with weight gain. *Supplemental Table 5.*

### **Discussion**

In patients with HFpEF enrolled in TOPCAT-Americas, weight losses of 5% or more during the follow-up were frequent (almost half of the patients experienced at least one episode of weight loss  $\geq 5\%$ ) and were associated with an increased risk of subsequent mortality, irrespective of baseline BMI. Spironolactone induced only slight body weight reductions ( $\approx 0.6\%$  of body weight i.e.,  $\approx 0.5$  Kg in a 70 Kg person and  $\approx 0.6$  Kg in the average 94 Kg patient enrolled in TOPCAT-Americas) early after its introduction and up to a maximum of 8-12 months of follow-up. Weight gains were

not associated with poor outcomes and spironolactone reduced the probability of weight gains  $\geq 5\%$  within the first 8-12 months of follow-up.

These findings are clinically important, as they show that weight losses (but not weight gains) of 5% or more in body weight (i.e.,  $\geq 3.5$  Kg loss in a 70 Kg person and  $\geq 4.7$  Kg loss in the average 94 Kg patient enrolled in TOPCAT-Americas) are associated with an increased risk of subsequent mortality (both from cardiovascular and non-cardiovascular causes), and weight losses  $\geq 10\%$  may also be associated with a higher risk of HF hospitalizations in HFpEF. Clinicians should be wary of HFpEF patients losing  $\geq 5\%$  of body weight, and, if the weight loss is unintentional, a thorough investigation of the cause of weight loss should be performed. Also important is the notion that spironolactone does not induce important weight loss. The average HFpEF patient enrolled in TOPCAT-Americas experienced a transient decrease of 0.6 Kg in body weight up to 8-12 months after the introduction of spironolactone, possibly due to an early natriuretic effect.<sup>18</sup> This effect was larger than that seen in the HOMAGE (Heart OMics in AGEing) trial of 0.3 Kg decrease over a 9-month spironolactone treatment period.<sup>19</sup> Patients enrolled in HOMAGE were at risk for developing HF but did not have HF signs or symptoms; therefore, it is likely that overt HFpEF patients enrolled in TOPCAT-Americas had more congestion that could be relieved with spironolactone treatment, thus supporting the early natriuretic effect hypothesis.

Importantly, HFpEF patients losing  $\geq 10\%$  of body weight (i.e.,  $\geq 7$  Kg loss in a 70 Kg person) over a median follow-up of 3 years, may not benefit from spironolactone anymore, likely because they are “too sick” to benefit from the treatment. In this regard, both in TOPCAT and in the Irbesartan in Heart Failure With Preserved Ejection Fraction (I-Preserve) trials, patients with lower levels of natriuretic peptides

and lower overall risk (more frequently obese) were those who benefited the most from spironolactone and irbesartan, respectively.<sup>20, 21</sup>

Similar findings to those here reported, have been described in HFrEF populations. For example, in the *Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca* (GISSI-HF) and the Valsartan Heart Failure Trial (Val-HeFT) studies, patients experiencing at least one episode of weight loss  $\geq 5\%$  from baseline had an increased risk of subsequent mortality.<sup>6</sup> However, weight loss  $\geq 5\%$  was much more frequent in HFpEF patients from TOPCAT-Americas than in HFrEF patients from GISSI-HF and Val-HeFT; this may be due to the older age and greater comorbid burden of HFpEF patients compared with HFrEF. The Candesartan in Heart failure: Reduction in Mortality and morbidity (CHARM) programme including both HFrEF and HFpEF patients also showed a strong and independent association between a weight loss  $\geq 5\%$  and an increased risk of subsequent mortality without significant differences (i.e., interaction) between HFrEF and HFpEF and BMI below or above the median of  $27.5 \text{ Kg/m}^2$ .<sup>7</sup> Similarly, in TOPCAT-Americas baseline obesity (BMI  $\geq 30 \text{ Kg/m}^2$  vs.  $< 30 \text{ Kg/m}^2$ ) did not influence the prognostic impact of weight loss, suggesting that even in obese patients an unintentional weight loss  $\geq 5\%$  should be a source of concern.

Contrary to weight loss, weight gain  $\geq 5\%$  was not associated with subsequent outcomes, a finding consistent with other studies where dyspnea was a much stronger predictor of rehospitalizations than weight gain.<sup>11</sup> Still, spironolactone reduced the probability of gaining weight  $\geq 5\%$  within the first 12 months post spironolactone initiation.

In our analysis, elderly women with worse HF symptoms were the most likely to experience important weight losses during the follow-up. This may indicate that these patients (elderly women with severe symptoms) are more susceptible to cardiac cachexia and wasting, possibly through mechanisms of enhanced neurohormonal activation and metabolic dysregulation.<sup>22</sup>

## **Limitations**

Some limitations should be acknowledged in our study. This was a post-hoc analysis of a randomized trial susceptible to observational bias, including the impossibility to infer causality. The reasons of body weight loss were not recorded in the CRF and could not be classified as intentional/nonintentional. Dry weight was not available in the dataset; however, weight loss was a strong predictor of death independently of HF symptoms and the use of diuretics. We could not determine the cause of weight loss or whether this was intentional or unintentional. Given the age and severity of this HFpEF population, we assume that most patients did not lose weight intentionally. Moreover, cardiac cachexia assessments such as muscle or fat mass wasting were not available. The average spironolactone dose in TOPCAT-Americas was inferior to 25 mg/day,<sup>23</sup> thus we cannot ascertain if higher doses would have produced greater weight changes. Furthermore, at 1 year of follow-up 25% of patients reported to have discontinued spironolactone treatment and 18% of patients reported to have discontinued placebo.<sup>23</sup> It is possible that the discontinuation rates were higher than reported; thus, treatment discontinuation might have contributed to the lack of effect in body weight observed after 1 year of treatment.

## **Conclusion**



In patients with HFpEF enrolled in TOPCAT-Americas, weight losses of 5% or more during the follow-up were frequent and independently associated with an increased risk of subsequent mortality, irrespective of baseline BMI. Spironolactone induced only slight body weight reductions early after its introduction and up to a maximum of 8-12 months of follow-up.

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**Disclosures**

The authors have no relevant conflicts of interest to report regarding the content of this study.

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Table 1. Baseline patients' characteristics comparing patients who lost  $\geq 5\%$  of their body weight during the follow-up vs. those who did not

Variable	Weight loss $\geq 5\%$		P-value
	No	Yes	
N. =1765	941	824	-
Age, yr	70.8 $\pm$ 9.8	72.3 $\pm$ 9.5	<0.001
Women	489 (52.0%)	394 (47.8%)	0.082
White race	733 (77.9%)	649 (78.8%)	0.91
Weight, Kg	93.7 $\pm$ 25.2	94.8 $\pm$ 25.1	0.37
BMI, Kg/m <sup>2</sup>	33.7 $\pm$ 8.1	34.0 $\pm$ 8.2	0.34
BMI >30 Kg/m <sup>2</sup>	336 (35.9%)	287 (35.0%)	0.69
NYHA III	302 (32.1%)	318 (38.6%)	0.004
SBP, mmHg	128 $\pm$ 16	127 $\pm$ 16	0.67
Heart rate, bpm	69 $\pm$ 12	69 $\pm$ 11	0.32
LVEF, %	58 $\pm$ 8	58 $\pm$ 8	0.33
Hypertension	852 (90.5%)	735 (89.3%)	0.39
Diabetes	423 (45.0%)	365 (44.3%)	0.78
Atrial fibrillation	236 (25.1%)	210 (25.5%)	0.84
Previous MI	290 (30.8%)	277 (33.6%)	0.21
Previous stroke	82 (8.7%)	68 (8.3%)	0.73
Previous HFH	566 (60.1%)	475 (57.6%)	0.29
COPD	138 (14.7%)	153 (18.6%)	0.027
eGFR, ml/min	65 $\pm$ 23	64 $\pm$ 20	0.18
Hemoglobin, g/dL	12.7 $\pm$ 2.9	12.7 $\pm$ 2.1	0.95
Potassium, mmol/L	4.2 $\pm$ 0.4	4.2 $\pm$ 0.5	0.20
ACEi/ARBs	741 (78.7%)	643 (78.0%)	0.72
Beta-blockers	722 (76.7%)	657 (79.7%)	0.13
Diuretics*	824 (87.6%)	738 (89.6%)	0.19

Legend: BMI, body mass index; NYHA, New York Heart Association; SBP, systolic blood pressure; LVEF, left ventricular ejection fraction; HFH, heart failure hospitalization; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; ACEi/ARBs, angiotensin converting enzyme inhibitors/angiotensin receptor blockers.

\*87% of diuretics were loop diuretics.

Table 2. Spironolactone effect on body weight over time

Weight changes (%)	N (%) Spiro. (Total =8207)	N (%) Placebo (Total =7959)	Spiro. vs. Placebo $\beta$ / OR (95%CI)	P-value
<b>Continuous weight</b>				
Overall effect *	-	-	-0.28 (-0.67 to 0.12)	0.17
<12 months	-	-	-0.55 (-0.82 to -0.29)	<0.0001
$\geq$ 12 months	-	-	0.01 (-0.66 to 0.68)	0.97
<b><math>\geq</math>5% weight loss</b>				
Overall effect	1438 (17.5)	1334 (16.8)	1.10 (0.85-1.44)	0.47
<12 months	365	302	1.37 (0.93-2.02)	0.11
$\geq$ 12 months	1073	1032	1.07 (0.74-1.53)	0.73
<b><math>\geq</math>10% weight loss</b>				
Overall effect	521 (6.4)	519 (6.5)	1.09 (0.72-1.66)	0.67
<12 months	92	73	1.78 (0.88-3.60)	0.11
$\geq$ 12 months	429	446	0.99 (0.62-1.58)	0.97
<b><math>\geq</math>5% weight gain</b>				
Overall effect	903 (11.0)	931 (11.7)	0.82 (0.60-1.13)	0.23
<12 months	213	287	0.58 (0.36-0.93)	0.024
$\geq$ 12 months	690	644	0.94 (0.61-1.44)	0.77
<b><math>\geq</math>10% weight gain</b>				
Overall effect	279 (3.4)	312 (3.9)	0.69 (0.38-1.26)	0.23
<12 months	48	83	0.39 (0.14-1.10)	0.074
$\geq$ 12 months	231	229	0.88 (0.43-1.81)	0.72

Legend: Spiro., spironolactone; OR, odds ratio.

\*Treatment-by-time interaction P =0.0015 (see also Figure 1).

The "Total" represents the number of observations in panel/longitudinal data.

The  $\beta$  coefficients are obtained from a mixed effects linear regression model and the ORs from a mixed effects logistic regression model.

All models adjusted on age, sex, race, NYHA class, systolic blood pressure, diabetes, atrial fibrillation, previous myocardial infarction, previous heart failure hospitalization, estimated glomerular filtration rate, diuretic use, and baseline weight.

Table 3. Association between body weight changes and subsequent outcomes

Outcome	HR (95%CI)	P-value	Treatment-by-Weight change interaction P
<b>Primary</b>			
≥10% weight loss	1.37 (1.07-1.76)	0.013	0.83***
≥5% weight loss	1.17 (0.96-1.43)	0.13	0.55**
Ref.*	-	-	
≥5% weight gain	1.08 (0.85-1.37)	0.53	0.55**
≥10% weight gain	1.09 (0.76-1.57)	0.63	0.83***
<b>Cardiovascular death</b>			
≥10% weight loss	1.73 (1.18-2.54)	0.005	0.11***
≥5% weight loss	1.47 (1.07-2.01)	0.017	0.18**
Ref.*	-	-	
≥5% weight gain	1.06 (0.71-1.59)	0.78	0.18**
≥10% weight gain	0.82 (0.42-1.63)	0.59	0.11***
<b>Non-cardiovascular death</b>			
≥10% weight loss	2.57 (1.73-3.82)	<0.0001	0.30***
≥5% weight loss	2.42 (1.71-3.41)	<0.0001	0.70**
Ref.*	-	-	
≥5% weight gain	1.20 (0.73-1.97)	0.47	0.70**
≥10% weight gain	1.62 (0.86-3.05)	0.13	0.30***
<b>All-cause death</b>			
≥10% weight loss	2.08 (1.58-2.74)	<0.0001	0.045***
≥5% weight loss	1.84 (1.46-2.31)	<0.0001	0.12**
Ref.*	-	-	
≥5% weight gain	1.11 (0.81-1.52)	0.50	0.12**
≥10% weight gain	1.14 (0.72-1.80)	0.57	0.045***

Legend: HR, hazard ratio from time-updated Cox models.

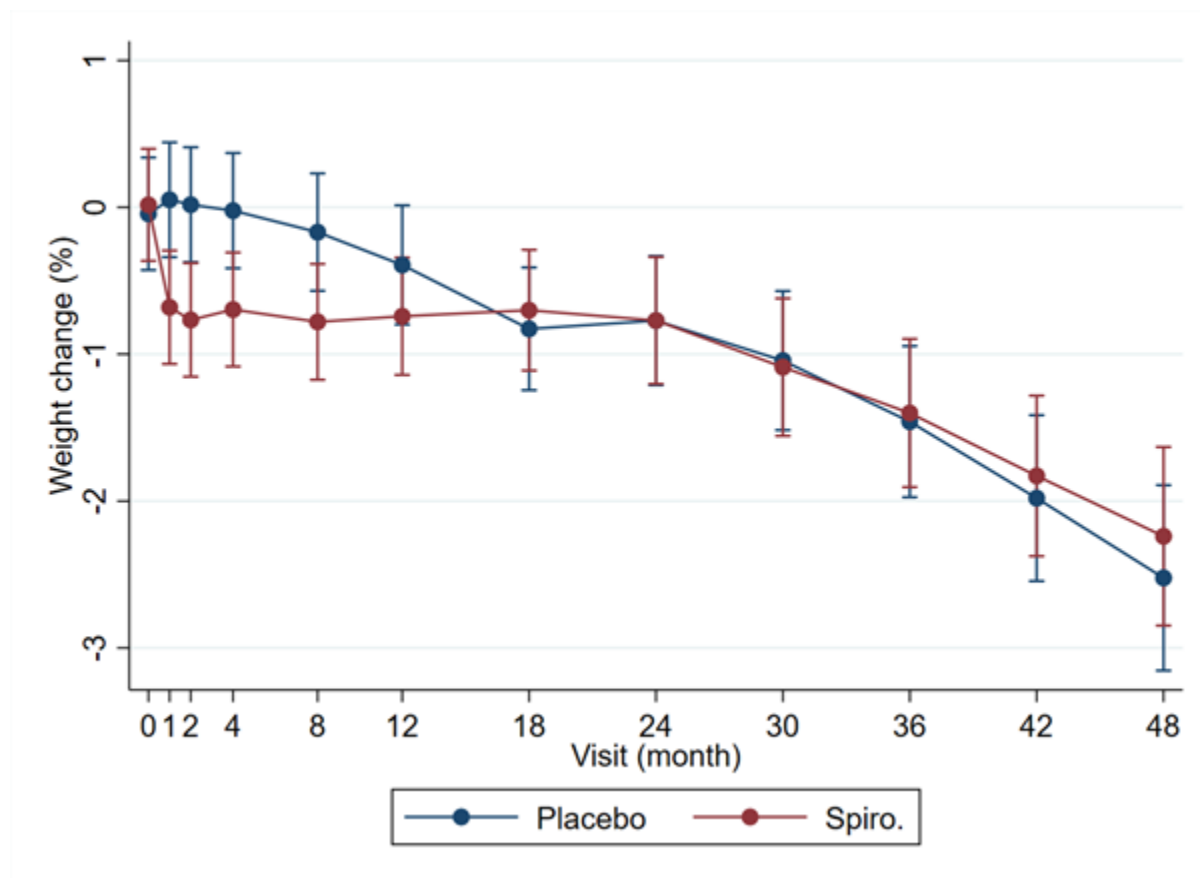
All models adjusted on age, sex, race, NYHA class, systolic blood pressure, diabetes, atrial fibrillation, previous myocardial infarction, previous heart failure hospitalization, estimated glomerular filtration rate, diuretic use, and baseline weight. A statistically significant interaction was observed between a ≥10% weight loss and treatment (spironolactone or placebo) for all-cause mortality (see Supplemental Table 2 for subgroup analysis).

\*The referent category is -4.9% to +4.9% weight change for the ≥5% weight change models and -9.9% to +9.9% weight change for the ≥10% weight change models.

\*\*P-value for interaction for ≥5% weight change.

\*\*\*P-value for interaction for ≥10% weight change.

Figure 1. Spironolactone effect on body weight change over time



Legend: Body weight change, represented by % of change from baseline.

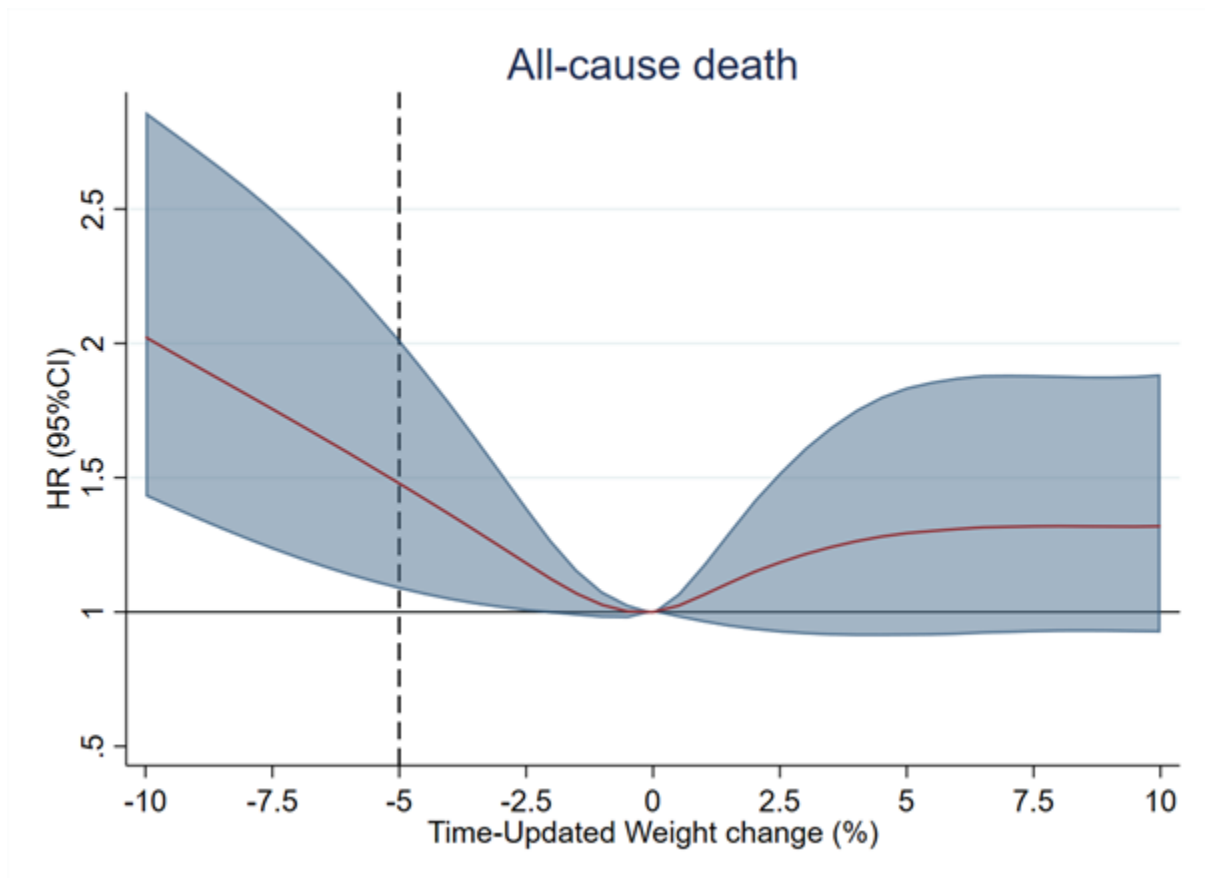
$\beta = -0.55$  (-0.82 to -0.29) before month 12 and  $\beta = 0.01$  (-0.66 to 0.68) at month 12 and after, treatment-by-time interaction  $P = 0.0015$ .

Caption: Spironolactone induces slight body weight reductions ( $\approx 0.6\%$  of body weight i.e., 0.4-0.5 Kg in a 70 Kg person) early after its introduction (1 month) and up to 8-12 months of follow-up. After 12 months there is no difference between spironolactone and placebo.

The number of patients in the spironolactone and placebo groups is similar throughout the follow-up. For example, at month 8 = 805 (50.8%) spironolactone vs. 779 (49.2%) placebo, and at month 12 = 773 (50.9%) spironolactone vs. 745 (49.1%) placebo.



Graphical Abstract. Association between body weight changes and subsequent death



Legend: HR, hazard ratio from time-updated Cox models.  
Model adjusted on age, sex, race, NYHA class, systolic blood pressure, diabetes, atrial fibrillation, previous myocardial infarction, previous heart failure hospitalization, estimated glomerular filtration rate, diuretic use, and baseline weight.

