

# Weight loss in heart failure is associated with increased mortality only in non-obese patients without diabetes

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## Abstract

**Background** Weight loss (WL) is an independent predictor of mortality in patients with heart failure (HF). Moderate WL is recommended for overweight or obese patients with type 2 diabetes mellitus (DM). The aim of this study was to assess the prognostic impact of body weight reduction on survival in patients with both HF with reduced ejection fraction (HFrEF) and DM.

**Methods** The study comprised patients with HFrEF at the outpatient clinic. WL was defined as a body weight reduction of at least 7.5% during at least 6 months. Clinical features and 1 year mortality were analysed in WL and DM groups. Multivariate regression model was chosen to assess the predictive role of WL in HF patients with and without DM. The analysis regarding obesity before HF was also performed.

**Results** The study comprised 777 patients with HFrEF. Mean age was  $53.2 \pm 9.2$ , 12.0% were women, mean EF was  $23.7 \pm 6.0$  %, and New York Heart Association III or IV class, DM, and WL were found in 60.5%, 33.3%, and 47.1% patients, respectively. WL was more prevalent in diabetic patients, comparing with those without DM (53.7% vs. 43.8%, respectively, 0.01), and was associated with higher 1 year mortality only in non-diabetic group (17.6% for WL vs. 8.2% for non-WL, log-rank 0.001). In the multivariate analysis, WL was associated with a higher risk of 1 year mortality in non-diabetic patients: HR 1.76 (1.05–2.95), 0.03 and only in the subgroup without obesity: HR 2.35 (1.28–4.32), 0.006. In non-diabetic patients with obesity and in diabetic patients regardless of weight status, WL was not associated with worse prognosis (thereof, WL was excluded from the multivariate models).

**Conclusions** Overall, WL in HFrEF has emerged as a predictor of unfavourable outcomes only in non-obese patients without DM. More importantly, this study has identified that the presence of DM (irrespective of weight status) or the presence of obesity in non-diabetic patients abolished the unfavourable impact of WL on long-term outcomes.

**Keywords** Heart failure; Weight loss; Type 2 diabetes mellitus; Body wasting

Received: 23 January 2019; Revised: 15 May 2019; Accepted: 12 June 2019

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## Introduction

The obesity is a risk factor of cardiovascular disease and mortality in the general population<sup>1,2</sup>. Obesity paradox has been

reported in heart failure (HF), other chronic diseases (i.e. chronic kidney disease, chronic obstructive pulmonary disease, and cancer), and acute coronary syndromes.<sup>3–7</sup> As opposed to healthy population, HF patients with overweight

or obesity had better survival than those with body mass index (BMI)  $< 25 \text{ kg/m}^2$ . Noteworthy, the obesity paradox has not been confirmed in HF patients with type 2 diabetes mellitus (DM).<sup>8,9</sup>

Besides the body weight, prognosis is also affected by oedema-independent changes of body mass occurring during HF. Weight loss (WL) worsens the prognosis in HF, and this effect is independent of BMI before the first symptoms of HF as well as of other known risk factors of mortality.<sup>1</sup> The most predictive cut-off point for impaired prognosis associated with WL in HF has been established at  $\text{WL} \geq 7.5\%$ .<sup>10,11</sup> Based on these observations, current guidelines do not recommend body mass reduction in HF patients with overweight or moderate obesity (with  $\text{BMI} < 35 \text{ kg/m}^2$ ).<sup>12</sup>

According to various registries and prospective trials, 27% to 44% of HF patients have concomitant DM.<sup>13</sup> The Clinical Practice Recommendations of the American Diabetes Association suggest moderate (about 7%) body mass reduction 'for all overweight or obese individuals who have or are at risk for diabetes to prevent or delay DM'.<sup>14</sup> The implementation of this recommendation in pre-diabetic or diabetic HF patients could have been associated with the increased risk of death.<sup>10</sup>

Until now, no evidence-based recommendation for body weight management in overweight or obese patients with chronic HF and DM has been proposed. To our knowledge, there are no studies on the association between WL and mortality in HF patients with and without DM. Currently, therapeutic approach in overweight or obese HF patients in diabetic and non-diabetic patients is the same. Little is known about the differences in clinical status and outcomes in these two groups.

The purpose of the study was to analyse the association between WL and mortality in HF patients with DM, also in overweight or obese subgroup.

## Materials and methods

### Study population

The study is a retrospective analysis of 777 patients with chronic HF with reduced ejection fraction (HFrEF) fulfilling eligibility criteria listed in the succeeding text. Patients were recruited in an outpatient HF clinic in the Silesian Centre for heart Disease, Zabrze Poland between January 2004 and March 2013. There were 1853 consecutive patients included, of which data on LVEF were available in 1139 patients and  $\text{EF} < 40\%$  was found in 982 patients. Finally, 877 patients had HF duration at least 6 months. Data on co-morbidities, drugs, 1 year mortality, and biochemical parameters were available for all patients.

The eligibility criteria

The inclusion criteria included

1. the diagnosis of HFrEF,
2. age of 18 years or older,
3. the timing of HF onset (first symptoms of HF) could be established with 1 month precision,
4. the body weight within 1 year prior to the onset of HF could be identified,
5. the duration of HF signs/symptoms was at least 6 months,
6. the maximal tolerated dosages of recommended drugs were reached for at least 3 months, and
7. THE glucose/diabetic status at the time of study entry (index date) was available.

The exclusion criteria included

1. the presence of signs or symptoms of fluid retention on clinical examination at index date (including orthopnoea, ankle swelling, distended jugular veins, hepatomegaly, pulmonary rales, and the presence of pleural effusion).

### Assessment of heart failure

The diagnosis of HFrEF has been established according to the European Society of Cardiology (ESC) guidelines for the diagnosis and treatment of HF. HFrEF was confirmed in symptomatic patients with left ventricular ejection fraction (LVEF) below 40% measured in transthoracic echocardiography.<sup>12</sup>

### Assessment of diabetes mellitus

Diabetes mellitus was diagnosed in patients with clinical symptoms of diabetes and fasting hyperglycaemia or using oral glucose tolerance test. The venous blood samples were centrifuged immediately after sampling and assayed in the certified laboratory. The diagnosis of DM was confirmed when 2 h blood glucose concentrations in oral glucose tolerance test were at least 11.1 mmol/L. Patients with previously diagnosed DM were also included into the diabetic group. Patients with suspected or diagnosed type 1 DM were excluded. Suspicion of type 1 DM was defined as the early onset of DM (before the age of 40) with the need of insulin therapy as the initial treatment.

### Assessment of body weight status and weight change

Body weight and height were measured at the day of blood sampling (index date) using certified scale (B150L, Radwag, Radom, Poland). By dividing weights in kilograms by height in metres squared, we have calculated BMI.

Body weight within a 1 year prior to HF onset was identified based on the available medical records and medical history collected from the patient and his or her family. To avoid the possible influence of asymptomatic water retention on the weight before HF, the value established at least 2 months before HF diagnosis was taken as the weight before HF. When more than one body weight reading was available, we took the average of these measurements as the final weight before HF. If weights in this period differed by more than 2 kg, the patient was not included in the study. All weight measurements were indexed to height measurements using Quetelet formula.

Weight change was calculated as the difference between weight before HF and index weight and expressed as percentage of weight before HF:

$$\text{Weight change [\%]} = \left[ \frac{(\text{weight before HF} - \text{weight index})}{\text{weight before HF}} \right] \times 100\%$$

According to weight change, patients were divided into two groups:

- WL  $\geq$  7.5%
- non-WL defined as WL less than 7.5%, stable weight, or weight gain.<sup>10,11</sup>

### Mortality assessment

For all patients, the all-cause mortality data in 1 year follow-up were obtained from the Polish Ministry of the Interior.

### Assessment of co-variables

Co-variables including clinical, laboratory, echocardiography, and functional parameters as well as co-morbidities and drugs were assessed during index visit.

The New York Heart Association (NYHA) functional class was combined and expressed as I + II and III + IV.

Blood samples were taken in a standardized fashion in the morning (between 8 and 10 a.m., after at least a 10 h fasting period) and 30 min resting in supine position in a quiet, environmentally controlled room. Commercially available reagents (Roche Diagnostics, Switzerland) were used for measurements of serum N-terminal-pro B type natriuretic peptide (NT-proBNP) concentrations, high-sensitivity C-reactive protein, fasting glucose, glycated haemoglobin expressed in % (HbA1C), total cholesterol, low-density lipoproteins, high-density lipoproteins, triglycerides, albumin, bilirubin, sodium, and creatinine. The estimated glomerular filtration rate was calculated using Chronic Kidney Disease Epidemiology Collaboration formula.<sup>15,16</sup>

Heart failure with reduced ejection fraction was confirmed in symptomatic patients by measuring of LVEF using Simpson method in transthoracic echocardiography. The examinations were performed by experienced and physician in a certified laboratory (Hewlett-Packard, Andover, MA, USA or Vivid E6 or E9 echocardiograph, GE Healthcare, United Kingdom).

The resting heart rate, systolic (SBP), and systolic blood pressure (DBP) were measured after 30 min resting in supine position in a quiet, environmentally controlled room. The peak oxygen consumption (peak VO<sub>2</sub>) measurement in the cardiopulmonary exercise test was performed by experienced technician in the Silesian Centre for Heart Disease Laboratory of Functional Tests. The cardiopulmonary exercise test was evaluated using monitored treadmill (GE T-2100 Treadmill with Vmax Encore 29c analyser, Viasys Healthcare, USA).

The drug administration rates and doses of beta-blockers, angiotensin-converting-enzyme inhibitors, angiotensin-receptor blockers, mineralocorticoid receptor antagonists, statins, insulin, and oral hypoglycaemic drugs were assessed. The maximal recommended doses of drugs were taken from the ESC HF guidelines, and the per cent of recommended doses of beta-blockers, angiotensin-converting enzyme/angiotensin-receptor blockers, or mineralocorticoid receptor antagonists were calculated according to formula<sup>12</sup>:

$$\% \text{recommended dose} = \frac{\text{administered dose [mg]}}{\text{maximal recommended dose [mg]}} \times 100\%$$

Medical records were reviewed, and co-morbidities such as hypertension, DM, hypercholesterolaemia, and hypertriglyceridemia were recognized based on clinical history, current medication, or actual measurements of respective variables. History of smoking was defined as current or previous use of tobacco products.

### Bioethics Committee

All procedures have been approved by the Bioethics Committee of the Medical University of Silesia (KNW/0022/KB/5/14) and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

### Statistical methods

The normality of selected variables was tested using Shapiro–Wilk test. None of them had normal distribution. Continuous variables were presented as medians and interquartile range. Categorical variables were shown as percentages. Patients with DM and without DM, as well as with WL and without WL, were compared using nonparametric Mann–Whitney *U* test for continuous variables and  $\chi^2$  test for categorical data

with Yates' correction if applicable. Survival between the groups was compared with log-rank test. Kaplan–Meier curves were drawn to show the cumulative survival in 1 year observation. Multivariate analysis was calculated using Cox regression. All variables presented in *Table 1* were included in the multivariate analysis. During initial analyses, correlations between variables were calculated and correlated parameters with lower load were excluded: peak  $\text{VO}_2 < 14$  (correlated with peak  $\text{VO}_2$ ); % BMI during HF  $< 20$  and % BMI before HF  $\geq 25$  (correlated with BMI before HF); % WL  $\geq 6\%$  and % WL (correlated with % WL  $\geq 7.5\%$ ); LVEF (correlated with LVEF  $< 25\%$ ); insulin administration (correlated with fasting glucose); and SBP (correlated with DBP). As only 42 patients in NYHA class I were included in the study, the percentage of NYHA class III/IV was used to evaluate NYHA class in the model. Stepwise analysis was performed with  $P < 0.05$  for inclusion and  $P > 0.2$  for exclusion from model in overall population, as well as in subgroups with DM and without DM. Another analyses were made in the group without DM for patients with normal weight or overweight before HF (BMI  $< 30 \text{ kg/m}^2$ ) and obesity before HF. Separate correlation analyses were made in the subgroup of patients without DM—peak  $\text{VO}_2 < 14$ , % WL  $> 6\%$ , % WL, SBP, and NYHA class were excluded. As only 144 patients without DM with obesity before HF were included, the number of parameters included in the model was limited to 10—variables with the lowest loads in the normalized Varimax test were excluded.

Statistical significance was defined as  $P < 0.05$ . All statistical analyses were performed using Statsoft Statistica software.

## Results

There were 777 patients with HFrEF included in the study, of whom 33.3% had DM, 76.1% were overweight or obese before, and 62.9% during HF. Underweight was found in 1.3% patients before HF and 6.6% during HF, while WL (at least 7.5%) was observed in 47.1% patients. The median duration of HF (and also the median time of body weight change) was 41.5 months (interquartile range 55.4) (*Figure 1*). Baseline characteristics are presented in *Tables 1* and *2*.

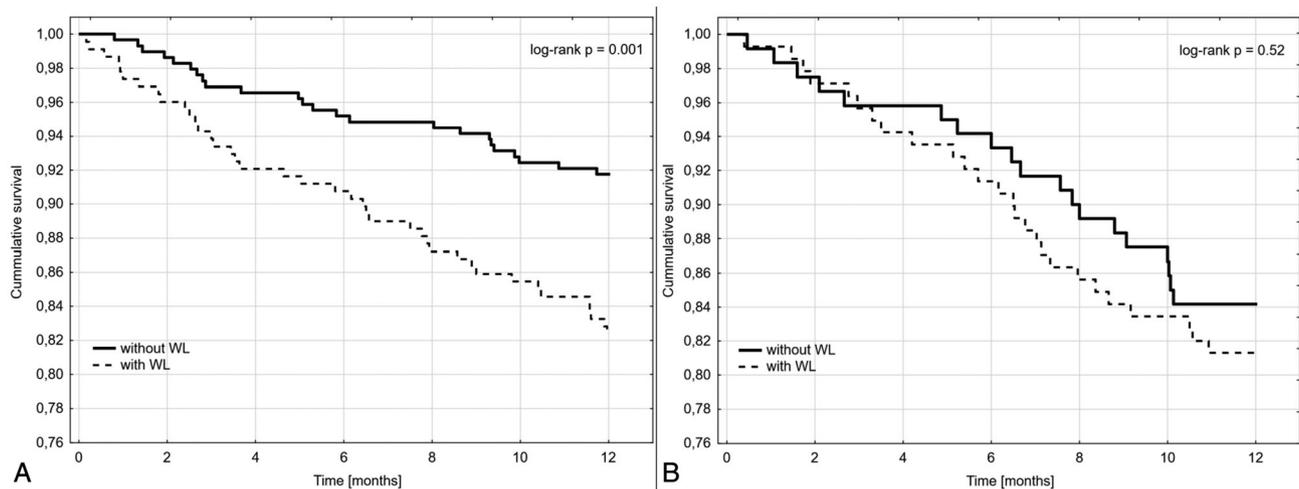
Significant WL was found more often in diabetic patients, comparing with those without DM: 53.7% vs. 43.8% (0.01), and was associated with a worse 1 year mortality in non-diabetic patients (17.6% for WL vs. 8.3% for non-WL, log-rank 0.001) but not in diabetic individuals (18.7% for WL vs. 15.8% for non-WL, log-rank 0.53). Noteworthy, 1 year mortality in both subgroups of diabetic patients was similar to mortality of non-DM patients who had WL (18.7% vs. 17.6%, log-rank 0.53 and 15.8% vs. 17.6%, log-rank 0.65). In patients with obesity before HF, no differences in 1 year mortality between

**Table 1** Clinical characteristics and treatment during initial visit categorized according to diabetes status

	Without DM N = 518	With DM N = 259	P
Female, %	11.2	11.2	0.99
Age [years]	54 [11]	55 [8]	0.001
Ischaemic aetiology, %	58.9	75.0	<0.0001
Duration of HF symptoms [months]	39.7 [56.2]	45.5 [53.5]	0.26
Weight before HF [kg]	80.0 [19.0]	90.0 [20.0]	<0.0001
BMI before HF [ $\text{kg/m}^2$ ]	27.1 [4.2]	30.0 [4.7]	<0.0001
Obese or overweight before HF, %	70.1	88.0	<0.0001
Underweight before HF, %	1.5	0.8	0.57
Weight index [kg]	77.2 [19.0]	83.1 [20.0]	<0.0001
BMI index [ $\text{kg/m}^2$ ]	25.9 [4.0]	27.8 [4.6]	<0.0001
Obese or overweight at index date, %	58.9	71.0	0.0003
Underweight at index date, %	7.9	3.9	0.046
% WC, %	-6.0 [13.7]	-8.9 [15.2]	0.01
% WL of $\geq 6.0\%$ , %	50.0	57.1	0.06
% WL of $\geq 7.5\%$ , %	43.8	53.7	0.01
NYHA I (%)	6.4	2.8	0.0005
NYHA II (%)	38.4	28.4	
NYHA III (%)	47.8	55.2	
NYHA IV (%)	7.4	13.6	
NYHA III/IV, %	56.7	68.7	0.0003
LVEF [%]	23 [8]	23 [6]	0.42
LVEF $< 25\%$ , %	57.7	57.9	0.15
Peak $\text{VO}_2$ [ $\text{mL/kg/min}$ ]	15.0 [6.0]	13.9 [5.4]	0.03
Peak $\text{VO}_2 < 14 \text{ mL/kg/mL}$ , %	41.7	51.7	0.01
NT-proBNP [pg/mL]	1391 [2768]	1347 [2715]	0.51
Fasting glucose [mmol/L]	5.4 [1.0]	6.5 [2.6]	<0.0001
Haemoglobin, [g/L]	14.0 [1.9]	14.2 [2.1]	0.45
Bilirubin, [ $\mu\text{mol/L}$ ]	14.6 [10.8]	15.3 [13.0]	0.1
Albumin [g/L]	42 [5]	42 [6]	0.79
eGFR CKD-EPI [ $\text{mL/kg/1.73m}^2$ ]	85.5 [35.7]	79.9 [36.1]	0.002
Sodium [mmol/L]	136 [4]	136 [5]	0.06
hsCRP (mg/dL)	2.63 [4.83]	3.9 [6.05]	<0.0001
Total cholesterol [mmol/L]	4.36 [1.69]	4.28 [1.71]	0.11
LDL [mmol/L]	2.53 [1.3]	2.46 [1.26]	0.19
HDL [mmol/L]	1.16 [0.47]	1.07 [0.50]	0.003
TG [mmol/L]	1.18 [0.84]	1.33 [0.86]	0.02
Smokers (current or former), %	74.	71.0	0.58
Hypertension, %	51.5	69.6	0.0001
Hyperlipidemia, %	65.8	71.2	0.014
COPD, %	6.6	6.6	0.99
BB, %	98.6	98.4	0.72
BB dose, %	49.4 $\pm$ 30.4	50.5 $\pm$ 42	0.33
ACE/ARB, %	93.4	93.6	0.69
ACE/ARB dose, %	59.0 $\pm$ 48.9	63.0 $\pm$ 80	0.26
MRA, %	93.7	92.0	0.5
MRA dose %	118.6 $\pm$ 65.6	126.1 $\pm$ 100	0.43
Statin, %	61.4	68.3	0.06
Insulin, %	—	30.4	—
Oral diabetic drugs, %	—	48.4	—

ACE, angiotensin-converting-enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blocker; BMI, body mass index; COPD, chronic obstructive pulmonary disease; DM, type 2 diabetes; eGFR CKD-EPI, estimated glomerular filtration rate calculated by CKD-EPI formula; HDL, high-density lipoprotein; HF, heart failure; hsCRP, C-reactive protein assessed by high-sensitivity test; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal-pro BNP natriuretic peptide; NYHA, New York Heart Association class; peak  $\text{VO}_2$ , peak oxygen consumption in ergospirometry; TG, triglycerides; % WC, per cent of weight change; % WL, per cent of weight loss.

**Figure 1** Survival probability depending on the occurrence of weight loss (WL) in 1 year follow-up in patients without diabetes mellitus (A) and with diabetes mellitus (B)—Kaplan–Meier curves.



WL groups were observed in both diabetic (19.3% without and 15.6% with WL, 0.65) and non-diabetic (10.9% without WL and 13.5% with DM, 0.65) populations. In patients without obesity before HF, higher 1 year mortality was observed only in patients without DM (7.6% without and 20.3% with WL, 0.0003), but not in diabetic group (13.2% without and 22.6% with WL, 0.13).

In the multivariate analysis,  $WL \geq 7.5\%$  was an independent predictor of 1 year mortality only in patients without DM. The analyses in subgroups of BMI revealed that  $WL \geq 7.5\%$  was predictor of mortality only in non-diabetic patients without obesity before HF (Table 3).

## Discussion

We showed that WL during HF did not improve survival in HF patients. Moreover, WL seems to worsen the prognosis in HF patients without DM and without obesity, but not among those with DM and/or obesity. The risk of death in 1 year follow-up in non-diabetic patients with WL was similar to both groups with DM. In other words, DM was an equivalent of WL in HF patients. It was confirmed that at least 6% WL in 6 months is an independent risk factor for mortality in HF. We showed that at least 7.5% of WL in HF is a negative prognostic factor only in non-diabetic HF patients, particularly without obesity.

To our best knowledge, our report is the first to show that WL in HF patients with DM may not affect prognosis. The pathomechanism of this phenomenon, as well as the protective factors, is not known.

There were some differences in the patients' characteristics that might explain differences in survival between diabetic and non-diabetic groups, but all of them were included in the multivariate analyses in overall study population.

The impact of WL on mortality depends on the changes of fat/lean tissue mass. Lean body mass loss is correlated with increased mortality, while fat tissue loss may be associated with decreased mortality.<sup>17</sup> Moreover, 'not all fat is equal'.<sup>18</sup> Losing visceral adipose tissue may be beneficial, while reducing subcutaneous adipose tissue may have opposite effect. Thus, the summary effect of WL is the combination of body composition changes in different body compartments.<sup>19</sup> Unfortunately, we had no data on body composition or distribution.

Our results may be consistent with the outcomes of Look AHEAD study, which did not confirm the prognostic benefits of intensive lifestyle intervention (ILI) and subsequent WL in comparison with education in overweight or obese diabetic patients (without HF).<sup>20</sup>

In contrast to cachexia definition and most of previous WL studies in HF, we chose different time interval of body mass changes. Instead of fixed 6 or 12 month period, we measured weight changes from the onset of HF (stable, oedema-free body mass during the year before the onset of HF) till the index date. It may be considered as a limitation of our study, but body mass changes assessment in regular 6 month follow-up periods in a real-life conditions may be difficult. In our study, no difference in HF duration between DM groups was found, but patients with WL were characterized by a shorter observation time (which is equivalent to HF duration).

Another important issue regarding to WL is intention of weight change. Williamson *et al.* showed that unintentional

**Table 2** Clinical characteristics and treatment during initial visit categorized according to the weight loss status

	Without weight loss $\geq 7.5\%$ $n = 411$	With weight loss $\geq 7.5\%$ $n = 366$	<i>P</i>
Female, %	12.9	10.9	0.69
Age [years]	54 [9]	55 [10]	0.19
Ischaemic aetiology, %	64.5	64.5	0.88
Duration of HF symptoms [months]	44.2 [55.0]	37.4 [54.0]	0.02
Weight before HF [kg]	83.0 [18.2]	74.0 [19.5]	<0.0001
BMI before HF [kg/m <sup>2</sup> ]	27.1 [5.6]	29.4 [6.2]	<0.0001
Obese or overweight before HF, %	70.3	82.5	<0.0001
Underweight before HF, %	1.9	0.5	0.16
Weight index [kg]	81.0 [18.0]	86.5 [22.0]	<0.0001
BMI index [kg/m <sup>2</sup> ]	27.8 [5.5]	24.8 [5.3]	<0.0001
Obese or overweight at index date	76.9	47.3	0.0003
Underweight at index date, %	1.9	11.7	<0.001
% WC, %	2.8 [11.4]	-14.1 [8.0]	<0.0001
NYHA I, %	2.8	6.4	0.0005
NYHA II, %	28.4	38.4	
NYHA III, %	55.2	47.8	
NYHA IV, %	13.6	7.4	
NYHA III/IV, %	53.0	68.9	0.0003
LVEF, %	24 [8]	22 [7]	<0.0001
LVEF <25%, %	51.6	64.8	0.15
Peak VO <sub>2</sub> [mL/kg/min]	14.8 [6.3]	14.2 [5.4]	0.07
Peak VO <sub>2</sub> < 14 mL/kg/mL, %	43.3	47.0	0.01
NT-proBNP [pg/mL]	1051 [1743]	2088 [3484]	<0.0001
Fasting glucose [mmol/L]	5.6 [1.5]	5.6 [1.4]	0.91
Haemoglobin, [g/L]	14.1 [2.1]	14.2 [1.8]	0.9
Bilirubin, [ $\mu$ mol/L]	13.2 [9.4]	16.0 [14.6]	<0.0001
Albumin [g/L]	42 [5]	42 [5]	0.03
eGFR CKD-EPI [mL/kg/1.73m <sup>2</sup> ]	85.5 [34.4]	80.3 [38.4]	0.03
Sodium [mmol/L]	137 [5]	136 [5]	0.0001
hsCRP [mg/dL]	2.77 [4.60]	3.20 [7.13]	0.01
Total cholesterol [mmol/L]	4.48 [1.67]	4.24 [1.72]	0.04
LDL [mmol/L]	2.52 [1.38]	2.50 [1.27]	0.36
HDL [mmol/L]	1.13 [0.46]	1.14 [0.52]	0.94
TG [mmol/L]	1.31 [0.92]	1.15 [0.75]	0.0002
Smokers (current or former), %	74.9	71.6	0.58
Hypertension, %	58.4	56.3	0.0001
Hyperlipidemia, %	69.8	68.0	0.014
BB, %	99.3	97.8	0.72
BB dose, %	50.5 $\pm$ 30.2	49.8 $\pm$ 30.7	0.67
ACE/ARB, %	95.9	91.5	0.69
ACE/ARB dose, %	66.7 $\pm$ 53.0	53.4 $\pm$ 46.3	<0.0001
MRA, %	90.8	95.9	0.5
MRA dose %	115.4 $\pm$ 68.8	125.4 $\pm$ 60.7	0.007
Statin, %	66.7	60.4	0.07
Insulin	9.0	13.6	—
Oral diabetic drugs, %	18.9	16.4	—

ACE, angiotensin-converting-enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blocker; BMI, body mass index; COPD, chronic obstructive pulmonary disease; DM, type 2 diabetes; eGFR CKD-EPI, estimated glomerular filtration rate calculated by CKD-EPI formula; HDL, high-density lipoprotein; HF, heart failure; hsCRP, C-reactive protein assessed by high-sensitivity test; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal-pro BNP natriuretic peptide; NYHA, New York Heart Association class; peak VO<sub>2</sub>, peak oxygen consumption in ergospirometry; TG, triglycerides; % WC, per cent of weight change; % WL, per cent of weight loss.

WL in diabetic individuals 40–64 years of age without HF did not affect prognosis (in multivariate analysis), while intentional WL reduced the risk of death, with the most beneficial effect for WL of 20–29 lbs.<sup>21</sup> Intentional WL is supposed to be related to increased physical activity, as well as limited energy intake, which decrease insulin resistance. Unintentional WL is mainly caused by escalated inflammation, anorexia, or cachexia due to chronic disease. We were unable to distinguish between intentional and non-intentional WL, which is one of the main limitation of

our study. Nevertheless, there is an evidence that intentional WL 'owing to ill health or physicians' advice' increased risk of all-cause mortality similar to unintentional WL.<sup>22</sup> Based on our clinical experience, there could be a significant bias in the intention-to-lose-weight assessment, as in patients undergoing ILL; WL related to inflammation or cachexia might also occur.

Inversed association between body weight and NT-proBNP concentrations has been previously described.<sup>23</sup> The possible link between adipose tissue, obesity, and the

**Table 3** Multivariate analysis of predictors of 1 year mortality in overall population and in patients without diabetes

Parameter	Overall population		
	Overall n = 777	Without DM N = 518	With DM N = 259
Age [years] (per 1 year increase)	—	1.03 (1.01–1.06), 0.035	—
Peak VO <sub>2</sub> [mL/kg/mL] (per 1 unit increase)	0.90 (0.85–0.95), 0.0001	0.86 (0.81–0.93), P < 0.0001	0.89 (0.82–0.96), 0.004
HR [bpm] (per 1 bpm increase)	—	1.02 (1.01–1.04), 0.003	—
NYHA III/IV (vs. NYHA I/II)	2.14 (1.23–3.74), 0.007	2.63 (1.28–5.39), 0.008	—
WL ≥ 7.5% (yes vs. no)	—	2.24 (1.32–3.83), 0.003	—
ACEI/ARB usage (yes vs. no)	0.35 (0.21–0.59), P < 0.0001	0.38 (0.20–0.73), 0.004	0.23 (0.11–0.51), 0.0003
MRA usage (yes vs. no)	—	0.37 (0.14–0.97), 0.04	—
Bilirubin [μmol/L] (per 10 units increase)	1.06 (1.01–1.10), 0.02	—	1.07 (1.02–1.12), 0.007
NT-proBNP [pg/mL] (per 1000 units increase)	1.06 (1.01–1.17), 0.01	—	1.08 (1.01–1.11), 0.03
Fasting glucose [mmol/L] (per 1 unit increase)	1.17 (1.07–1.27), 0.0004	—	1.18 (1.06–1.31), 0.003
% BB recommended dose [%] (per 10% increase)	0.92 (0.85–0.99), 0.03	—	—

Parameter	Patients without DM	
	BMI before HF < 30 kg/m <sup>2</sup> n = 374	BMI before HF ≥ 30 kg/m <sup>2</sup> n = 144
NT-proBNP [pg/mL] (per 1000 units increase)	1.10 (1.02–1.19), 0.01	—
HR [bpm] (per 1 bpm increase)	1.02 (1.01–1.04), 0.04	—
Peak VO <sub>2</sub> [mL/kg/mL] (per 1 unit increase)	0.86 (0.80–0.93), 0.0002	0.81 (0.71–0.92), 0.001
Age [years] (per 1 year increase)	1.05 (1.02–1.09), 0.002	—
% WL ≥ 7.5% (yes vs. no)	2.35 (1.28–4.32), 0.006	—
BB usage (yes vs. no)	0.08 (0.2–0.36), 0.001	—
LVEF [%] (per 1 unit increase)	—	0.86 (0.79–0.93), 0.0001

BB, beta-blocker; BMI, body mass index; bpm, beats per minute; DM, type 2 diabetes; HF, heart failure; HR, heart rate; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal-pro BNP natriuretic peptide; NYHA, New York Heart Association class; peak VO<sub>2</sub>, peak oxygen consumption in ergospirometry; % WL, per cent of weight loss.

heart may be mediated by natriuretic peptides.<sup>24</sup> In Look AHEAD study, in overweight or obese patients with DM (subjects without HF), weight reduction during ILI was associated with increase of NT-proBNP concentrations.<sup>17</sup> After bariatric surgery and following WL in patients without HF, higher NT-proBNP concentrations were found in 3, 6, and 12 month follow-up.<sup>25</sup> Moreover, body wasting is related to higher NT-proBNP concentrations, but not LVEF changes.<sup>26</sup> In our study, patients with WL had two-fold higher NT-proBNP concentrations than those without WL. Interestingly, subjects with WL had also a lower LVEF and higher NYHA class, which may suggest that higher NT-proBNP was associated with more advanced HF rather than with fat tissue reduction.

Anker *et al.* analysed data from the SOLVD and V-HeFT II trials and showed that WL during 1 year is the strongest predictor of mortality in HF patients.<sup>10</sup> The same results were obtained by Pocock *et al.* in the analyses of CHARM trial. Reduction of body mass by 1% in 6 months increased the mortality risk by 5%.<sup>27</sup> On the other hand, Trullas *et al.* showed that body wasting was not associated with mortality in HF patients in the Spanish RICA Registry.<sup>28</sup> The differences may be explained by the different number of diabetic patients in the analysed groups. In CHARM trial and RICA Register, DM was found in 38.8% and 44.2%, respectively. According to our results, diabetic patients

without WL had similar outcomes in comparison with patients with WL. Thus, the epidemiology of conventional risk factors in HF patients may be modified by DM coexistence. The more DM patients, the weaker association between WL and mortality may be observed.

In some studies regarding body wasting, patients with DM were not included. Christensen *et al.* re-assessed the prevalence of cachexia (10.5%) in an outpatient HF population but excluded diabetic patients from the analysis. They reported that insulin resistance in diabetic patients could interfere with the study outcome.<sup>29</sup> In our opinion, there is a need of further studies in this field. It would be very interesting and informative to reanalyse populations from 'heart failure paradox' studies, regarding WL and DM.

Interestingly, higher peak VO<sub>2</sub> was related to lower mortality in all analysed groups (Table 3). The finding is consistent with latest studies and significant, as peak VO<sub>2</sub> may be improved during careful exercise training.<sup>30–32</sup>

Our study has a few limitations and some of them (lack of data on body distribution or intention to change body weight) were discussed earlier. Large proportion of patients from the initial population was excluded (58%), mainly due to lack of LVEF assessed in the time of index visit. Besides, the analysis is retrospective, and no data on duration of DM, physical activity, and diet were gathered. As the study included patients treated between 2003 and 2011, most

patients were not subjected to the current standard-of-care in terms of usage of implanted cardioverters-defibrillators or cardiac resynchronization therapy devices. It may probably influence the mortality rates in our study.

In conclusion, WL in HF<sub>r</sub>EF has emerged as a predictor of unfavourable outcomes only in non-obese patients without DM. More importantly, this study has identified that the presence of DM (irrespective of weight status) or the presence of obesity in non-diabetic patients abolished the unfavourable impact of WL on long-term outcomes.

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## Acknowledgement

The authors of this manuscript certify that they comply with the ethical guidelines for authorship and publishing in the *Journal of Cachexia, Sarcopenia and Muscle*.<sup>33</sup>

## Conflict of interest

The authors declare that they have no conflict of interest.

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