

Supplementary material

The value of spot urinary creatinine as a marker of muscle wasting in patients with new-onset or worsening heart failure

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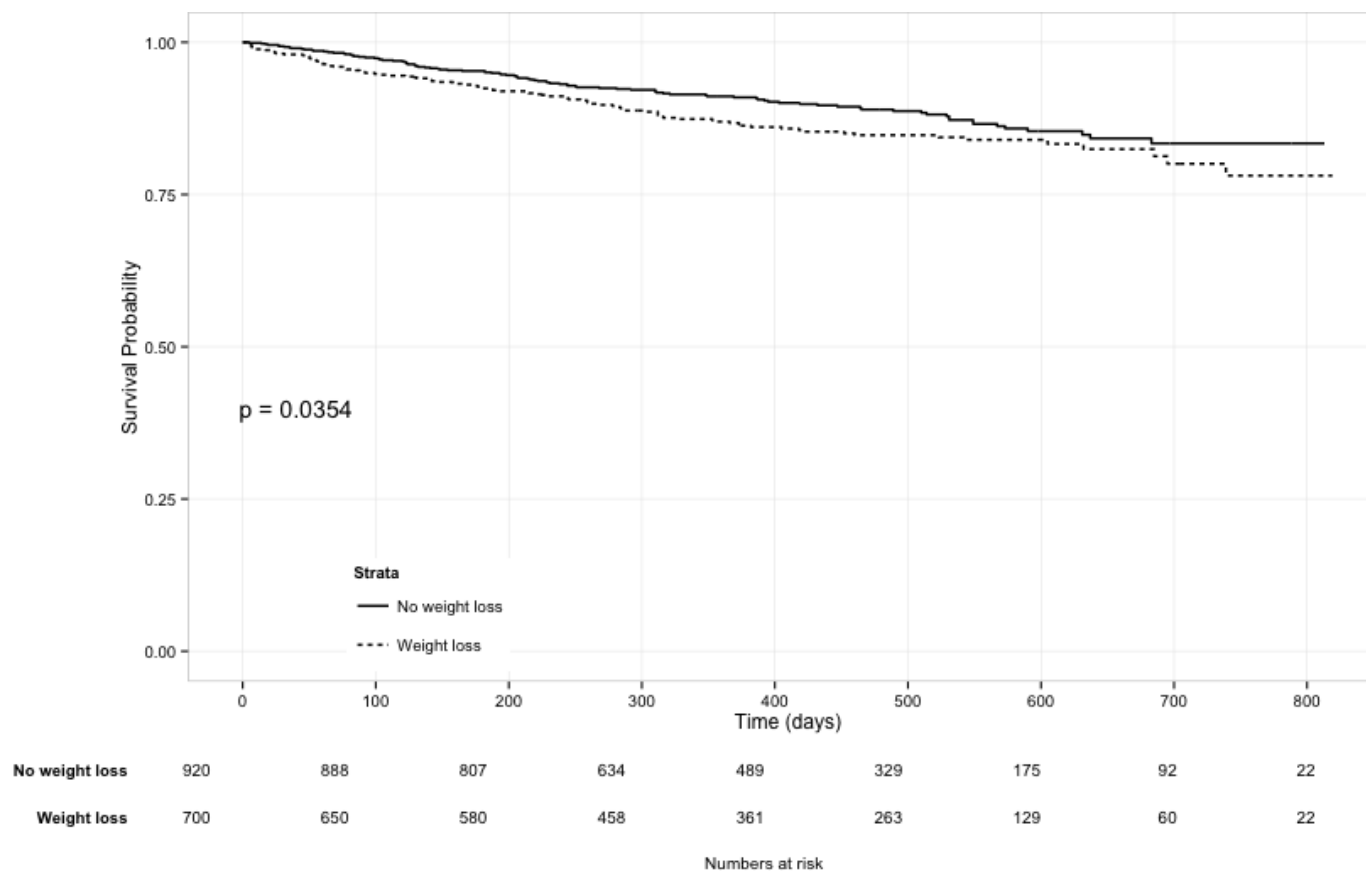
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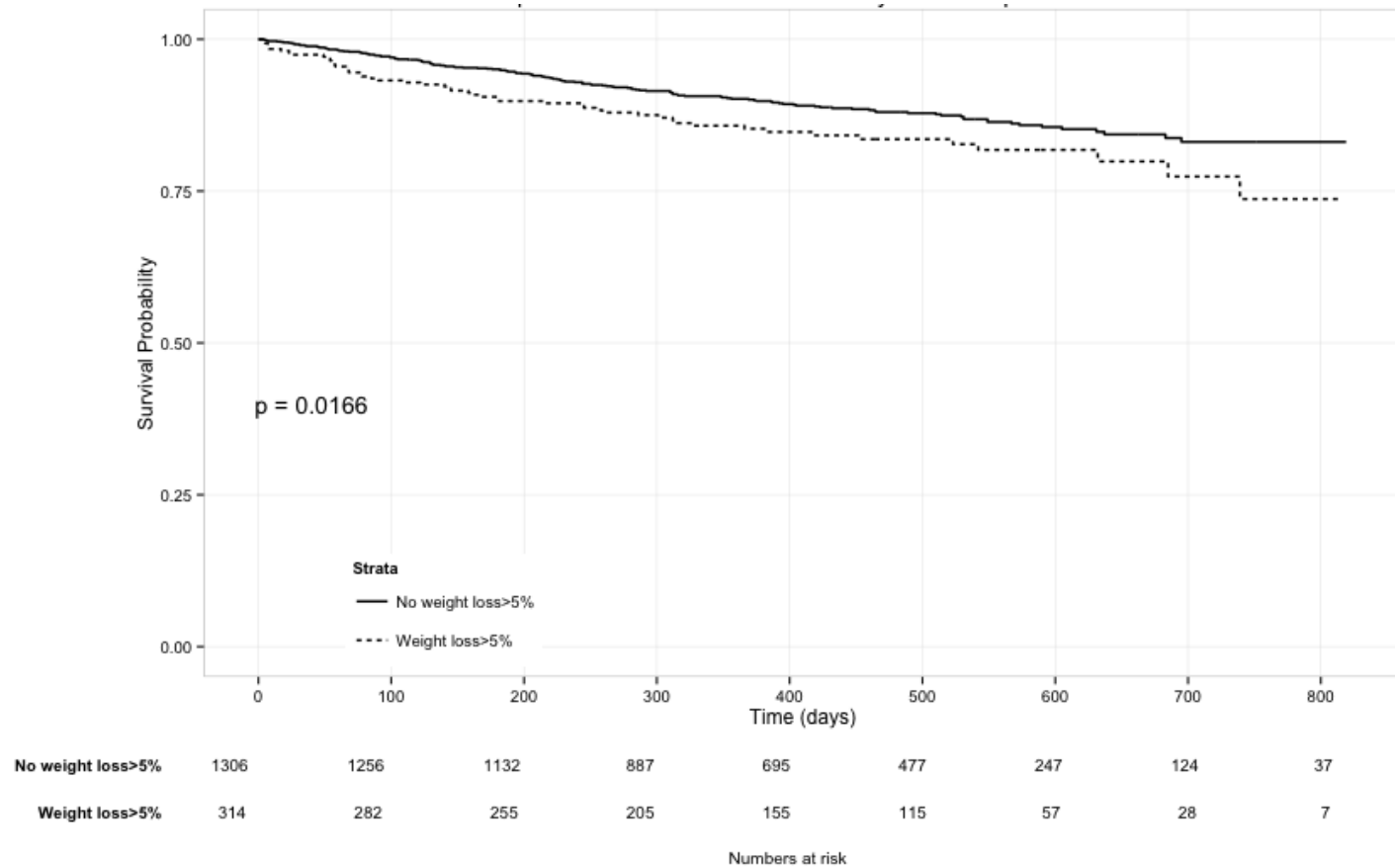
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Supplementary figure S1 Kaplan Meier survival curve (index cohort) for combined endpoint (all-cause mortality or HF hospitalization) according to weight loss (yes/no)*



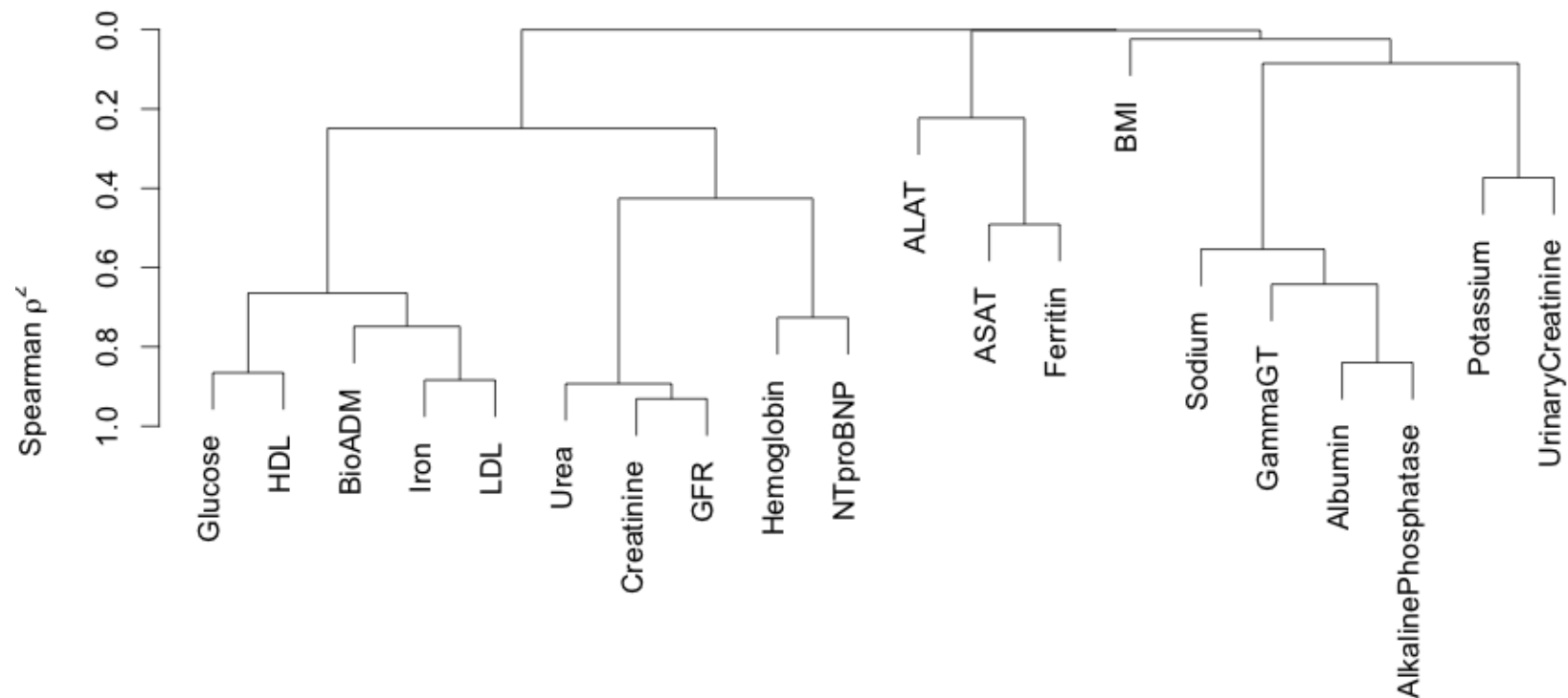
* Follow-up started at 9 months (=0 days)

Supplementary figure S2 Kaplan Meier survival curve (index cohort) for combined endpoint (all-cause mortality or HF hospitalization) according to percentage weight loss (above or below 5%)*



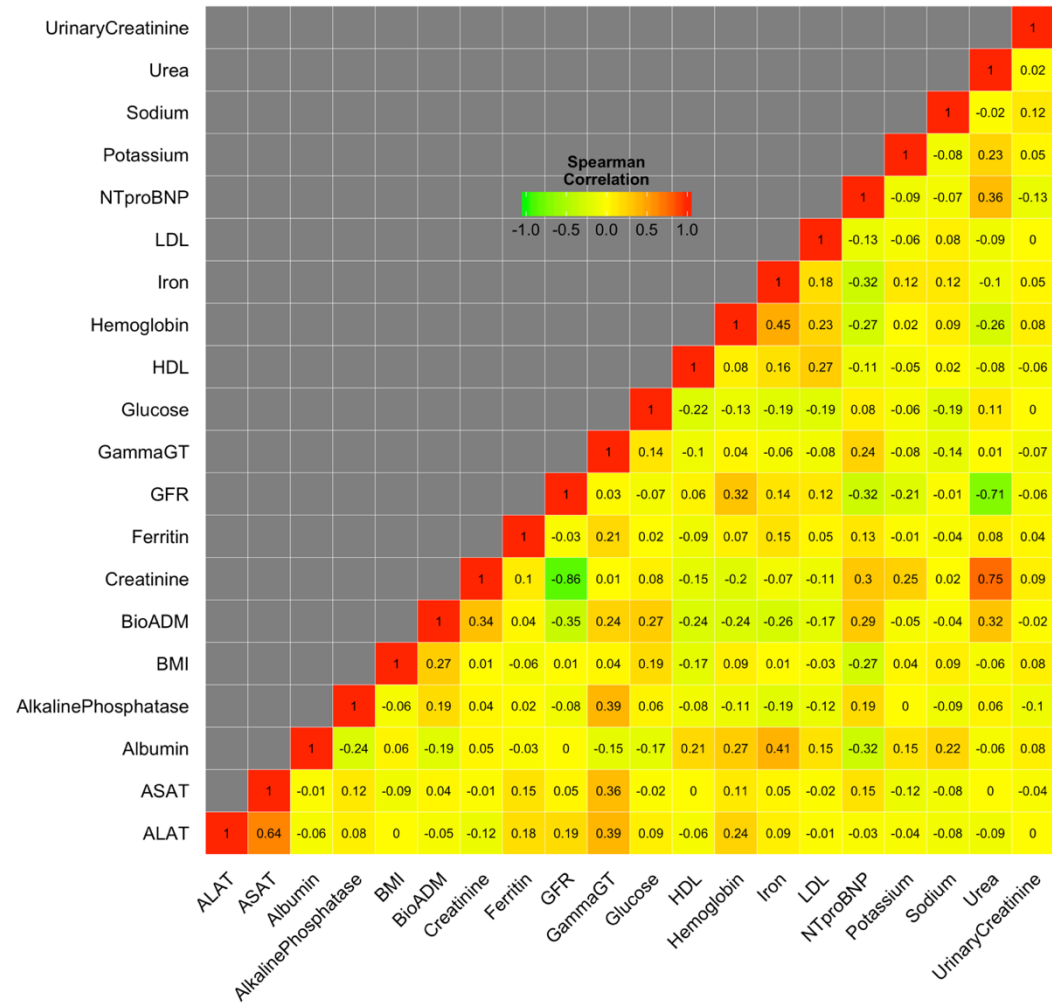
* Follow-up started at 9 months (=0 days)

Supplementary Figure S3 Biomarker position of spot urinary creatinine depicted in hierarchical cluster analysis (validation cohort)



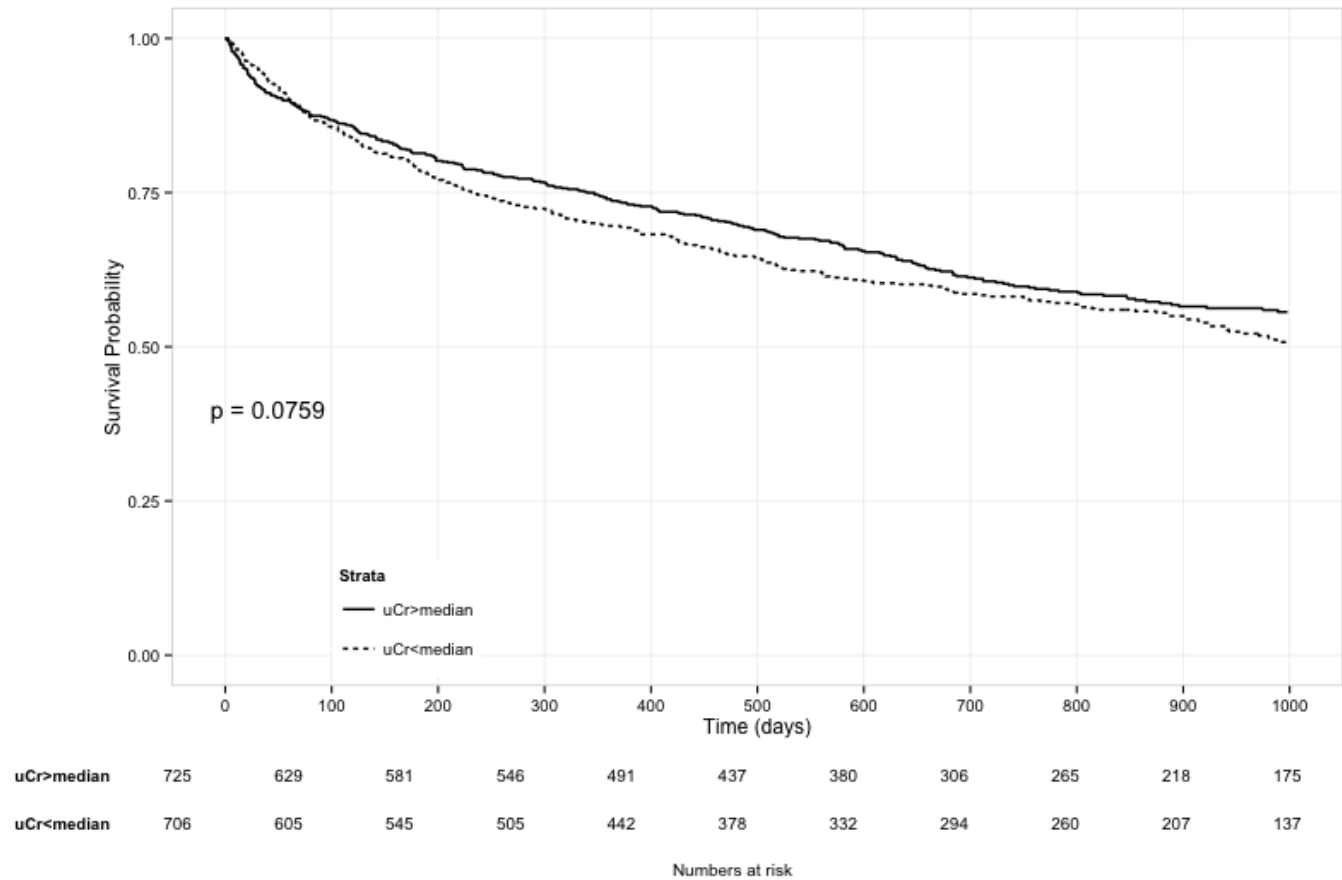
Abbreviations: ALAT, alanine transaminase; ASAT, aspartate transaminase; Bio-ADM, biologically active adrenomedullin; BMI, body mass index; Gamma-GT, gamma glutamyl transpeptidase; GFR, glomerular filtration rate; HDL, high density lipoprotein; LDL, low density lipoprotein; NT-proBNP, N-terminal pro-brain natriuretic peptide.

Supplementary Figure S4 Biomarker position of spot urinary creatinine depicted in a correlation heatmap (validation cohort)



Abbreviations: ALAT, alanine transaminase; ASAT, aspartate transaminase; Bio-ADM, biologically active adrenomedullin; BMI, body mass index; Gamma-GT, gamma glutamyl transpeptidase; GFR, glomerular filtration rate; HDL, high density lipoprotein; LDL, low density lipoprotein; NT-proBNP, N-terminal pro-brain natriuretic peptide.

Supplementary figure S5 Kaplan Meier survival curve (validation cohort) for combined endpoint (all-cause mortality or HF hospitalization) according to urinary creatinine value (above/equal to or below the median)



Abbreviations: uCR: urinary creatinine

Supplementary table S1 Baseline characteristics of included and excluded patients for the index cohort

Variables *	Included	Excluded	P-value
N	2315	201	
Demographics			
Men %(n))	73.3 (1696)	74.6 (150)	0.736
Age (years)	68.9 ± 11.9	69.0 ± 12.3	0.865
NYHA class %(n))			0.484
	I 2.2 (52)	2.0 (4)	
	II 34.9 (807)	30.3 (61)	
	III 48.3 (1119)	54.2 (109)	
	IV 11.6 (269)	12.4 (25)	
LVEF (%)	31.0 ± 10.5	30.6 ± 11.1	0.637
Anthropometrics			
Weight (kg) at baseline	81.7 ± 18.2	82.9 ± 22.1	0.466
Weight (kg) at 9 months	82.3 ± 18.6	84.2 ± 20.3	0.246
Change in weight (kg)	-0.3 ± 13.9	-0.3 ± 13.9	0.782

>5% weight loss (%(n))	21.4 (371)	17.7 (26)	0.290
>5% weight gain (%(n))	19.7 (341)	23.1 (34)	0.313
Height (cm)	170.9 ± 9.1	171.3 ± 9.6	0.583
BMI (kg/m ²) at baseline	27.9 ± 5.4	28.1 ± 6.7	0.578
BMI (kg/m ²) at 9 months	28.0 ± 5.6	28.3 ± 6.0	0.502
Change in BMI (kg/m ²)	0.0 ± 3.1	-0.1 ± 4.5	0.695
Clinical Profile at baseline			
SBP (mmHg)	125 ± 22	123 ± 19	0.260
DBP (mmHg)	75 ± 13	75 ± 13	0.650
HR (beats/min)	80 ± 20	81 ± 20	0.329
Peripheral oedema above ankle (%(n))	29.9 (576)	27.9 (48)	0.647
Orthopnoea (%(n))	34.8 (805)	36.8 (74)	0.629
Rales > 1/3 up lung fields (%(n))	19.4 (231)	17.0 (17)	0.651
Elevated JVP (%(n))	33.4 (510)	34.4 (44)	0.899
Hepatomegaly (%(n))	14.2 (328)	15.0 (30)	0.839
Clinical congestion score (%(n))	2 [1-4]	2 [1-4]	0.696

6MWT (meters)		224 [0-352]	157 [0-330]	0.008
Medical history, %(n)				
NYHA class prior to decompensation/worsening HF				0.035
	I	8.9 (205)	14.4 (29)	
	II	45.9 (1062)	39.3 (79)	
	III	29.5 (683)	33.3 (67)	
	IV	3.2 (74)	4.0 (8)	
Previous HF hospitalization		31.4 (726)	33.8 (68)	0.520
Hypertension		62.9 (1455)	56.7 (114)	0.100
Atrial fibrillation		45.1 (1045)	48.8 (98)	0.361
Coronary artery disease		45.0 (1041)	44.8 (90)	1.000
Myocardial infarction		38.2 (884)	39.3 (79)	0.813
PCI		21.8 (504)	19.9 (40)	0.597
CABG		17.3 (400)	16.4 (33)	0.832
Pacemaker		7.4 (171)	6.0 (12)	0.548
ICD		7.9 (182)	11.4 (23)	0.100

Biventricular Pacer (CRT) and ICD	6.8 (158)	7.5 (15)	0.844
Diabetes mellitus	33.0 (764)	27.4 (55)	0.119
COPD	17.4 (402)	16.9 (34)	0.949
Peripheral artery disease	11.2 (259)	7.0 (14)	0.084
Stroke	9.2 (212)	10.4 (21)	0.632
Medication history, (%(n)) at baseline			
Loop diuretics	99.6 (2305)	99.0 (199)	0.563
ACEi/ARB	72.1 (1668)	75.6 (152)	0.316
% on target dose	13.4 (310)	12.9 (26)	0.941
Beta-blockers	83.1 (1924)	84.1 (169)	0.799
% on target dose	5.5 (127)	5.5 (11)	1.000
MRA	53.6 (1241)	48.8 (98)	0.212
Digoxin	19.2 (444)	23.4 (47)	0.177
Plasma laboratory values			
Hemoglobin (g/dL)	13.3 [11.9-14.5]	13.5 [12.1-14.4]	0.612
Sodium (mmol/L)	140 [137-142]	139 [137-141]	0.050

Potassium (mmol/L)	4.2 [3.9-4.6]	4.2 [3.9-4.5]	0.287
Creatinine (umol/L)	102 [83-129]	99 [82-124]	0.749
BUN (mmol/L)	11.0 [7.4-17.5]	11.7 [8.0-18.7]	0.291
eGFR (ml/min/1.73m ²)	59.7 [44.3-78.7]	62.2 [44.2-78.2]	0.667
Albumin (g/L)	33 [27-38]	34 [29-40]	0.050
NT pro-BNP (ng/L)	4210 [2343-8486]	5207 [2505-8125]	0.265
NGAL (ng/mL)	60.8 [37.5-96.6]	61.1 [39.7-101.0]	0.052

* Categorical variables were presented as %(numbers)) and continuous variables were presented as mean ± standard deviation or median [interquartile range] as appropriate.

Abbreviations: 6MWT, 6 minute walking test; ACEi, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; BMI, body mass index; BUN, blood urea nitrogen; CABG, coronary artery bypass graft surgery; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, heart rate; ICD, implantable cardioverter defibrillator; JVP, jugular venous pressure; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonists; NGAL, neutrophil gelatinase-associated lipocalin; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; SBP, systolic blood pressure

Supplementary table S2 Baseline characteristics of included and excluded patients for the validation cohort

Variable *	Included patients	Excluded patients	P-value
N	1431	307	
Demographics			
Men (%(n))	68.4 (979)	54.1 (166)	<0.001
Age (years)	73.5 ± 10.5	74.4 ± 11.5	0.239
LVEF (%)	40.6 ± 12.8	44.9 ± 13.5	<0.001
Anthropometrics			
Weight (kg) at baseline	82.5 ± 20	80.5 ± 20.5	0.129
Height (kg)	168.2 ± 10.3	166.8 ± 11.0	0.054
BMI (kg/m ²) at baseline	29.1 ± 6.3	29.0 ± 6.9	0.788
Clinical Profile			
SBP (mmHg)	126 ± 22	125 ± 25	0.528
DBP (mmHg)	69 ± 13	69 ± 15	0.874
HR (beats/min)	74 ± 16	78 ± 17	<0.001
Peripheral oedema above ankle (%(n))	29.7 (385)	35.1 (87)	0.108

Rales > 1/3 up lung fields (%(n))	6.9 (32)	14.1 (18)	0.015
Elevated JVP (%(n))	30.0 (374)	34.4 (76)	0.217
Hepatomegaly (%(n))	4.0 (52)	3.2 (8)	0.671
Clinical congestion score (%(n))	2 [1-3]	2 [1-3]	0.237
Medical History, %(n))			
NYHA class prior to hospitalization			0.065
	I 1.0 (15)	0.7 (2)	
	II 42.3 (605)	34.9 (107)	
	III 43.0 (616)	50.8 (156)	
	IV 13.6 (194)	13.7 (42)	
Previous HF hospitalization	28.0 (396)	21.5 (64)	0.028
Hypertension	57.9 (825)	59.3 (182)	0.711
Atrial fibrillation	45.2 (643)	38.6 (117)	0.041
Coronary artery disease	56.1 (800)	49.5 (150)	0.042
Myocardial infarction	50.1 (717)	43.4 (132)	0.039
PCI	18.7 (266)	19.7 (59)	0.745

CABG	18.8 (269)	12.7 (39)	0.014
Pacemaker	6.2 (89)	8.5 (26)	0.190
Biventricular Pacer (CRT) and ICD	3.4 (49)	2.0 (6)	0.247
Diabetes mellitus	32.8 (466)	30.9 (95)	0.581
COPD	17.4 (247)	23.6 (72)	0.015
Peripheral artery disease	23.5 (327)	15.7 (47)	0.004
Stroke	18.7 (266)	16.2 (49)	0.332
Plasma laboratory values			
Hemoglobin (g/dL)	13.2 [11.9-14.5]	13.0 [11.4-14.4]	0.045
Sodium (mmol/L)	139 [137-141]	139 [137-141]	0.005
Potassium (mmol/L)	4.3 [4.0-4.6]	4.3 [3.9-4.6]	0.380
Creatinine (umol/L)	98 [81-125]	96 [74-124]	0.126
BUN (mmol/L)	8.6 [6.5-11.6]	8.9 [6.4-12.9]	0.452
eGFR (ml/min/1.73m ²)	60.0 [46.0-60.0]	60.0 [42.5-60.0]	0.379
NT pro-BNP (ng/L)	1311 [494-3302]	1818 [620-4742]	0.002

* Categorical variables were presented as %(numbers)) and continuous variables were presented as mean ± standard deviation or median [interquartile range] as appropriate.

Abbreviations: See supplementary table S1

Supplementary table S3 Multivariable linear regression model for predictors of percentage weight change from baseline (per unit increase) for the index cohort*

Variable	Beta Coefficient	T value	P-value
Log urinary creatinine	0.529	1.855	0.064
NT-proBNP	-0.927	-3.126	0.002
BMI	-2.991	-10.552	<0.001

* Adjusted $r^2 = 0.12$, other continuous variables are presented per standard deviation

Abbreviations: BMI, body mass index; NT-proBNP, N-terminal pro-brain natriuretic peptide

Supplementary table S4 Baseline characteristics according to quartiles of urinary creatinine for the validation cohort

Variables *	Q1	Q2	Q3	Q4	P-value
N	374	349	353	355	
Urinary creatinine (mmol/L)	1.5 [1.0-1.8]	2.9 [2.6-3.5]	5.1 [4.6-6.1]	10.7 [8.6-13.6]	
Demographics					
Men %(n)	63.1 (236)	66.5 (232)	66.6 (235)	77.7 (276)	<0.001
Age (years)	72.8 ± 11.1	74.5 ± 9.9	74.3 ± 10.6	72.7 ± 10.3	0.884
LVEF (%)	40.6 ± 12.7	40.5 ± 13.3	42.1 ± 12.6	39.2 ± 12.6	0.369
Anthropometrics					
Weight (kg) at baseline	78.6 ± 18.6	82.1 ± 20.7	83.2 ± 21.7	86.3 ± 18.1	<0.001
Height (cm)	166.2 ± 10.2	167.8 ± 10.0	168.4 ± 10.4	170.4 ± 10.2	<0.001
BMI (kg/m ²) at baseline	28.3 ± 5.9	29.2 ± 6.8	29.3 ± 7.1	29.6 ± 5.3	0.008

Clinical Profile at baseline					
SBP (mmHg)	126 ± 22	126 ± 23	126 ± 22	127 ± 21	0.800
DBP (mmHg)	70 ± 12	68 ± 13	69 ± 13	71 ± 13	0.260
HR (beats/min)	74 ± 17	73 ± 16	73 ± 17	74 ± 17	0.527
Peripheral oedema above ankle (% <i>(n)</i>)	32.8 (111)	27.8 (88)	31.8 (102)	26.2 (84)	0.159
Rales > 1/3 upper lung fields (% <i>(n)</i>)	12.1 (14)	9.6 (10)	2.4 (3)	4.1 (5)	0.003
Elevated JVP (% <i>(n)</i>)	29.1 (94)	31.2 (95)	29.2 (88)	30.3 (97)	0.879
Clinical congestion score	0.3 [0-1.0]	0.3 [0-1.0]	0.3 [0-1.0]	0.3 [0-1.0]	0.068
KCCQ	44 [27-64]	43 [28-60]	46 [33-67]	47 [32-67]	0.011
EQ5D	60 [50-70]	60 [50-70]	60 [50-70]	60 [50-75]	0.196

Medical history, %(n))

NYHA class prior to **0.021**

hospitalization

I	1.1 (4)	0.6 (2)	0.6 (2)	2.0 (7)	
II	39.6 (148)	41.8 (146)	41.9 (148)	45.9 (163)	
III	47.3 (177)	43.0 (150)	39.7 (140)	42.0 (149)	
IV	12.0 (45)	14.6 (51)	17.8 (63)	9.9 (35)	
Previous HF hospitalization	28.3 (105)	27.5 (95)	31.4 (110)	24.6 (86)	0.517
Hypertension	54.8 (205)	61.5 (214)	59.9 (209)	55.8 (197)	0.869
Atrial Fibrillation	49.1 (182)	43.6 (151)	43.2 (152)	44.9 (158)	0.257
Myocardial infarction	48.9 (183)	50.3 (175)	50.7 (179)	50.7 (180)	0.621
PCI	18.5 (69)	16.5 (57)	23.0 (81)	16.8 (59)	0.888

CABG	17.7 (66)	19.2 (67)	18.2 (64)	20.3 (72)	0.460
Pacemaker	4.5 (17)	6.3 (22)	6.5 (23)	7.6 (27)	0.095
Biventricular Pacer (CRT) and ICD	3.5 (13)	2.9 (10)	3.1 (11)	4.2 (15)	0.568
Diabetes Mellitus	30.8 (114)	35.8 (124)	33.5 (118)	31.1 (110)	0.915
COPD	19.7 (73)	18.8 (65)	15.8 (55)	15.3 (54)	0.068
Peripheral artery disease	22.6 (83)	27.4 (93)	19.6 (67)	24.3 (84)	0.818
Medication history, (%(n)) at baseline					
Loop diuretics	99.7 (373)	98.0 (342)	98.0 (346)	99.2 (352)	0.483
Loop diuretic doses (40 mg of furosemide equivalents)	40 [40-80]	45 [40-80]	40 [40-80]	40 [40-80]	0.020
ACEi/ARB	74.1 (227)	66.5 (232)	69.1 (244)	79.7 (283)	0.073
Beta-blockers	69.5 (260)	71.1 (248)	71.4 (252)	77.5 (275)	0.022

MRA	32.1 (120)	34.4 (120)	31.4 (111)	33.0 (117)	0.987
Plasma laboratory values					
Hemoglobin (g/dL)	13.1 [11.7-14.5]	12.9 [11.8-14.3]	13.2 [11.6-14.4]	13.7 [12.5-14.9]	0.842
Sodium (mmol/L)	139 [137-141]	139 [137-141]	139 [137-141]	140 [138-142]	<0.001
Potassium (mmol/L)	4.3 [4.0-4.5]	4.3 [4.0-4.6]	4.3 [4.0-4.6]	4.3 [4.0-4.6]	0.044
Creatinine (μmol/L)	90 [76-113]	102 [86-132]	105 [82-135]	97 [82-121]	0.032
BUN (mmol/L)	8 [6.2-10.8]	9 [6.9-12.8]	8.9 [6.5-12.4]	8.4 [6.6-10.7]	0.616
eGFR (ml/min/1.73m ²)	60.0 [53.0-60.0]	57.0 [42.0-60.0]	58.0 [41.0-60.0]	60.0 [48.0-60.0]	0.153
NT pro-BNP (ng/L)	1510 [589-4008]	1462 [547-4072]	1535 [522-3573]	917 [325-2269]	0.009
Urinary sodium/creatinine ratio	46 [28-67]	20 [13-30]	11 [7-16]	5 [3-8]	<0.001

* Categorical variables were presented as %(numbers)) and continuous variables were presented as mean ± standard deviation or median [interquartile range] as appropriate.

Abbreviations: See supplementary table S1

Supplementary table S5 Multivariable linear regression model for predictors of baseline urinary creatinine for the validation cohort*

Variable	Beta Coefficient	T value	P-value
Sodium	0.081	3.370	0.001
Height	0.089	3.213	0.001
Weight	0.074	2.700	0.007
Potassium	0.049	1.958	0.050
Years since first HF diagnosis	0.044	1.870	0.062
Peripheral oedema	-0.098	-1.820	0.069

* Adjusted $r^2 = 0.04$, continuous variables are presented per standard deviation

Abbreviations: HF, heart failure

Supplementary table S6 Cox regression analysis of urinary creatinine for all-cause mortality and combined endpoint for the validation cohort

Validation cohort	All-cause mortality		Combined endpoint	
	HR [CI]	P-value	HR [CI]	P-value
Urinary creatinine per log decrease	1.14 [1.03-1.27]	0.015	1.15 [1.05-1.26]	0.002
Adjusted for BMI, age, sex, eGFR, and loop diuretic dose	1.13 [1.01-1.27]	0.039	1.16 [1.05-1.28]	0.004
Adjusted for the above with the addition of the BIOSTAT risk model ^a	1.08 (0.96-1.22)	0.191	1.05 (0.95-1.16)	0.352

Abbreviations: HR, hazard ratio; CI, confidence interval; BMI, body mass index; eGFR, estimated glomerular filtration rate

^a Variables in the BIOSTAT risk score:

All-cause mortality: age, log blood urea nitrogen (BUN), log NT-proBNP, haemoglobin, and beta-blocker use at baseline

Combined endpoint: age, HF hospitalization in previous year, presence of oedema, log NT-proBNP, systolic blood pressure, haemoglobin, high-density lipoprotein, sodium, and beta-blocker use at baseline