Supplementary Online Content

Segar MW, Patel RB, Patel KV, et al. Association of visit-to-visit variability in kidney function and serum electrolyte indexes with risk of adverse clinical outcomes among patients with heart failure with preserved ejection fraction. *JAMA Cardiol.* Published online November 18, 2020. doi:10.1001/jamacardio.2020.5592

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods. Study Population and Laboratory Assessment

Study Population

In brief, the TOPCAT trial was a double-blind, parallel group, placebo-controlled randomized clinical trial that examined the cardiovascular effects of spironolactone among patients with chronic HFpEF and was conducted between August 2006 and January 2012 in 233 centers across the United States, Canada, Brazil, Argentina, Russia and Georgia [1]. The study included a total of 3,445 patients (aged between 50 and 90 years) with at least one symptom of HF, left ventricular (LV) ejection fraction of ≥45%, and either a history of hospitalization within the previous 12 months or an elevated natriuretic peptide level (brain natriuretic peptide [BNP] ≥100 pg/mL or N-terminal pro-BNP [NT-proBNP] ≥360 pg/mL) within 60 days prior to randomization. Entry serum potassium levels had to be <5.0 mEq/L. Key exclusion criteria included estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m^2 or serum creatinine >2.5 mg/dL. Participants were randomly assigned to receive either spironolactone 15 mg daily or placebo in a 1:1 ratio. The drug could be uptitrated to a maximum of 45 mg daily over 4 months.

Laboratory Assessment

Hemoglobin, BNP, and NT-proBNP levels were measured from blood samples obtained from trial participants at baseline or within 60 days prior to enrollment.

References

1. Pitt B, Pfeffer MA, Assmann SF, et al. Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med.* 2014;370(15):1383-1392.

Supplemental Table 1. Baseline characteristics among participants included and excluded from the primary analysis across laboratory values.

	Sodium		Potassium		Chloride		BUN		Creatinine	
	Excluded	**Included**	**Excluded**	**Included**	**Excluded**	**Included**	**Excluded**	**Included**	**Excluded**	**Included**
N	252	3193	250	3195	352	3093	966	2479	254	3191
Age	70.6 (9.9)	68.4 (9.5)	70.6 (9.9)	68.4 (9.5)	69.3 (9.7)	68.5 (9.6)	68.2 (9.4)	68.7 (9.7)	70.6 (9.9)	68.4 (9.5)
Female	145 (57.5)	1627 (51.0)	143 (57.2)	1629 (51.0)	191 (54.3)	1581 (51.1)	539 (55.8)	1233 (49.7)	144 (56.7)	1628 (51.0)
Race										
White	185 (73.4)	2877 (90.1)	184 (73.6)	2878 (90.1)	284 (80.7)	2778 (89.8)	856 (88.6)	2206 (89.0)	187 (73.6)	2875 (90.1)
Black	56 (22.2)	246 (7.7)	55 (22.0)	247 (7.7)	57 (16.2)	245 (7.9)	85 (8.8)	217 (8.8)	56 (22.0)	246 (7.7)
Other	11 (4.4)	70 (2.2)	11 (4.4)	70 (2.2)	11 (3.1)	70 (2.3)	25 (2.6)	56 (2.3)	11 (4.3)	70 (2.2)
Placebo treatment arm	138 (54.8)	1585 (49.6)	136 (54.4)	1587 (49.7)	187 (53.1)	1536 (49.7)	492 (50.9)	1231 (49.7)	136 (53.5)	1587 (49.7)
SBP	128.3 (18.0)	129.3 (13.6)	128.5 (17.9)	129.3 (13.6)	128.6 (16.3)	129.3 (13.7)	129.9 (14.2)	128.9 (13.9)	128.5 (17.8)	129.3 (13.6)
BMI	33.7 (9.2)	31.9 (6.9)	33.8 (9.2)	31.9 (6.9)	32.9 (8.4)	32.0 (6.9)	31.9 (7.0)	32.1 (7.1)	33.8 (9.2)	31.9 (6.9)
NYHA class III/IV	126 (51.0)	1010 (31.6)	125 (51.0)	1011 (31.7)	175 (50.4)	961 (31.1)	341 (35.5)	795 (32.1)	125 (50.2)	1011 (31.7)
Alcohol use										
0	209 (83.6)	2472 (77.4)	207 (83.5)	2474 (77.5)	296 (84.6)	2385 (77.1)	812 (84.2)	1869 (75.4)	209 (82.9)	2472 (77.5)
1-5	29 (11.6)	551 (17.3)	29 (11.7)	551 (17.3)	41 (11.7)	539 (17.4)	118 (12.2)	462 (18.6)	30 (11.9)	550 (17.2)
5-10	9 (3.6)	117 (3.7)	9 (3.6)	117 (3.7)	10 (2.9)	116 (3.8)	28 (2.9)	98 (4.0)	9 (3.6)	117 (3.7)
10+	1 (0.4)	51 (1.6)	1 (0.4)	51 (1.6)	1 (0.3)	51 (1.6)	4 (0.4)	48 (1.9)	2 (0.8)	50 (1.6)
Smoking	27 (10.8)	333 (10.4)	27 (10.9)	333 (10.4)	44 (12.6)	316 (10.2)	116 (12.0)	244 (9.8)	28 (11.1)	332 (10.4)
Atrial fibrillation	90 (36.0)	1124 (35.2)	90 (36.3)	1124 (35.2)	123 (35.1)	1091 (35.3)	280 (29.0)	934 (37.7)	88 (34.9)	1126 (35.3)
Diabetes										
None	136 (54.4)	2188 (68.5)	135 (54.4)	2189 (68.5)	211 (60.3)	2113 (68.3)	673 (69.8)	1651 (66.6)	133 (52.8)	2191 (68.7)
Insulin dependent	53 (21.2)	374 (11.7)	52 (21.0)	375 (11.7)	59 (16.9)	368 (11.9)	96 (10.0)	331 (13.4)	54 (21.4)	373 (11.7)
Non-insulin dependent	61 (24.4)	630 (19.7)	61 (24.6)	630 (19.7)	80 (22.9)	611 (19.8)	195 (20.2)	496 (20.0)	65 (25.8)	626 (19.6)
ACEi/ARB use	204 (81.6)	2696 (84.5)	203 (81.9)	2697 (84.4)	293 (83.7)	2607 (84.3)	805 (83.6)	2095 (84.5)	208 (82.5)	2692 (84.4)
Diuretic use	211 (84.4)	2606 (81.6)	210 (84.7)	2607 (81.6)	270 (77.1)	2547 (82.4)	698 (72.5)	2119 (85.5)	213 (84.5)	2604 (81.6)
Insulin use	53 (21.2)	374 (11.7)	52 (21.0)	375 (11.7)	59 (16.9)	368 (11.9)	96 (10.0)	331 (13.4)	54 (21.4)	373 (11.7)
Sodium, mmol/L	140.1 (9.8)	141.1 (6.1)	140.1 (9.9)	141.1 (6.1)	140.6 (8.6)	141.1 (6.2)	141.2 (10.4)	141.0 (4.0)	140.1 (9.8)	141.1 (6.1)
Potassium, mmol/L	4.2 (0.6)	4.3 (0.5)	4.2 (0.6)	4.3 (0.5)	4.2 (0.6)	4.2 (0.5)	4.3 (0.5)	4.2 (0.4)	4.2 (0.7)	4.3 (0.5)
Chloride, mmol/L	99.1 (20.1)	98.6 (21.3)	99.1 (20.2)	98.6 (21.3)	71.7 (50.2)	101.7 (11.1)	94.7 (29.4)	100.2 (16.7)	99.1 (20.0)	98.6 (21.3)
BUN, mg/dL	19.1 (19.5)	15.7 (13.5)	19.2 (19.5)	15.7 (13.5)	16.4 (18.7)	15.9 (13.4)	3.9 (14.5)	20.6 (10.7)	19.2 (19.7)	15.7 (13.5)

Creatinine, mg/dL	1.2 (0.4)	1.1 (0.3)	1.2 (0.4)	1.1 (0.3)	1.2 (0.3)	1.1 (0.3)	1.1 (0.3)	1.1 (0.3)	1.2 (0.4)	1.1 (0.3)
Glucose, mg/dL	126.1 (61.7)	114.0 (48.8)	125.4 (60.2)	114.1 (49.0)	121.2 (59.5)	114.1 (48.7)	114.4 (47.6)	115.1 (50.8)	125.7 (60.9)	114.0 (48.9)
Hemoglobin, mg/dL	12.0 (3.6)	13.3 (2.1)	12.0 (3.6)	13.3 (2.1)	12.6 (3.3)	13.2 (2.1)	13.4 (2.6)	13.1 (2.2)	12.0 (3.6)	13.3 (2.1)

Abbreviations:

ACEi/ARB, angiotensin converting enzyme inhibitor / angiotensin receptor blocker; SBP, systolic blood pressure; BMI, body mass index; NYHA, New York Heart Association; CVD, cardiovascular disease; BUN, blood urea nitrogen; BNP, brain natriuretic peptide; NT-proBNP, N-terminal prohormone brain natriuretic peptide

Supplemental Table 2. Significant predictors of blood urea nitrogen (BUN) and creatinine variability assessed by ASV.

Covariate	Coefficient (95% CI)	P-value
BUN		
Americas cohort (ref: non-Americas cohort)	1.20 (0.68, 1.72)	<0.001
Spironolactone treatment arm	0.99 (0.59, 1.39)	<0.001
In-hospital enrollment stratum (ref: natriuretic peptide enrollment arm)	0.78 (0.30, 1.25)	0.001
Baseline laboratory value	0.20 (0.18, 0.22)	<0.001
Loop-diuretic dose at baseline	0.01 (0.008, 0.16)	<0.001
Change in loop-diuretic dose at month 4	0.006 (0.0009, 0.01)	0.006
Black race	0.90 (0.16, 1.66)	0.02
Creatinine		
Americas cohort (ref: non-Americas cohort)	0.028 (0.02, 0.04)	<0.001
Spironolactone treatment arm	0.021 (0.01, 0.03)	<0.001
In-hospital enrollment stratum (ref: natriuretic peptide enrollment arm)	0.018 (0.008, 0.03)	<0.001
Female sex (ref: male sex)	0.022 (0.01, 0.03)	<0.001
Baseline laboratory value	0.13 (0.12, 0.15)	<0.001
ACEi/ARB medication use	0.016 (0.005, 0.03)	0.006
Loop-diuretic dose at baseline	0.00024 (0.0002, 0.0003)	<0.001

Supplemental Table 3. Associations of coefficient of variation (CV) among 5 laboratory measures with the primary composite end point (top) and all-cause mortality (bottom).

	Model 1		Model 2		Model 3	
	HR per 1-SD higher CV (95% CI)	**P-value**	**HR per 1-SD higher CV (95% CI)**	**P-value**	**HR per 1-SD higher CV (95% CI)**	**P-value**
Outcome: Primary composite outcome						
BUN	1.22 (1.13-1.31)	<0.001	1.21 (1.11-1.30)	<0.001	1.24 (1.11-1.39)	<0.001
Creatinine	1.22 (1.13-1.32)	<0.001	1.17 (1.08-1.26)	<0.001	1.16 (1.04-1.29)	0.009
Sodium	1.15 (1.05-1.25)	0.003	1.15 (1.04-1.23)	0.005	1.21 (1.02-1.37)	0.02
Potassium	1.19 (1.10-1.29)	<0.001	1.18 (1.08-1.28)	<0.001	1.24 (1.03-1.57)	0.01
Chloride	1.12 (1.03-1.23)	0.01	1.14 (1.03-1.25)	0.008	1.25 (1.09-1.44)	0.001
Outcome: All-cause mortality						
BUN	1.18 (1.08-1.28)	<0.001	1.12 (1.03-1.23)	0.01	1.12 (1.01-1.22)	0.04
Creatinine	1.18 (1.10-1.27)	<0.001	1.14 (1.05-1.23)	0.002	1.13 (1.02-1.27)	0.03
Sodium	1.14 (1.03-1.25)	0.01	1.12 (1.02-1.24)	0.02	1.15 (0.98-1.35))	0.08
Potassium	1.11 (1.02-1.21)	0.02	1.09 (1.00-1.19)	0.049	1.10 (0.97-1.22)	0.13
Chloride	1.15 (1.05-1.25)	0.003	1.16 (1.05-1.28)	0.003	1.29 (1.12-1.49)	<0.001

BUN, blood urea nitrogen.
Model 1 – adjusted for age, sex, race, education level, treatment arm, country of enrollment, and enrollment stratum (either elevated NP levels of HF hospitalization).
Model 2 – covariates in Model 1 + BMI, SBP, diabetes status (none, insulin dependent, non-insulin dependent), alcohol use, smoking history, history of atrial fibrillation, ACEi/ARB use (yes/no), history of CVD, New York Heart Association (NYHA) class, and baseline respective laboratory value (either BUN, creatinine, potassium, sodium, or chloride).
Model 3 – covariates of Model 2 + percent change in respective laboratory value, variability in SBP and BMI, and spironolactone and loop diuretic medication dose as a time varying covariate.

Supplemental Table 4. Associations of standard deviation (SD) among 5 laboratory measures with the primary composite end point (top) and all-cause mortality (bottom).

	Model 1		Model 2		Model 3	
	HR per 1-SD higher SD (95% CI)	**P-value**	**HR per 1-SD higher SD (95% CI)**	**P-value**	**HR per 1-SD higher SD (95% CI)**	**P-value**
Outcome: Primary composite outcome						
BUN	1.25 (1.18-1.34)	<0.001	1.18 (1.09-1.28)	<0.001	1.23 (1.09-1.38)	<0.001
Creatinine	1.27 (1.20-1.35)	<0.001	1.18 (1.10-1.28)	<0.001	1.15 (1.03-1.29)	0.009
Sodium	1.14 (1.05-1.25)	0.003	1.14 (1.04-1.25)	0.006	1.21 (1.02-1.37)	0.02
Potassium	1.20 (1.10-1.29)	<0.001	1.18 (1.08-1.28)	<0.001	1.15 (1.05-1.25)	0.002
Chloride	1.12 (1.02-1.22)	0.01	1.13 (1.03-1.24)	0.008	1.27 (1.05-1.53)	0.01
Outcome: All-cause mortality						
BUN	1.22 (1.13-1.32)	<0.001	1.15 (1.04-1.27)	0.005	1.17 (1.03-1.32)	0.02
Creatinine	1.16 (1.10-1.23)	<0.001	1.13 (1.05-1.22)	0.001	1.10 (0.99-1.19)	0.06
Sodium	1.13 (1.02-1.24)	0.01	1.12 (1.01-1.24)	0.03	1.14 (0.98-1.34))	0.09
Potassium	1.11 (1.03-1.21)	0.01	1.09 (1.00-1.18)	0.054	1.22 (1.03-1.40)	0.02
Chloride	1.14 (1.04-1.25)	0.004	1.16 (1.05-1.28)	0.003	1.28 (1.11-1.47)	0.001

BUN, blood urea nitrogen.
Model 1 – adjusted for age, sex, race, education level, treatment arm, country of enrollment, and enrollment stratum (either elevated NP levels of HF hospitalization).
Model 2 – covariates in Model 1 + BMI, SBP, diabetes status (none, insulin dependent, non-insulin dependent), alcohol use, smoking history, history of atrial fibrillation, ACEi/ARB use (yes/no), history of CVD, New York Heart Association (NYHA) class, and baseline respective laboratory value (either BUN, creatinine, potassium, sodium, or chloride).
Model 3 – covariates of Model 2 + percent change in respective laboratory value, variability in SBP and BMI, and spironolactone and loop diuretic medication dose as a time varying covariate.

Supplemental Table 5. Baseline characteristics across quintiles of creatinine variability assessed by ASV.

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	P-value
n	651	649	645	633	613	
ASV, mg/dL	0.04 (0.02)	0.07 (0.01)	0.11 (0.01)	0.17 (0.02)	0.33 (0.16)	<0.01
Demographic						
Age, years	67.6 (9.2)	67.4 (9.6)	68.6 (9.3)	69.1 (9.6)	69.3 (9.7)	<0.01
Female	347 (53.3)	316 (48.7)	348 (54.0)	327 (51.7)	290 (47.3)	0.08
Race						<0.01
White	617 (94.8)	601 (92.6)	585 (90.7)	550 (86.9)	522 (85.2)	
Black	24 (3.7)	39 (6.0)	41 (6.4)	68 (10.7)	74 (12.1)	
Other	10 (1.5)	9 (1.4)	19 (2.9)	15 (2.4)	17 (2.8)	
Americas	217 (33.3)	252 (38.8)	344 (53.3)	389 (61.5)	377 (61.5)	<0.01
Spironolactone treatment arm	305 (46.9)	300 (46.2)	311 (48.2)	328 (51.8)	360 (58.7)	<0.01
Clinical Characteristics						
SBP, mmHg	129.9 (12.6)	129.7 (13.3)	129.2 (13.4)	128.8 (13.9)	128.7 (15.0)	0.48
BMI, kg/m2	30.8 (6.4)	31.5 (6.7)	32.0 (6.7)	32.7 (7.2)	32.7 (7.3)	<0.01
NYHA class III-IV	182 (28.0)	200 (30.8)	197 (30.5)	206 (32.6)	226 (36.9)	0.01
Alcoholic drinks per week						0.68
0	520 (79.9)	506 (78.0)	486 (75.5)	490 (77.4)	470 (76.7)	
1-5	100 (15.4)	107 (16.5)	123 (19.1)	106 (16.7)	114 (18.6)	
5-10	23 (3.5)	25 (3.9)	23 (3.6)	29 (4.6)	17 (2.8)	
10+	8 (1.2)	11 (1.7)	11 (1.7)	8 (1.3)	12 (2.0)	
Current smoking	75 (11.5)	72 (11.1)	65 (10.1)	47 (7.4)	73 (11.9)	0.12
Variability in SBP	9.5 (6.3)	9.9 (7.3)	10.9 (7.7)	11.6 (8.0)	12.0 (8.4)	<0.01
Variability in BMI	0.5 (0.8)	0.6 (0.7)	0.5 (0.6)	0.6 (0.6)	0.7 (0.7)	<0.01
Medical History						
History of CVD	217 (33.3)	228 (35.1)	240 (37.2)	262 (41.4)	270 (44.0)	<0.01
Atrial fibrillation	221 (33.9)	226 (34.8)	217 (33.7)	241 (38.1)	221 (36.1)	0.46
Diabetes status						<0.01
None	495 (76.0)	472 (72.7)	433 (67.2)	424 (67.0)	367 (59.9)	
Insulin dependent	38 (5.8)	52 (8.0)	67 (10.4)	93 (14.7)	123 (20.1)	
Non-Insulin dependent	118 (18.1)	125 (19.3)	144 (22.4)	116 (18.3)	123 (20.1)	
ACEi/ARB medication	549 (84.3)	557 (85.8)	518 (80.3)	538 (85.1)	530 (86.5)	0.02
Loop diuretic medication	508 (78.0)	511 (78.7)	514 (79.7)	538 (85.1)	533 (86.9)	<0.01
Average loop diuretic dose at baseline, mg	53.7 (44.4)	57.3 (59.2)	66.3 (76.2)	78.9 (131.3)	87.3 (103.2)	<0.01

Average loop diuretic dose at month 4, mg	74.5 (74.3)	57.2 (51.7)	89.1 (98.6)	98.3 (166.6)	101.5 (118.7)	0.08
Laboratory						
Sodium, mmol/L	141.8 (4.5)	141.3 (9.1)	141.0 (4.2)	140.7 (7.2)	140.7 (4.0)	0.01
Potassium, mmol/L	4.3 (0.4)	4.3 (0.5)	4.3 (0.4)	4.2 (0.4)	4.2 (0.4)	0.54
Chloride, mmol/L	99.2 (20.4)	97.3 (25.1)	98.6 (21.3)	99.1 (19.1)	98.9 (19.9)	0.48
BUN, mg/dL	12.9 (10.6)	13.9 (12.3)	14.9 (14.1)	16.7 (13.4)	20.3 (15.4)	<0.01
Creatinine, mg/dL	1.0 (0.2)	1.0 (0.2)	1.1 (0.3)	1.1 (0.3)	1.2 (0.4)	<0.01
Glucose, mg/dL	108.9 (40.8)	110.6 (39.7)	115.6 (47.8)	114.0 (51.9)	121.3 (61.0)	<0.01
Hemoglobin, g/dL	13.4 (1.8)	13.5 (1.9)	13.2 (2.5)	13.2 (1.9)	12.9 (2.4)	<0.01
BNP, pg/mL	355.1 (374.3)	307.9 (336.0)	392.7 (522.4)	371.2 (418.9)	390.1 (358.7)	0.42
NT-proBNP, pg/mL	986.3 (1125.8)	1411.3 (1718.6)	1434.7 (2279.3)	1474.4 (1704.4)	1870.7 (3253.4)	0.04
Z-score	-0.1 (0.7)	-0.1 (0.8)	0.0 (1.2)	-0.0 (0.9)	0.1 (1.2)	0.06

*Abbreviations:*ACEi/ARB, angiotensin converting enzyme inhibitor / angiotensin receptor blocker; SBP, systolic blood pressure; BMI, body mass index; NYHA, New York Heart Association; CVD, cardiovascular disease; BUN, blood urea nitrogen; BNP, brain natriuretic peptide; NT-proBNP, N-terminal prohormone brain natriuretic peptide

Supplemental Table 6. Associations of average successive variability (ASV) among 5 laboratory measures with the primary composite outcome after further adjustment for NP Z-score. Primary composite outcome is a composite of aborted cardiac arrest, hospitalization for management of heart failure, or cardiovascular death.

	Model 4	
	HR per 1-SD higher ASV (95% CI)	**P-value**
BUN	1.26 (1.10-1.44)	0.001
Creatinine	1.29 (1.13-1.47)	<0.001
Sodium	1.32 (1.08-1.62)	0.008
Potassium	1.22 (1.03-1.45)	0.02
Chloride	1.24 (0.99-1.55)	0.06

BUN, blood urea nitrogen.
Cox Model adjusted for age, sex, race, education level, treatment arm, country of enrollment, enrollment stratum (either elevated NP levels of HF hospitalization), BMI, SBP, diabetes status (none, insulin dependent, non-insulin dependent), alcohol use, smoking history, history of atrial fibrillation, ACEi/ARB use (yes/no), history of CVD, New York Heart Association (NYHA) class, and baseline respective laboratory value (either BUN, creatinine, potassium, sodium, or chloride), percent change in respective laboratory value, variability in SBP and BMI, spironolactone and loop diuretic medication dose as a time varying covariate, and NP Z-score.

Supplemental Table 7. Associations of average successive variability (ASV), coefficient of variation (CV), and standard deviation (SD) among 5 laboratory measures with the primary composite outcome in the Americas cohort. The number of events were 379 (28.0%), 419 (26.5%), 419 (26.5%), 420 (26.5%), and 417 (26.5%) for BUN, creatinine, sodium, potassium, and chloride, respectively.1

	Model 1		Model 2		Model 3	
	HR per 1-SD higher (95% CI)	**P-value**	**HR per 1-SD higher (95% CI)**	**P-value**	**HR per 1-SD higher (95% CI)**	**P-value**
Variability: ASV						
BUN	1.24 (1.16-1.33)	<0.001	1.14 (1.05-1.24)	0.002	1.26 (1.11-1.44)	0.001
Creatinine	1.29 (1.20-1.39)	<0.001	1.16 (1.07-1.25)	<0.001	1.28 (1.12-1.46)	<0.001
Sodium	1.19 (1.09-1.30)	<0.001	1.25 (1.10-1.41)	<0.001	1.27 (1.03-1.57)	0.03
Potassium	1.15 (1.06-1.26)	0.001	1.14 (1.04-1.26)	0.005	1.21 (1.01-1.44)	0.04
Chloride	1.08 (1.00-1.17)	0.042	1.14 (0.99-1.31)	0.06	1.26 (1.01-1.59)	0.045
Variability: CV						
BUN	1.21 (1.11-1.32)	<0.001	1.19 (1.09-1.31)	<0.001	1.27 (1.12-1.44)	<0.001
Creatinine	1.24 (1.14-1.35)	<0.001	1.17 (1.07-1.28)	<0.001	1.17 (1.04-1.31)	0.007
Sodium	1.25 (1.10-1.42)	<0.001	1.24 (1.08-1.42)	0.002	1.16 (0.97-1.39)	0.11
Potassium	1.18 (1.08-1.29)	<0.001	1.16 (1.06-1.28)	0.002	1.08 (0.95-1.24)	0.25
Chloride	1.21 (1.07-1.37)	0.002	1.22 (1.07-1.41)	0.004	1.28 (1.09-1.51)	0.003
Variability: SD						
BUN	1.25 (1.17-1.33)	<0.001	1.17 (1.08-1.28)	<0.001	1.26 (1.13-1.40)	<0.001
Creatinine	1.29 (1.21-1.37)	<0.001	1.19 (1.09-1.29)	<0.001	1.16 (1.05-1.27)	0.002
Sodium	1.25 (1.09-1.42)	0.001	1.24 (1.08-1.42)	0.002	1.15 (0.96-1.38)	0.13
Potassium	1.18 (1.08-1.29)	<0.001	1.16 (1.06-1.28)	0.001	1.08 (0.94-1.23)	0.30
Chloride	1.19 (1.06-1.34)	0.003	1.22 (1.06-1.39)	0.004	1.27 (1.08-1.46)	0.008

BUN, blood urea nitrogen.
Model 1 – adjusted for age, sex, race, education level, treatment arm, country of enrollment, and enrollment stratum (either elevated NP levels of HF hospitalization).

Model 2 – covariates in Model 1 + BMI, SBP, diabetes status (none, insulin dependent, non-insulin dependent), alcohol use, smoking history, history of atrial fibrillation, ACEi/ARB use (yes/no), history of CVD, New York Heart Association (NYHA) class, and baseline respective laboratory value (either BUN, creatinine, potassium, sodium, or chloride).
Model 3 – covariates of Model 2 + percent change in respective laboratory value, variability in SBP and BMI, and spironolactone and loop diuretic medication dose as a time varying covariate.

Supplemental Table 8. Associations of ASV among 5 laboratory measures with the primary composite outcome in the placebo (top) and spironolactone (bottom) treatment arms.

	Model 1		Model 2		Model 3	
	HR per 1-SD higher ASV (95% CI)	**P-value**	**HR per 1-SD higher ASV (95% CI)**	**P-value**	**HR per 1-SD higher ASV (95% CI)**	**P-value**
Placebo treatment arm						
BUN	1.21 (1.12-1.31)	<0.001	1.23 (1.09-1.39)	0.001	1.27 (1.04-1.56)	0.02
Creatinine	1.18 (1.08-1.29)	<0.001	1.14 (1.01-1.29)	0.03	1.39 (1.14-1.69)	0.001
Sodium	1.17 (1.03-1.34)	0.02	1.14 (0.99-1.31)	0.05	1.52 (1.03-2.26)	0.04
Potassium	1.14 (1.02-1.28)	0.02	1.13 (1.00-1.27)	0.049	1.39 (1.08-1.79)	0.01
Chloride	1.14 (1.01-1.28)	0.03	1.15 (1.00-1.32)	0.043	1.38 (0.94-2.02)	0.09
Spironolactone treatment arm						
BUN	1.22 (1.12-1.32)	<0.001	1.12 (1.01-1.24)	0.03	1.30 (1.03-1.65)	0.02
Creatinine	1.28 (1.19-1.37)	<0.001	1.17 (1.08-1.28)	<0.001	1.19 (1.02-1.42)	0.03
Sodium	1.19 (1.05-1.34)	0.005	1.20 (1.05-1.36)	0.005	1.22 (1.05-1.49)	0.01
Potassium	1.19 (1.07-1.31)	0.001	1.18 (1.06-1.32)	0.003	1.16 (1.00-1.41)	0.045
Chloride	1.05 (0.92-1.20)	0.46	1.07 (0.93-1.23)	0.36	1.20 (0.87-1.66)	0.26

BUN, blood urea nitrogen.
Model 1 – adjusted for age, sex, race, education level, treatment arm, country of enrollment, and enrollment stratum (either elevated NP levels of HF hospitalization).
Model 2 – covariates in Model 1 + BMI, SBP, diabetes status (none, insulin dependent, non-insulin dependent), alcohol use, smoking history, history of atrial fibrillation, ACEi/ARB use (yes/no), history of CVD, New York Heart Association (NYHA) class, and baseline respective laboratory value (either BUN, creatinine, potassium, sodium, or chloride).
Model 3 – covariates of Model 2 + percent change in respective laboratory value, variability in SBP and BMI, and spironolactone and loop diuretic medication dose as a time varying covariate.

Supplemental Table 9. Sensitivity analyses: Associations of ASV in renal function laboratory measures with the primary composite outcome among tertiles of the MAGGIC risk score.

	Tertile 1		Tertile 2		Tertile 3	
	HR per 1-SD higher ASV (95% CI)	**P-value**	**HR per 1-SD higher ASV (95% CI)**	**P-value**	**HR per 1-SD higher ASV (95% CI)**	**P-value**
BUN	1.14 (1.01-1.29)	0.03	1.52 (1.26-1.83)	<0.001	1.19 (1.02-1.38)	0.02
Creatinine	1.35 (1.16-1.57)	<0.001	1.15 1.01-1.31)	0.041	1.21 (1.04-1.41)	0.01

BUN, blood urea nitrogen

Model was adjusted for treatment arm, country of enrollment, alcohol use, history of atrial fibrillation, percent change in respective laboratory value, variability in SBP and BMI, and spironolactone and loop diuretic medication dose as a time varying covariate.

Supplemental Table 10. Comparison of Cox proportional hazard model discrimination (Harrell's C-statistic) for predicting all-cause mortality with MAGGIC risk score and addition of percent change or ASV in kidney function parameters. Comparison between models was determined using the De Long's test.

	MAGGIC risk score alone	MAGGIC risk score + percent change in laboratory measure	MAGGIC risk score + ASV in laboratory measure	P-value comparison (MAGGIC risk score alone vs. MAGGIC risk score + percent change)	P-value comparison (MAGGIC risk score alone vs. MAGGIC risk score + ASV)
BUN	0.64	0.64	0.67	p=0.35	p<0.001
Creatinine	0.65	0.65	0.67	P=0.22	p<0.001
ASV, average successive variability; BUN, blood urea nitrogen					

Supplemental Table 11. Baseline characteristics across quintiles of sodium variability assessed by ASV.

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	P-value
n	868	648	513	612	552	
ASV, mEq/L	1.0 (0.4)	1.8 (0.2)	2.5 (0.2)	3.4 (0.4)	6.1 (1.9)	<0.01
Demographic						
Age, years	69.3 (9.8)	69.2 (9.4)	68.1 (9.3)	68.1 (9.5)	66.6 (9.2)	<0.01
Female	431 (49.7)	336 (51.9)	256 (49.9)	308 (50.3)	296 (53.6)	0.61
Race						<0.01
White	773 (89.1)	585 (90.3)	449 (87.5)	545 (89.1)	525 (95.1)	
Black	77 (8.9)	48 (7.4)	53 (10.3)	52 (8.5)	16 (2.9)	
Other	18 (2.1)	15 (2.3)	11 (2.1)	15 (2.5)	11 (2.0)	
Americas	542 (62.4)	368 (56.8)	256 (49.9)	277 (45.3)	139 (25.2)	<0.01
Spironolactone treatment arm	428 (49.3)	327 (50.5)	234 (45.6)	335 (54.7)	284 (51.4)	0.04
Clinical Characteristics						
SBP, mmHg	128.2 (13.8)	130.3 (14.1)	129.0 (14.3)	129.2 (13.3)	130.2 (12.2)	0.03
BMI, kg/m2	32.2 (7.1)	32.3 (7.0)	31.8 (6.7)	31.8 (7.2)	31.5 (6.2)	0.20
NYHA class III-IV	267 (30.8)	198 (30.6)	179 (34.9)	197 (32.2)	169 (30.6)	0.48
Alcoholic drinks per week						0.29
0	644 (74.2)	514 (79.3)	400 (78.1)	483 (78.9)	431 (78.1)	
1-5	161 (18.5)	105 (16.2)	86 (16.8)	103 (16.8)	96 (17.4)	
5-10	45 (5.2)	18 (2.8)	18 (3.5)	19 (3.1)	17 (3.1)	
10+	18 (2.1)	11 (1.7)	7 (1.4)	7 (1.1)	8 (1.4)	
Current smoking	79 (9.1)	56 (8.6)	59 (11.5)	67 (10.9)	72 (13.0)	0.08
Variability in SBP	11.5 (8.0)	10.9 (7.1)	11.2 (7.9)	10.3 (7.7)	9.6 (7.2)	<0.01
Variability in BMI	0.6 (0.8)	0.6 (0.7)	0.5 (0.6)	0.6 (0.6)	0.6 (0.8)	0.62
Medical History						
History of CVD	342 (39.4)	276 (42.6)	210 (40.9)	231 (37.7)	161 (29.2)	<0.01
Atrial fibrillation	347 (40.0)	230 (35.5)	186 (36.3)	200 (32.7)	161 (29.2)	<0.01
Diabetes status						<0.01
None	583 (67.2)	450 (69.4)	332 (64.8)	406 (66.3)	417 (75.5)	
Insulin dependent	111 (12.8)	78 (12.0)	58 (11.3)	81 (13.2)	46 (8.3)	
Non-Insulin dependent	174 (20.0)	120 (18.5)	122 (23.8)	125 (20.4)	89 (16.1)	
ACEi/ARB medication	716 (82.5)	545 (84.2)	438 (85.4)	520 (85.0)	477 (86.4)	0.33
Loop diuretic medication	726 (83.6)	545 (84.2)	423 (82.5)	506 (82.7)	406 (73.6)	<0.01

Average loop diuretic dose at baseline, mg	77.5 (128.0)	69.9 (77.6)	68.6 (74.2)	69.3 (73.3)	58.5 (64.2)	0.35
Average loop diuretic dose at month 4, mg	93.3 (156.1)	89.8 (103.5)	84.4 (87.7)	88.8 (97.9)	71.7 (62.5)	0.83
Laboratory						
Sodium, mmol/L	141.0 (6.0)	140.8 (7.1)	141.4 (4.2)	141.1 (7.2)	141.4 (5.3)	0.38
Potassium, mmol/L	4.2 (0.5)	4.3 (0.4)	4.3 (0.4)	4.3 (0.5)	4.3 (0.5)	0.26
Chloride, mmol/L	99.8 (18.4)	98.4 (22.0)	98.4 (22.2)	98.2 (21.3)	97.7 (23.5)	0.42
BUN, mg/dL	17.6 (12.7)	16.8 (13.2)	15.5 (13.4)	15.0 (13.9)	12.5 (14.3)	<0.01
Creatinine, mg/dL	1.1 (0.3)	1.1 (0.3)	1.1 (0.3)	1.1 (0.3)	1.1 (0.3)	0.01
Glucose, mg/dL	111.6 (44.3)	115.3 (49.7)	116.3 (49.2)	115.3 (52.2)	112.6 (50.0)	0.32
Hemoglobin, g/dL	13.1 (2.2)	13.2 (1.9)	13.2 (2.0)	13.3 (2.4)	13.6 (1.9)	<0.01
BNP, pg/mL	377.8 (487.6)	340.2 (328.9)	336.6 (385.4)	356.8 (342.6)	420.5 (438.2)	0.53
NT-proBNP, pg/mL	1406.0 (1823.4)	1300.0 (1599.8)	1434.2 (1378.1)	1879.5 (3630.0)	1026.4 (1071.4)	0.08
Z-score	-0.0 (1.0)	-0.1 (0.8)	-0.1 (0.8)	0.1 (1.3)	-0.0 (0.9)	0.54

Abbreviations: ACEi/ARB, angiotensin converting enzyme inhibitor / angiotensin receptor blocker; SBP, systolic blood pressure; BMI, body mass index; NYHA, New York Heart Association; CVD, cardiovascular disease; BUN, blood urea nitrogen; BNP, brain natriuretic peptide; NT-proBNP, N-terminal prohormone brain natriuretic peptide

Supplemental Table 12. Baseline characteristics across quintiles of potassium variability assessed by ASV.

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	P-value
n	667	682	598	624	624	
ASV, mEq/L	0.12 (0.04)	0.22 (0.03)	0.31 (0.03)	0.43 (0.04)	0.68 (0.18)	<0.01
Demographic						
Age, years	68.1 (9.3)	68.4 (9.4)	68.1 (9.6)	68.3 (9.7)	69.1 (9.6)	0.29
Female	349 (52.3)	349 (51.2)	284 (47.5)	327 (52.4)	320 (51.3)	0.42
Race						0.04
White	616 (92.4)	618 (90.6)	528 (88.3)	559 (89.6)	557 (89.3)	
Black	35 (5.2)	52 (7.6)	52 (8.7)	48 (7.7)	60 (9.6)	
Other	16 (2.4)	12 (1.8)	18 (3.0)	17 (2.7)	7 (1.1)	
Americas	302 (45.3)	327 (47.9)	317 (53.0)	315 (50.5)	323 (51.8)	0.04
Spironolactone treatment arm	297 (44.5)	337 (49.4)	312 (52.2)	333 (53.4)	329 (52.7)	0.01
Clinical Characteristics						
SBP, mmHg	130.0 (13.5)	129.3 (13.4)	128.8 (13.8)	129.4 (13.7)	128.8 (13.8)	0.51
BMI, kg/m2	31.8 (6.9)	31.6 (6.4)	32.1 (6.9)	32.3 (7.0)	32.0 (7.2)	0.55
NYHA class III-IV	179 (26.8)	191 (28.0)	197 (32.9)	204 (32.7)	240 (38.5)	<0.01
Alcoholic drinks per week						0.32
0	516 (77.4)	530 (77.8)	445 (74.4)	495 (79.3)	488 (78.2)	
1-5	124 (18.6)	113 (16.6)	110 (18.4)	96 (15.4)	108 (17.3)	
5-10	18 (2.7)	24 (3.5)	28 (4.7)	25 (4.0)	22 (3.5)	
10+	9 (1.3)	14 (2.1)	15 (2.5)	7 (1.1)	6 (1.0)	
Current smoking	55 (8.2)	70 (10.3)	70 (11.7)	70 (11.2)	68 (10.9)	0.33
Variability in SBP	9.9 (7.4)	10.5 (7.7)	11.2 (7.5)	10.9 (7.6)	11.4 (7.9)	<0.01
Variability in BMI	0.5 (0.8)	0.5 (0.6)	0.6 (0.7)	0.6 (0.6)	0.7 (0.8)	<0.01
Medical History						
History of CVD	253 (37.9)	260 (38.1)	247 (41.3)	242 (38.8)	219 (35.1)	0.52
Atrial fibrillation	224 (33.6)	225 (33.0)	208 (34.8)	230 (36.9)	237 (38.0)	0.28
Diabetes status						0.04
None	469 (70.3)	480 (70.5)	419 (70.1)	410 (65.7)	411 (65.9)	
Insulin dependent	64 (9.6)	64 (9.4)	70 (11.7)	85 (13.6)	92 (14.7)	
Non-Insulin dependent	134 (20.1)	137 (20.1)	109 (18.2)	129 (20.7)	121 (19.4)	
ACEi/ARB medication	558 (83.7)	571 (83.7)	502 (84.1)	533 (85.4)	533 (85.4)	0.82
Loop diuretic medication	554 (83.1)	542 (79.5)	481 (80.6)	510 (81.7)	520 (83.3)	0.32

Average loop diuretic dose at baseline, mg	65.1 (68.5)	72.6 (87.6)	65.4 (77.1)	74.6 (138.0)	74.3 (73.0)	0.68
Average loop diuretic dose at month 4, mg	70.3 (49.6)	105.2 (122.3)	80.7 (104.0)	93.1 (170.9)	90.3 (95.0)	0.33
Laboratory						
Sodium, mmol/L	141.5 (4.3)	141.6 (4.0)	140.8 (7.2)	140.9 (7.2)	140.6 (7.3)	0.01
Potassium, mmol/L	4.3 (0.4)	4.2 (0.4)	4.2 (0.5)	4.3 (0.5)	4.2 (0.5)	0.01
Chloride, mmol/L	98.4 (20.7)	98.1 (22.7)	97.7 (23.1)	98.5 (22.3)	100.2 (16.8)	0.28
BUN, mg/dL	15.5 (13.1)	14.6 (12.9)	15.8 (13.1)	16.2 (14.2)	16.5 (14.2)	0.10
Creatinine, mg/dL	1.0 (0.3)	1.1 (0.3)	1.1 (0.3)	1.1 (0.3)	1.1 (0.3)	<0.01
Glucose, mg/dL	113.6 (49.0)	110.3 (39.6)	112.9 (49.1)	117.1 (54.6)	116.7 (51.8)	0.07
Hemoglobin, g/dL	13.3 (1.7)	13.2 (2.2)	13.3 (2.1)	13.3 (2.1)	13.1 (2.4)	0.22
BNP, pg/mL	384.5 (548.8)	314.9 (287.3)	374.3 (418.9)	396.0 (434.0)	365.7 (337.7)	0.51
NT-proBNP, pg/mL	1396.1 (1959.5)	1249.5 (1626.5)	1316.1 (1983.9)	1322.9 (1281.8)	1852.3 (3248.3)	0.20
Z-score	-0.0 (1.1)	-0.1 (0.7)	-0.0 (1.0)	-0.0 (0.9)	0.1 (1.1)	0.27

Abbreviations: ACEi/ARB, angiotensin converting enzyme inhibitor / angiotensin receptor blocker; SBP, systolic blood pressure; BMI, body mass index; NYHA, New York Heart Association; CVD, cardiovascular disease; BUN, blood urea nitrogen; BNP, brain natriuretic peptide; NT-proBNP, N-terminal prohormone brain natriuretic peptide

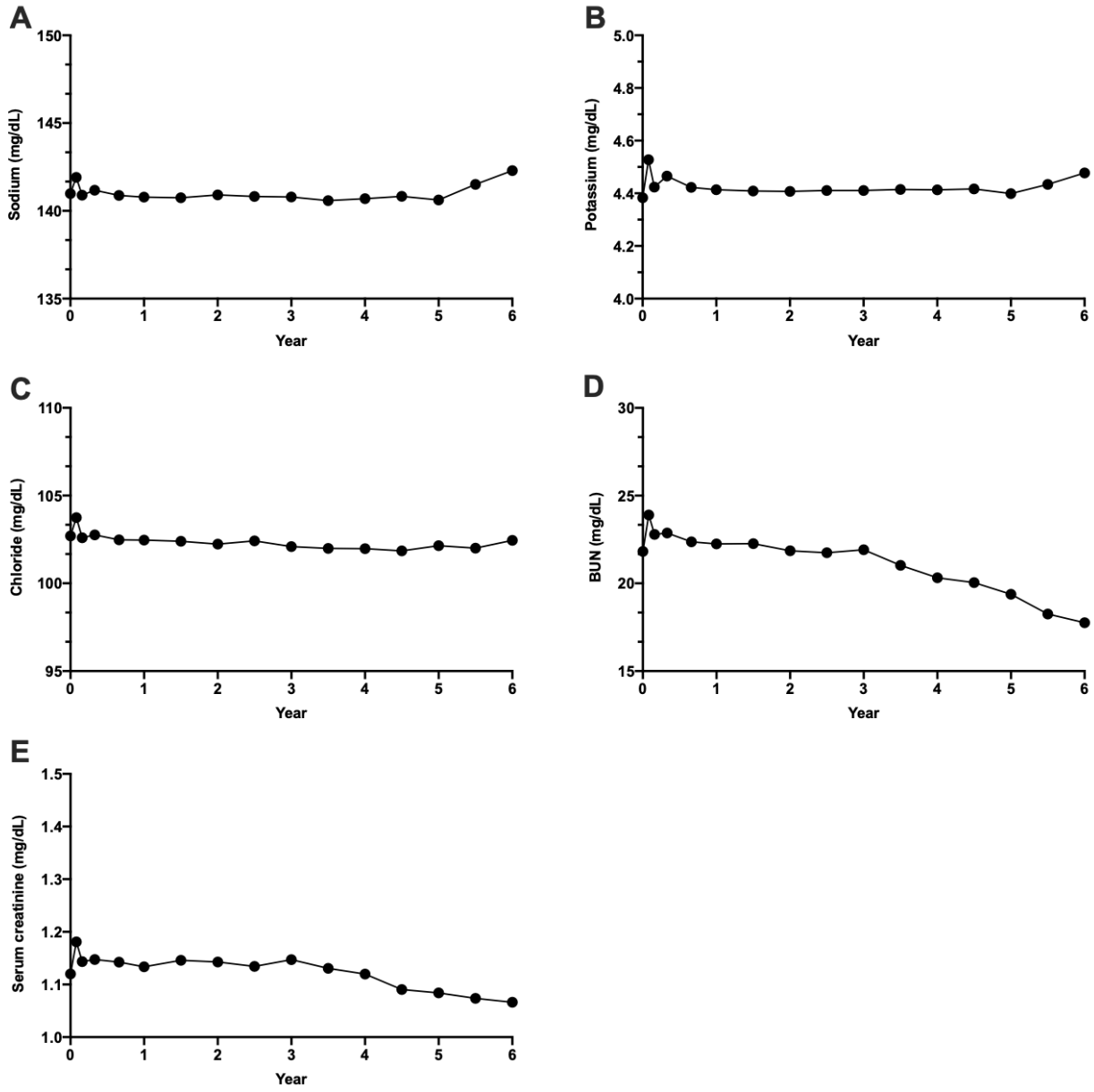
Supplemental Table 13. Baseline characteristics across quintiles of chloride variability assessed by ASV.

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	P-value
n	775	614	648	458	598	
ASV, mEq/L	1.0 (0.4)	1.8 (0.2)	2.6 (0.3)	3.7 (0.4)	7.7 (4.0)	<0.01
Demographic						
Age, years	68.6 (9.6)	69.6 (9.6)	68.9 (9.9)	68.1 (9.4)	67.0 (9.1)	<0.01
Female	364 (47.0)	314 (51.1)	328 (50.6)	257 (56.1)	318 (53.2)	0.03
Race						0.04
White	702 (90.6)	551 (89.7)	560 (86.4)	413 (90.2)	552 (92.3)	
Black	56 (7.2)	49 (8.0)	64 (9.9)	37 (8.1)	39 (6.5)	
Other	17 (2.2)	14 (2.3)	24 (3.7)	8 (1.7)	7 (1.2)	
Americas	433 (55.9)	370 (60.3)	380 (58.6)	215 (46.9)	176 (29.4)	<0.01
Spironolactone treatment arm	397 (51.2)	286 (46.6)	320 (49.4)	241 (52.6)	313 (52.3)	0.21
Clinical Characteristics						
SBP, mmHg	129.2 (13.8)	129.0 (13.8)	128.7 (15.0)	130.4 (13.0)	129.4 (12.4)	0.33
BMI, kg/m2	31.9 (6.9)	32.0 (7.6)	32.3 (7.1)	32.4 (6.7)	31.4 (6.3)	0.12
NYHA class III-IV	229 (29.6)	201 (32.7)	211 (32.6)	143 (31.2)	177 (29.6)	0.58
Alcoholic drinks per week						0.30
0	583 (75.2)	466 (76.0)	504 (77.8)	352 (76.9)	480 (80.3)	
1-5	141 (18.2)	116 (18.9)	105 (16.2)	77 (16.8)	100 (16.7)	
5-10	32 (4.1)	20 (3.3)	30 (4.6)	22 (4.8)	12 (2.0)	
10+	18 (2.3)	11 (1.8)	9 (1.4)	7 (1.5)	6 (1.0)	
Current smoking	76 (9.8)	52 (8.5)	58 (9.0)	48 (10.5)	82 (13.7)	0.08
Variability in SBP	11.0 (7.8)	11.4 (7.9)	11.1 (7.6)	11.1 (8.0)	9.6 (7.0)	<0.01
Variability in BMI	0.5 (0.6)	0.6 (0.7)	0.6 (0.6)	0.6 (1.0)	0.6 (0.9)	0.15
Medical History						
History of CVD	296 (38.2)	239 (38.9)	243 (37.5)	169 (36.9)	216 (36.1)	0.90
Atrial fibrillation	299 (38.6)	219 (35.7)	235 (36.3)	163 (35.6)	175 (29.3)	0.01
Diabetes status						0.03
None	539 (69.5)	412 (67.2)	415 (64.0)	304 (66.4)	443 (74.1)	
Insulin dependent	87 (11.2)	75 (12.2)	94 (14.5)	57 (12.4)	55 (9.2)	
Non-Insulin dependent	149 (19.2)	126 (20.6)	139 (21.5)	97 (21.2)	100 (16.7)	
ACEi/ARB medication	645 (83.3)	517 (84.2)	543 (83.8)	390 (85.2)	512 (85.6)	0.79
Loop diuretic medication	644 (83.2)	515 (83.9)	556 (85.8)	379 (82.8)	453 (75.8)	<0.01

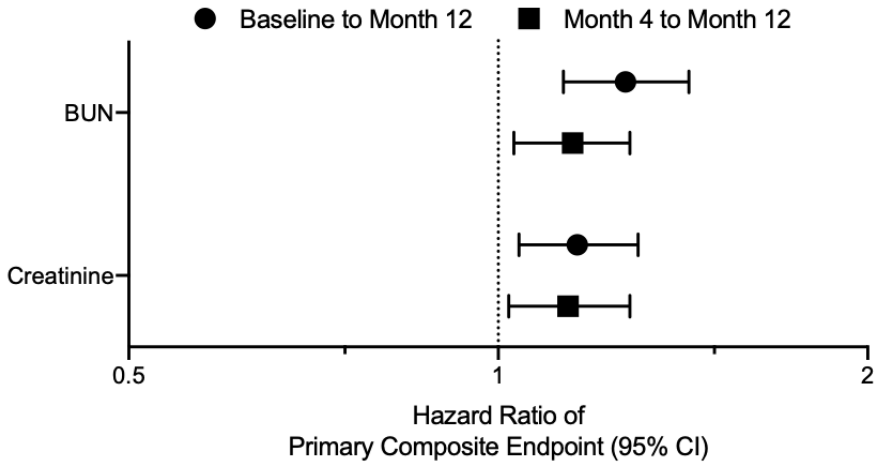
Average loop diuretic dose at baseline, mg	70.7 (99.8)	69.9 (84.9)	73.4 (114.6)	72.2 (85.4)	69.8 (66.9)	0.99
Average loop diuretic dose at month 4, mg	87.7 (107.6)	81.6 (93.6)	90.3 (157.7)	101.3 (116.7)	88.6 (89.3)	0.89
Laboratory						
Sodium, mmol/L	141.4 (4.0)	140.5 (9.2)	140.9 (3.9)	141.1 (8.0)	141.5 (5.0)	0.02
Potassium, mmol/L	4.3 (0.4)	4.2 (0.5)	4.2 (0.4)	4.2 (0.5)	4.2 (0.5)	0.10
Chloride, mmol/L	101.9 (10.3)	102.0 (10.6)	101.6 (11.3)	102.0 (10.5)	100.9 (12.9)	0.41
BUN, mg/dL	16.0 (11.6)	17.6 (14.5)	17.1 (13.5)	14.8 (14.0)	13.6 (13.7)	<0.01
Creatinine, mg/dL	1.1 (0.3)	1.1 (0.3)	1.1 (0.3)	1.1 (0.3)	1.1 (0.3)	0.04
Glucose, mg/dL	111.0 (41.8)	113.1 (45.4)	117.1 (55.8)	117.6 (50.1)	113.4 (50.7)	0.08
Hemoglobin, g/dL	13.3 (2.3)	13.2 (1.9)	13.1 (2.6)	13.4 (1.7)	13.3 (1.9)	0.05
BNP, pg/mL	362.8 (387.2)	331.1 (321.5)	324.3 (320.1)	460.7 (594.6)	390.7 (459.0)	0.07
NT-proBNP, pg/mL	1426.8 (1882.5)	1469.4 (1536.1)	1644.9 (2777.7)	1350.0 (1903.6)	1230.7 (2606.7)	0.73
Z-score	-0.0 (0.9)	-0.1 (0.7)	-0.0 (1.0)	0.1 (1.2)	-0.0 (1.1)	0.54

Abbreviations: ACEi/ARB, angiotensin converting enzyme inhibitor / angiotensin receptor blocker; SBP, systolic blood pressure; BMI, body mass index; NYHA, New York Heart Association; CVD, cardiovascular disease; BUN, blood urea nitrogen; BNP, brain natriuretic peptide; NT-proBNP, N-terminal prohormone brain natriuretic peptide

Supplemental Figure 1. The mean **A)** sodium, **B)** potassium, **C)** chloride, **D)** blood urea nitrogen (BUN), and **E)** creatinine for each visit.



Supplemental Figure 2. Sensitivity analyses: Associations of average successive variability (ASV) among kidney laboratory measures (blood urea nitrogen [BUN] and creatinine) from enrollment baseline to month 12 and from month 4 to month 12 with the primary composite outcome in the fully adjusted multivariable Cox proportional hazard model. Primary composite outcome is a composite of aborted cardiac arrest, hospitalization for management of heart failure, or cardiovascular death.



Supplemental Figure 3. Sensitivity analyses: **A)** blood urea nitrogen (BUN) and **B)** creatinine variability and risk of primary composite outcome across tertiles of the MAGGIC risk score. High/Low variability indicates variability above/below the median. Primary composite outcome is a composite of aborted cardiac arrest, hospitalization for management of heart failure, or cardiovascular death.