SUPPLEMENTAL MATERIAL

Table S1. Multivariable model of metolazone use utilized for propensity score determination.

Covariate	OR (95% CI)	P (Wald)
First dose of diuretic on admission in intravenous furosemide equivalents (per mg)	1.01 (1.007-1.01)	<0.001
Age at encounter (per year)	0.97 (0.96-0.98)	<0.001
Prior metolazone	3.01 (2.38-3.80)	<0.001
Blood urea nitrogen (mg/dL)	1.01 (1.009-1.02)	<0.001
Saint Raphael Campus vs. Yale New Haven Hospital	0.55 (0.46-0.65)	<0.001
Bridgeport Hospital vs. Yale New Haven Hospital	0.67 (0.54-0.83)	<0.001
Arrhythmia	1.85 (1.53-2.25)	<0.001
Fluid and electrolyte disorders	1.72 (1.43-2.07)	<0.001
Creatinine (mg/dL)	0.86 (0.81-0.93)	<0.001
Valvular disease	1.44 (1.20-1.73)	<0.001
Pulmonary circulatory disease	1.52 (1.23-1.88)	<0.001
Chloride (mEq/L)	0.96 (0.93-0.98)	<0.001
eGFR (ml/min/1.73m^2)	0.99 (0.986-0.996)	<0.001
Obesity	1.41 (1.16-1.71)	0.001
Hemoglobin (g/dL)	0.95 (0.92-0.98)	0.002
Drug abuse	0.58 (0.38-0.88)	0.011
Sodium (mEq/L)	1.03 (1.01-1.06)	0.011
Male sex	1.20 (1.03-1.40)	0.017
Diabetes with complications	1.33 (1.20-1.68)	0.019
Renal failure	1.48 (1.07-2.05)	0.019
White blood cell count	0.98 (0.97-0.998)	0.026
Anemia secondary to blood loss	0.54 (0.29-1.01)	0.055
Paralysis	0.35 (0.12-1.02)	0.055
Hypertension without complications	0.79 (0.62-1.02)	0.068
Platelet count	0.9993 (0.999-1.00)	0.068

Lymphoma	1.41 (0.91-2.18)	0.120
Diabetes without complications	1.16 (0.96-1.40)	0.125
Liver disease	1.22 (0.93-1.61)	0.150
COPD	0.87 (0.71-1.07)	0.192
Rheumatologic disease	0.80 (0.55-1.17)	0.257
Solid tumor without metastasis	0.78 (0.53-1.20)	0.277
Neurologic disease	0.85 (0.64-1.15)	0.307
Hypothyroidism	1.10 (0.90-1.35)	0.339
Elixhauser comorbidity index	0.96 (0.87-1.06)	0.282
Bicarbonate (mEq/L)	1.01 (0.99-1.03)	0.446
Coagulopathy	1.11 (0.83-1.49)	0.469
Metastatic cancer	0.83 (0.45-1.53)	0.549
Hypertension with complications	0.98 (0.73-1.33)	0.910
Readmission	0.99 (0.85-1.17)	0.940

AUC: 0.8312

Covariates presented in order of strongest to weakest predictors as determined by the absolute value of the z-score.

COPD: chronic obstructive pulmonary disease; eGFR: estimated glomerular filtration rate

Table S2. Relationships between metolazone and loop diuretic use with incident hyponatremia, incident hypokalemia and any WRF during heart failure hospitalization.

Outcome	Metolazone Hazard Ratio (95% CI)	P-Value	Loop Diuretic Hazard Ratio (95% CI)	P-Value
New Hyponatremia				
Univariate	2.50 (1.99-3.15)	<0.001	1.46 (1.30-1.63)	<0.001
Propensity Adjusted	2.23 (1.75-2.84)	<0.001	1.20 (1.05-1.38)	0.008
Propensity and MV Adjusted	2.06 (1.59-2.66)	<0.001	1.14 (0.97-1.34)	0.109
New Hypokalemia				
Univariate	2.96 (2.36-3.70)	<0.001	1.16 (1.03-1.32)	0.017
Propensity Adjusted	2.94 (2.34-3.69)	<0.001	0.96 (0.82-1.12)	0.580
Propensity and MV Adjusted	2.99 (2.34-3.81)	<0.001	0.96 (0.82-1.14)	0.672
Any WRF				
Univariate	2.31 (2.00-2.67)	<0.001	1.28 (1.19-1.37)	<0.001
Propensity Adjusted	2.50 (2.15-2.90)	<0.001	1.25 (1.16-1.35)	<0.001
Propensity and MV Adjusted	2.54 (2.17-2.97)	<0.001	1.23 (1.13-1.35)	<0.001

The unadjusted, propensity adjusted and propensity plus multivariable adjusted relationships between metolazone use and incident hyponatremia, incident hypokalemia, and any worsening renal function (WRF) as well as the relationships between increasing doses of loop diuretic are presented above. All metolazone propensity-adjusted analyses are also adjusted for peak loop diuretic dose received in the hospital in intravenous furosemide equivalents as a representation of loop diuretic requirement. Multivariable models included adjustment for age at encounter, race, sex, arrhythmia, valvular disease,

pulmonary circulatory disease, hypertension with and without complications, chronic obstructive pulmonary disease, diabetes with and without complications, hypothyroidism, renal failure, electrolyte disease, neurologic disease, paralysis, liver disease, lymphoma, malignancy with and without metastasis, rheumatologic disease, coagulopathy, obesity, anemia secondary to blood loss, drug abuse, Elixhauser comorbidity index, prior metolazone use, readmission, as well as baseline laboratory values including sodium, chloride, bicarbonate, blood urea nitrogen, white blood cell count, hemoglobin, platelets, glomerular filtration rate and length of stay. Any WRF was defined as a $\geq$ 20% decrease in estimated glomerular filtration rate from admission to the point of worst eGFR during the hospitalization. New hyponatremia was defined as a sodium level < 135 mEq/L and new hypokalemia was defined as a serum potassium <3.5 mEq/L that developed during the course of the hospitalization (i.e. patients with new electrolyte abnormalities did not meet these criteria at admission). All hazard ratios reported for furosemide are for every 100 mg of intravenous furosemide. MV: multivariable