SUPPLEMENTAL MATERIAL:

Tables:

Supplementary Table 1: Patient characteristics of the Penn cohort grouped by Peak diuretic efficiency:

	Diuretic Efficiency		
Characteristic	**Low (n=329)**	**High (n=328)**	**p-value**
Demographics			
Age (y)	65.8 ± 15.3	61.1 ± 15.3	<0.001*
Black race	66.5%	63.8%	0.484
Male	47.3%	61.9%	<0.001*
Medical History			
Hypertension	74.7%	72.0%	0.444
Diabetes	49.6%	38.2%	0.004*
Ischemic etiology	22.9%	27.4%	0.195
Ejection fraction ≥40%	34.0%	32.5%	0.692
Admission Physical Exam			
Heart rate (beats/min)	90.0 ± 20.3	89.1 ± 19.8	0.555
Systolic blood pressure (mmHg)	135.1 ± 36.1	135.8 ± 31.9	0.775
Jugular venous distention (≥ 12 cm water)	59.7%	61.6%	0.697
Edema > 1+	45.4%	47.2%	0.665
Hepatojugular reflux	22.5%	22.4%	0.989
Cardiac Function			
Ejection fraction (%)	28 (15, 45)	25 (15, 45)	0.307
Laboratory Values			
Serum sodium (mEq/L)	137.8 ± 5.2	138.7 ± 4.3	0.018*
B-type natriuretic peptide (pg/mL)	1529 (821, 2785)	1291 (659, 2348)	0.007*
eGFR (mL/min/1.73m^2)	53.3 ± 29.2	61.8 ± 26.7	<0.001*
BUN (mg/dL)	34.3 ± 24.2	27.9 ± 21.4	0.001*
Hemoglobin (g/dL)	11.8 ± 2.0	12.3 ± 2.1	0.010*
Right atrial pressure (mmHg)	11.9 ± 7.1	11.2 ± 6.7	0.573
Pulmonary capillary wedge pressure (mmHg)	23.1 ± 8.2	23.9 ± 8.4	0.583
Cardiac index (L/min/m^2)	2.1 ± 0.8	2.0 ± 0.5	0.387
Systemic vascular resistance (dyn·s/cm^5)	19.0 ± 7.9	20.4 ± 7.3	0.292
Medications (Admission)			
Beta blocker	67.3%	73.8%	0.077

ACE inhibitor or ARB	55.9%	68.4%	0.001*
Digoxin	22.0%	28.0%	0.092
Aldosterone antagonist	12.2%	20.0%	0.011*
Loop diuretic dose (mg)	80 (0, 160)	40 (20, 80)	0.033*
Thiazide diuretic	16.7%	10.2%	0.015*
Medications (Discharge)			
Beta blocker	67.3%	73.8%	0.077
ACE inhibitor or ARB	67.7%	85.0%	<0.001*
Digoxin	22.5%	26.9%	0.212
Aldosterone antagonist	15.7%	27.4%	0.001*
Loop diuretic dose (mg)	80 (40, 160)	80 (40, 160)	0.133
Thiazide diuretic	14.8%	7.1%	0.002*

eGFR: Estimated glomerular filtration rate, BUN: Blood urea nitrogen, ACE: Angiotensin converting enzyme inhibitor, ARB: Angiotensin receptor blocker. Diuretic efficiency was calculated as the average daily net fluid loss divided by the peak dose of loop diuretic administered in 24 hours (per 40 mg furosemide equivalents). Diuretic efficiency was then dichotomized about the median value in the ESCAPE trial (148 ml/40 mg) to allow direct comparison between cohorts.* Significant p value.

Supplementary Table 2: In hospital parameters of the Penn cohort grouped by Peak diuretic efficiency using the cut point from the ESCAPE trial:

	Diuretic Efficiency		
Characteristic	**Low (n=329)**	**High (n=328)**	**p-value**
Diuresis Related Parameters			
Cumulative IV loop diuretic dose (mg)	380 (160, 830)	240 (120, 495)	<0.001*
Average daily IV loop dose (mg/day)	60 (28, 114)	50 (24, 87)	0.008*
Peak IV loop diuretic dose in 24 hours (mg)	160 (80, 260)	80 (80, 160)	<0.001*
Continuous diuretic infusion	9.4%	2.4%	<0.001*
Adjuvant thiazide diuretic	20.1%	12.7%	0.011*
Time receiving IV diuretic (% of hospitalization)	64.9 ± 24.9	65.3 ± 24.9	0.867
Net fluid loss (L)	-1.2 (-5.1, 0.5)	-5.5 (-9.4, -3.1)	<0.001*
Fluid intake (L)	7.9 (5.1, 13.2)	6.3 (4.1, 9.9)	<0.001*
Fluid output (L)	9.7 (5.3, 16.0)	12.1 (7.5, 19.6)	<0.001*
Average net daily fluid loss (L)	0.2 (0.1, 0.6)	1.0 (0.7, 1.5)	<0.001*
Diuretic efficiency (mL fluid output/40mg furosemide equivalents)	122.6 (-79.3, 255.0)	832.8 (483.1, 1497.3)	<0.001*
Estimated peak dose diuretic efficiency (mL fluid output/40 mg furosemide equivalents)	56.4 (-34.6, 110.1)	382.8 (251.1, 638.8)	<0.001*
In-hospital inotropes			
Milrinone	19.5%	12.3%	0.014*
Dobutamine	3.0%	0.2%	0.003*
In-Hospital Maximum Change in Laboratory Parameters			
eGFR (%)	19.1 ± 16.2	14.0 ± 13.7	<0.001*
Worsening renal function	41.4%	31.1%	0.007*
Blood urea nitrogen (%)	-51.8 ± 57.6	-35.3 ± 45.1	<0.001*
Bicarbonate (%)	-21.0 ± 17.7	-22.6 ± 46.4	0.606
Admission to Discharge in Laboratory Parameters			
eGFR (%)	-0.8 ± 29.1	-2.0 ± 24.2	0.560
Worsening renal function	20.9%	13.9%	0.019*
Blood urea nitrogen (%)	-30.3 ± 56.7	-18.6 ± 48.3	0.007*
Bicarbonate (%)	-10.5 ± 18.2	-13.8 ± 47.5	0.299
Sodium (%)	0.9 ± 5.6	0.8 ± 3.0	0.764
Hospital Course			
Length of stay (days)	7 (4, 11)	5 (4, 8)	<0.001*
Discharge Physical Examination			

Jugular venous distention (≥ 8 cm H2O)	19.8%	20.1%	0.942
Edema > 1+	18.1%	15.1%	0.318
Hepatojugular reflux	3.8%	3.5%	0.898

eGFR: Estimated glomerular filtration rate. * Significant p value.

Supplementary Table 3: Univariate and multivariate associations with mortality in the Penn and ESCAPE cohorts

	Penn Cohort				
Univariate	**HR (95% CI)**	**P Value**	**Final model**	**HR (95% CI)**	**P Value**
Loop diuretic	1.6 (1.3-1.9)	<0.001	Loop diuretic	1.2 (0.9-1.6)	0.132
Net fluid output	1.0 (0.8-1.2)	0.929	Net fluid output	1.0 (0.7-1.2)	0.78
Diuretic efficiency	1.6 (1.3-2.0)	<0.001	Diuretic efficiency	1.4 (1.0-1.8)	0.023
Age (years)	1.03 (1.02-1.04)	<0.001	Age (per 10 years)	1.4 (1.2-1.5)	<0.001
Heart rate (per 10 BPM)	0.90 (0.86-0.95)	<0.001			
Systolic blood pressure (per 10 mmHg)	0.90 (0.87-0.93)	<0.001	Systolic blood pressure (per 10 mmHg)	0.92 (0.88-0.96)	<0.001
Loop dose at baseline (per 100 mg)	1.1 (1.05-1.2)	<0.001			
Serum sodium (per 5 meq/l)	0.79 (0.71-0.88)	<0.001	Serum sodium (per 5 meq/l)	0.89 (0.79-1.0)	0.071
Hemoglobin (g/dl)	0.89 (0.85-0.94)	<0.001			
Log B-type natriuretic peptide (pg/ml)	1.8 (1.3-2.4)	<0.001			
eGFR (per 10 ml/min/1.73m^2)	0.89 (0.85-0.92)	<0.001			
Blood urea nitrogen (per 10 mg/dl)	1.2 (1.2-1.2)	<0.001	Blood urea nitrogen (per 10 mg/dl)	1.1 (1.1-1.2)	<0.001
Black race	0.79 (0.64-0.98)	0.034	Race	1.3 (1.0-1.7)	0.043
Diabetes	1.2 (0.97-1.5)	0.093			
Ischemic etiology for HF	1.4 (1.1-1.8)	0.002			
Baseline edema	1.4 (1.1-1.7)	0.004			
Baseline digoxin use	1.4 (1.1-1.7)	0.008	Digoxin use	1.4 (1.1-1.8)	0.011
Baseline thiazide diuretic use	1.5 (1.1-2.0)	0.01	Thiazide diuretic use	1.3 (0.92-1.7)	0.143

ESCAPE Cohort

Univariate	HR (95% CI)	P Value	Final model	HR (95% CI)	P Value
Loop diuretic	2.5 (1.5-3.9)	<0.001	Loop diuretic	1.3 (0.7-2.4)	0.366
Net fluid output	1.0 (0.6-1.5)	0.86	Net fluid output	1.2 (0.7-2.1)	0.59
Diuretic efficiency	4.0 (2.3-6.8)	<0.001	Diuretic efficiency	2.9 (1.5-5.4)	0.001
Age (per 10 years)	1.3 (1.1- 1.5)	0.012	Age (per 10 years)	1.2 (0.94-1.5)	0.158
Systolic blood pressure (per 10 mmHg)	0.88 (0.76-1.0)	0.08			
Loop dose at baseline (per 100 mg)	1.2 (1.1-1.3)	<0.001	Loop dose at baseline (per 100 mg)	1.2 (1.0-1.3)	0.018
Serum sodium (per 5 meq/l)	0.67 (0.54-0.83)	<0.001	Serum sodium (per 5 meq/l)	0.80 (0.62-1.00)	0.096
Hemoglobin (per 1 g/dl)	1.04 (1.00-1.08)	0.043	Hemoglobin (per 1 g/dl)	1.04 (1.00-1.07)	0.041
eGFR (per 10 ml/min/1.73m^2)	0.79 (0.70-0.88)	<0.001			
Blood urea nitrogen (per 10 mg/dl)	1.3 (1.2-1.4)	<0.001	Blood urea nitrogen (per 10 mg/dl)	1.2 (1.1-1.3)	<0.001
Hypertension	0.70 (0.44-1.1)	0.124	Hypertension	0.58 (0.34-0.98)	0.043
Ischemic etiology for HF	2.1 (1.3-3.4)	0.003	Ischemic etiology for HF	1.54 (0.86-2.7)	0.143
Baseline beta blocker	0.67 (0.42-1.0)	0.079	Baseline beta blocker	0.60 (0.36-0.99)	0.046
Baseline ACE or ARB	0.43 (0.24-0.78)	0.006			
Baseline thiazide diuretic use	1.9 (1.1-3.3)	0.027			
Baseline jugular venous distension	1.5 (0.9-2.4)	0.088			
Baseline edema	1.9 (1.2-3.0)	0.006			

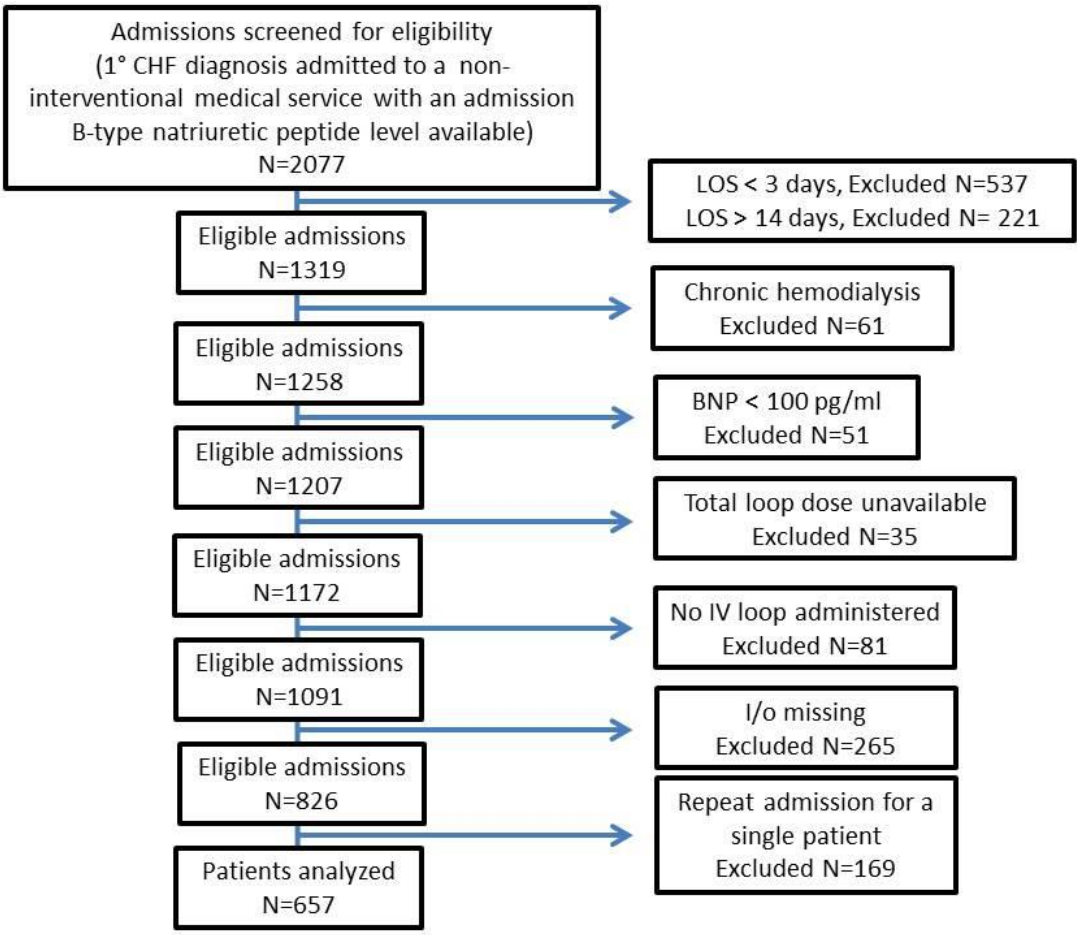
Supplementary Table 4: Association between diuretic efficiency and mortality in patients with and without preserved ejection fraction in the Penn cohort.

Patients with:	HR (95% CI)	p Value	p interaction
Ejection Fraction <40%	1.8 (1.4-2.4)	<0.001*	
Ejection Fraction ≥40%	1.4 (1.0-2.0)	0.074	0.245
Ejection Fraction <50%	1.8 (1.4-2.3)	<0.001*	
Ejection Fraction ≥50%	1.3 (0.9-2.1)	0.209	0.255

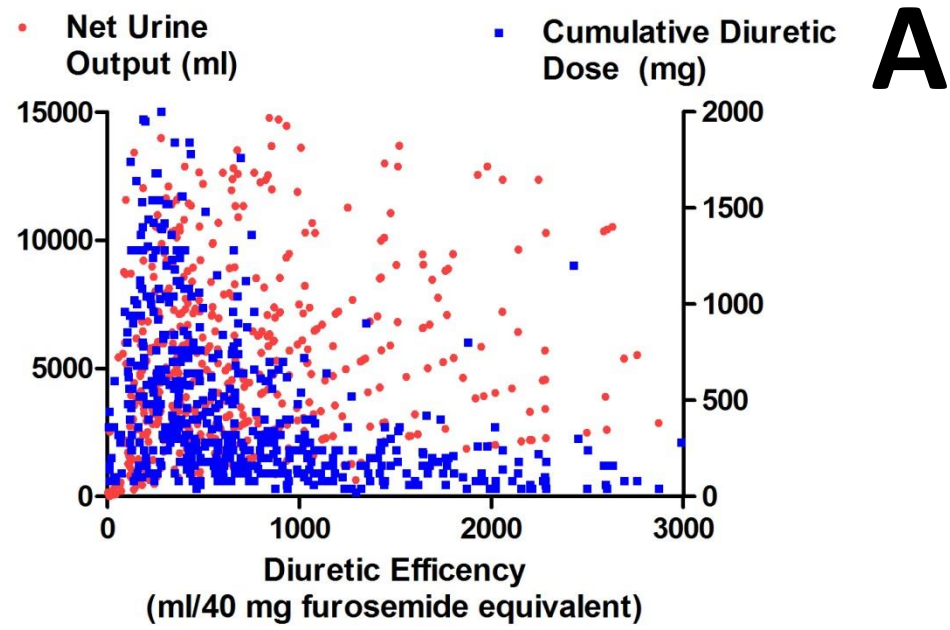
HR: Hazard ratio, CI: Confidence interval. Hazard ratios represent cumulative diuretic efficiencies below compared to above the median value.

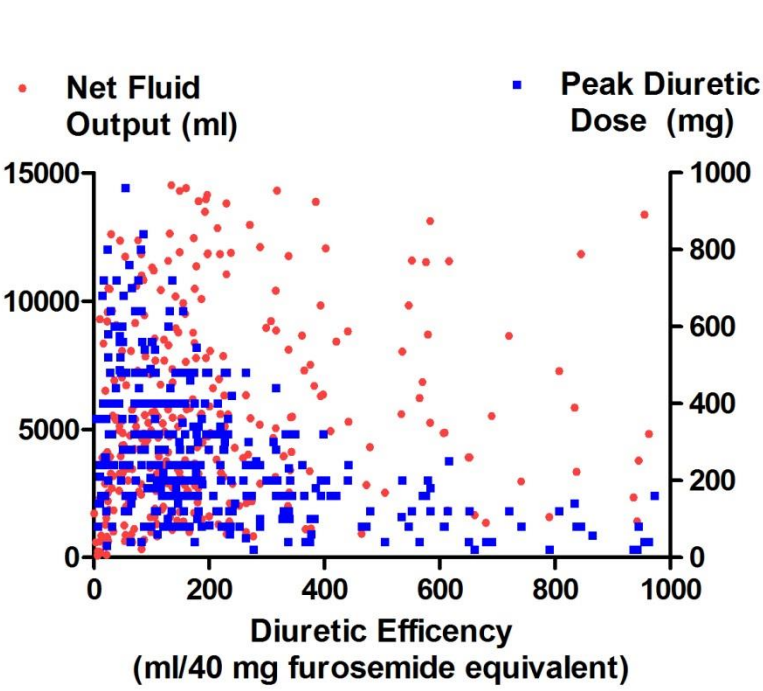
Figures:

Supplementary Figure 1: Consort diagram for the Penn Cohort

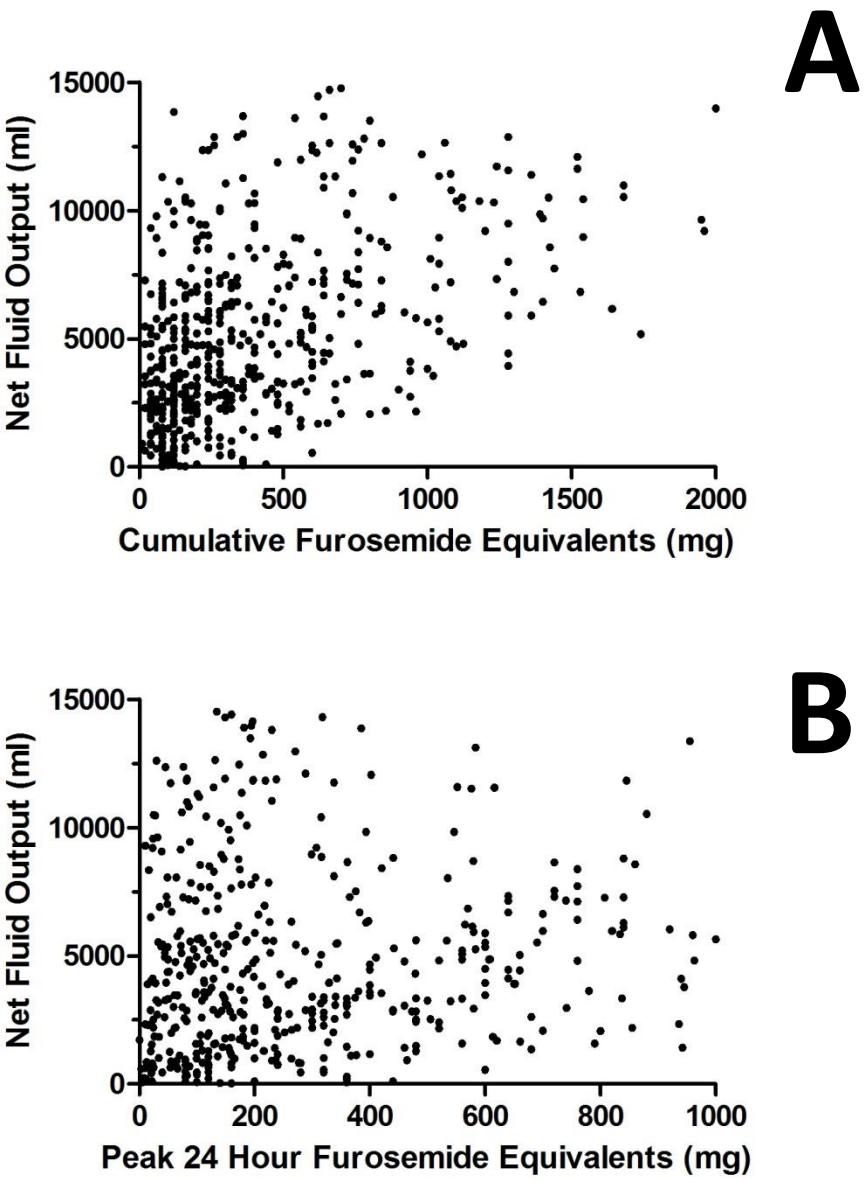


Supplementary Figure 2: Scatterplots of diuretic efficiency, loop diuretic dose, and net fluid output in the Penn (Panel A) and ESCAPE cohorts (Panel B)





Supplementary Figure 3: Scatterplots of loop diuretic dose and net fluid output in the Penn (Panel A) and ESCAPE cohorts (Panel B)



Supplementary Figure 4: Kaplan-Meier survival curves grouped by quartiles of diuretic efficiency in the Penn cohort (Panel A) and ESCAPE cohort (Panel B)