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Blood-Pressure Reduction Is Associated With Worsening In Renal Function But Does Not Prevent Successful Decongestion In Patients Treated For Acute Decompensated Heart Failure

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Blood-Pressure Reduction is Associated With Worsening in Renal Function but Does Not Prevent Successful Decongestion in Patients Treated for Acute Decompensated Heart Failure

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By

Alexander James Kula

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Abstract:

Background: Reductions in blood pressure are common during the treatment of acute decompensated heart failure (ADHF) and strongly associated with worsening renal function (WRF). However, it is unclear whether a decline in systolic blood pressure (SBP), and the associated deterioration in renal function, might limit successful diuresis.

Methods: We analyzed consecutive admissions with a primary discharge diagnosis of ADHF (n=657). Metrics of diuresis were assessed for their association with a decline in SBP from admission to discharge in addition to the use or titration of guideline recommended heart failure therapies (GDMT). SBP-reduction was defined as a relative reduction in SBP greater than the median value (>9.9%).

Results: Overall 77.6% of the population had a discharge SBP lower than the admission value. SBP-reduction resulted in significantly higher rates of WRF (OR= 1.9, p=0.004). Despite the negative impact on renal function, SBP-reduction was not associated with worse diuretic efficiency (p=0.274). Furthermore, the rate of hemoconcentration, net fluid loss, weight loss, adjuvant thiazide diuretic use, and loop diuretic infusion use was not different for patients with an SBP-reduction (p≤0.293for all). GDMT such as ACE-Is and beta blockers were associated with SBP-reduction but not with metrics of decongestion.

Conclusion: Despite apparent negative effects on renal function, a reduction in blood pressure or titration of GDMT did not appear to limit successful decongestion.

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Introduction:

Acute decompensated heart failure (ADHF) is a serious problem affecting over 1,000,000 Americans annually and is the most common hospital discharge diagnosis among Medicare beneficiaries.[1] A diagnosis of ADHF carries with it a poor prognosis with a one-year post-discharge mortality of 33%.[2-4] Six month readmission rates stand near 50%, reflecting the challenging problem of effectively managing ADHF.[5] The economic burden associated with ADHF is substantial and accounts for more than half of all heart failure expenditures.[6] To date, ADHF research has enjoyed limited success aside from the description of the poor survival associated with this condition.[7]

Underlying the challenge in treating ADHF are the complex pathophysiologic mechanisms involved in its genesis. On a fundamental level, ADHF is predominantly a disease of congestion and volume overload.[8,9] Patients suffering from ADHF often present with signs of excess volume such as peripheral edema, jugular venous distention, and dyspnea. Consequently, returning patients to a euvolemic state remains the primary treatment goal and one of the strongest predictors of survival in patients with heart failure. [10,11] The presence of volume overload likely plays a pathologic role and directly contributes to heart failure disease progression.[12] Venous congestion leads to increased sympathetic activity and activation of the renin-angiotensin-aldosterone system (RAAS), both of which increase cardiac strain and induce pathologic remodeling of the myocardium.[13] From a clinical standpoint, neurohormonal activation leads to progression of heart failure and worse outcomes.[14] Taking all of this information into consideration, finding effective treatments paradigms to remove volume in ADHF has been a top priority.

Loop diuretics have a longstanding utility in ADHF and remain the mainstay of therapy in congestive heart failure.[15] While treatment with loop-diuretics proves to be effective, there are limitations and drawbacks to its intensive and prolonged use.[16] Loop-diuretics inherently function to induce volume loss through natriuresis. One early-identified phenomenon was that repeated dosing results in reduced natriuresis and efficacy of the subsequent dose. This occurs on a dose-to-dose basis in a phenomenon known as diuretic braking.[17] It also occurs on a long-term, progressive basis which is termed diuretic resistance.[18] Both of these issues arise from renal compensation stemming from exposure to loop-diuretics. Increased sodium delivery to the tubule with diuretic therapy results in tubular hypertrophy, increased sodium absorption, and decreased diuretic responsiveness.[18,19] Furthermore, neurohormonal activation in response to diuretic therapy supports the tubular and vascular compensatory mechanisms that result in increased sodium avidity by the kidney and decreased diuretic responsiveness. To reach the important goal of decongestion, the dose of loop-diuretics is increased to overcome resistance. However, increased doses of loop-diuretics are linked to neurohormonal activation, and poorer outcomes.[20,21] Consequently, new heart failure treatment strategies must consider maintaining responsiveness to loop-diuretics while aiming to effectively remove excess fluid.

Guideline directed medical therapies (GDMT) temper the negative effects of neurohormonal activation that is the consequence of both ADHF physiology and diuretic therapy. Accordingly, initiating and increasing the dosages of these medications is another important goal recommended by heart failure guidelines to reduce mortality and disease progression.[22-24] The primary GDMTs include angiotensin converting enzyme

inhibitors (ACE-Is), Angiotensin II receptor blockers (ARBs), beta-blockers, and mineralocorticoid receptor antagonists (MRAs). Inhibition of the renin-angiotensin-aldosterone-system with ACE-Is reduces mortality, and this effect has been repeatedly proven in large clinical trials.[25-27] For patients who cannot tolerate ACE-Is, ARBs can be utilized as several large studies validated that they are comparable in efficacy.[28,29] Both of these medicines work to reduce mortality in heart failure by several mechanisms, many of which are still in the process of being studied. One readily observed action of ACE-Is/ARBs is to lower blood pressure, counteracting the vasoconstrictive effects and increased sodium reabsorption resulting from RAAS activation. RAAS mediated cardiac fibroblast proliferation and cardiomyocyte apoptosis that cause ventricular remodeling are also likely reduced both by lowering blood pressure and by the direct action of these medications on cardiac tissue.[30,31] However, side effects of these medications include cough (with ACE-Is), hyperkalemia, and a decrease in GFR. Beta-blockers are another important pillar of heart failure therapy. They are a longstanding component of therapy, and their use in heart failure is supported by multiple, large studies in the literature.[32-34] These medications work by inhibiting different elements of beta-adrenergic activation, reducing cardiac strain and oxygen consumption by lowering heart rate and cardiac contractility.[34] Finally, spironolactone and eplerenone are MRAs that function by displacing aldosterone from the mineralocorticoid receptor in the collecting duct of the nephron. Eplerenone additionally has been shown to reduce the aldosterone-mediated cardiac remodeling, demonstrating the advantages drawn from the direct effect of these medications on cardiac tissues.[35] As such, their use is recommended by guidelines

following major trials that demonstrated a survival benefit with the use of MRAs in heart failure.[36-38]

One consideration with the use of GDMT is the reduction of blood pressure caused by these therapies. The systolic blood pressure (SBP) decreases in response to ADHF therapy through combinations of the direct vascular effects of the medications, reduced cardiac contractility, and volume reduction. In some ways, this is a desirable outcome, and chronic therapies are tailored to reduce longstanding elevations in blood pressure. Hypertension is a common co-morbidity in heart failure, and on a chronic basis is associated with adverse cardiovascular morbidity and mortality. Accordingly, society guidelines recommend lowering blood pressure to improve cardiovascular outcomes and survival.[22] However, short-term reductions in blood pressure during hospitalization for ADHF may be antagonistic to the primary acute goals of ADHF therapies.

An emerging signal is that a decline in blood pressure during hospitalization strongly links to worsening renal function (WRF) during the treatment of ADHF. [39-42] WRF is an adverse outcome in heart failure, and is often defined in the literature as either a >20% decrease in GFR or a creatinine increase of 0.3 mg/dL.[43] Initial studies of WRF discovered that WRF was both a common feature in heart failure, and associated with a worse prognosis.[44] Relatedly, cardiorenal syndrome develops frequently in patients with heart failure. Cardiorenal syndrome is defined by a decrease in kidney function associated with heart failure. This loose definition incorporates kidney disease leading to cardiovascular disease, acute kidney injury in response to hear failure, and primarily, compromise of kidney function secondary to congestive heart failure.[45] Originally, decreases in cardiac output and blood pressure secondary to the hemodynamic

derangements of heart failure were thought to decrease renal perfusion and lead to damage. However, venous congestion has proven to more closely correlate with WRF while parameters of cardiac output poorly associate with WRF.[46,47] This new paradigm links the unfavorable prognosis seen with congestion, neurohormonal activation, and WRF. As our understanding of the cardiorenal syndrome grows, new opportunities are realized for improving ADHF outcomes.

It has become apparent that the cause of WRF is of more prognostic relevance than WRF itself.[43] Notably, WRF associated with SBP-reduction proved to be a phenotype not linked to worse prognosis, thus demonstrating the need for a better understanding of the relationship between blood pressure and WRF during ADHF.[42] Normally, maintenance of GFR across a wide range of blood pressures occurs primarily through renal autoregulation at the level of the glomerulus. The two primary mechanisms employed by the kidney to maintain GFR are tubuloglomelular feedback (TGF) and myogenic feedback. Both of these mechanisms ensure protection of the delicate glomerulus during periods of elevated blood pressure and maintenance of GFR as blood pressure decreases. TGF works by utilizing the macula densa to infer changes in blood pressure through the distal tubule flow. Nevertheless, recent data indicates that the myogenic response is the primary autoregulatory mechanism, especially in protecting the glomerulus from increases in blood pressure.[48] The myogenic response acts by measuring perturbations in blood pressure through stretch receptors in the afferent arteriole. Vascular tone of the afferent arteriole is then either increased or decreased in response to high or low blood pressure, respectively. The predominance of the myogenic response to

fluctuations in blood pressure explains why GFR is predominantly pressure dependent rather than flow dependent.[49] Moreover, it has been demonstrated that changes

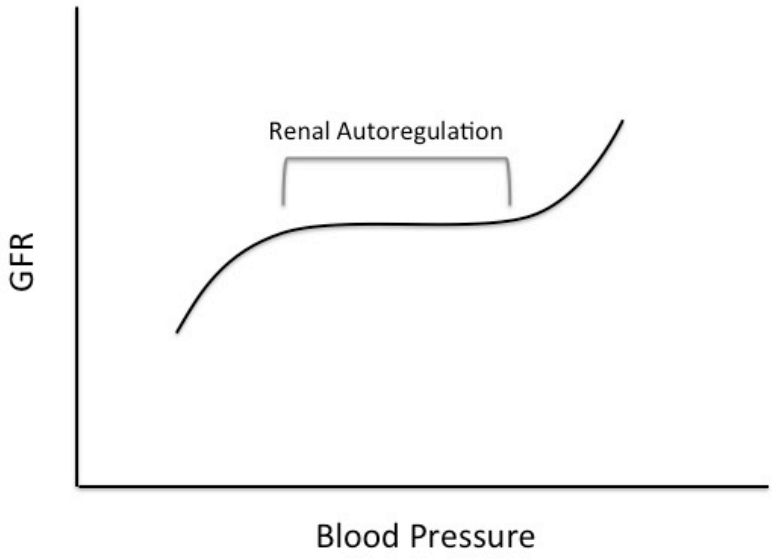

Figure 1: Theoretical diagram demonstrating the maintenance of GFR over a wide range of blood pressure by the process of renal autoregulation.

in systolic blood pressure, rather than diastolic blood pressure, is the primary stimulus for the myogenic autoregualtion. [48]

Despite the robust autoregulation seen in normal subjects, the GFR of ADHF patients is linked closely with changes in blood pressure. Congestive heart failure presents a unique environment in which the mechanisms for autoregulation are impaired.[50] Often this is attributable to damage of the regulatory mechanisms that occur

with common co-morbidities of heart failure. Longstanding hypertension leads to pathologic remodeling of the afferent arteriole which subsequently damages the ability to autoregulate.[51] Furthermore, the presence of diabetes can lead to alterations in both the vascular and possibly tubular components of renal autoregulation.[52]

Figure 2: Risk of WRF correlates to change in SBP in heart failure patients. *Adopted form Dupont, Eur. J. Heart Failure, 2013*

When examining the components of ADHF therapy, and their physiologic manifestations, the question arises whether they can ever be counterproductive. Many of the therapies currently employed in ADHF result in a reduction in blood pressure. Guidelines recommend using hospitalization for ADHF as an opportunity to optimize or initiate chronic oral medications such as beta-blockers, ace-inhibitors, and vasodilators, leading to the opportunity for further iatrogenic reduction in blood pressure. [23,24,53] Given that a reduction in blood pressure during the treatment of ADHF is strongly associated with WRF, and considering the kidney is the primary conduit by which volume is removed, it is unclear if elective titration of vasodilators and neurohormonal antagonists

may be contrary to the immediate goal of fluid removal in ADHF. Society guidelines do not address how, or if, these goals can be achieved simultaneously due to the paucity of evidence on the subject in the current literature.

Statement of Purpose:

To date, there is little research outlining the effect that initiating or increasing GDMT has on diuretic therapy during ADHF hospitalization. An important element to this puzzle is whether changes in systolic blood pressure impact diuresis with loop-diuretics. Especially when considering the failure of renal autoregulatory mechanisms in ADHF and the high rates of WRF as blood pressure decreases. Despite these challenges, further research is necessary to allow for evidence-based decision making for clinicians treating heart failure patients. This study acts as a first step in directly addressing this issue.

Aim 1: Determine whether a decrease in blood pressure from admission to discharge will affect decongestion as assessed by diuretic efficiency

Hypothesis 1: SBP-reduction, defined as a greater than median decrease in SBP from admission to discharge, will not reduce diuretic efficiency

Aim 2: Investigate the effect of initiating or titrating guideline recommended medications during hospitalization on blood pressure, renal function, and decongestion.

Hypothesis 2: GDMTs will increase rates of blood-pressure reduction and WRF, but will not affect diuretic efficiency.

Methods:

Cohort:

The study population was drawn from consecutive admissions to the Hospital of the University of Pennsylvania cardiology and internal medicine services between 2004 and 2009. Inclusion required a B-type natriuretic peptide (BNP) level of > 100pg/mL within 24 hours of admission, receipt of intravenous loop diuretics, and availability of data on fluid intake and output during the hospitalization. Patients selected had a length of stay between 2 and 14 days (excluding patients who underwent limited or extensive/complicated decongestion). Patients requiring renal replacement therapy were excluded. In the event of multiple hospitalizations for a single patient, only the first admission that satisfied the inclusion and exclusion criteria was used. Overall, a total of 657 were included in the cohort. The Social Security Death Index was used to determine all-cause mortality. Patient status was determined 2.5 years after discharge of the last patient in the data set.[54]

Variable Definitions:

The admission SBP was calculated as the average of the first 3 recorded values in the chart and discharge SBP from the last three. The relative (%) change in SBP was calculated by dividing the absolute SBP change by the calculated admission SBP. Glomerular Filtration Rate (GFR) was calculated using the four variable Modification in Diet for Renal Disease (MDRD) formula. WRF was defined as ≥ 20% decrease in GFR. This previously utilized definition accounts for the non-linear relationship between renal function and serum creatinine.[43,55] Conversely, improvement in renal function (IRF) was

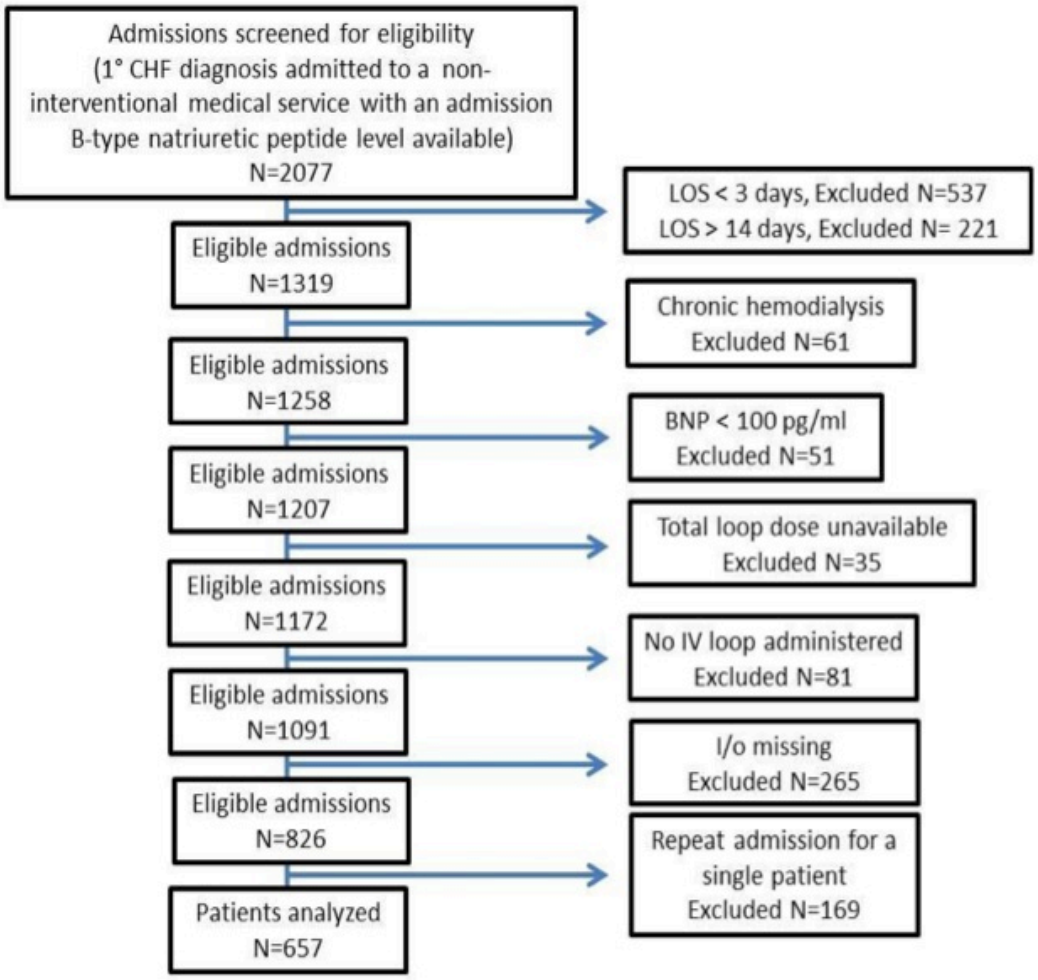

Figure 3: Consort Diagram

defined as a ≥20% increase in GFR. Comparisons in GFR were from admission to discharge unless otherwise stated. The average daily net fluid balance is the total net input/output divided by the length of stay (LOS). Hemoconcentration was defined as an increase in both hemoglobin (hgb) and hematocrit (hct) at discharge as compared to admission values consistant with our prior description of hemoconcentration in this populaiton.[56]

Loop diuretic doses were converted to furosemide equivalents with 1mg bumetanide = 20 mg torsemide = 80 mg furosemide for oral doses, and 1mg bumetanide = 20 torsemide = 40 furosemide for intravenous doses.[57,58] The total loop diuretic given during hospitalization is the sum of the total oral and IV loop diuretics given from admission to discharge. Diuretic efficiency (DE) was calculated by dividing the total net output during hospitalization by total IV loop-diuretic dose (40mg IV furosemide equivalents) during hospitalization.[59] High diuretic efficiency was defined as values above the median. For medication analysis, angiotensin converting enzyme inhibitors (ACE-Is) were converted to lisinopril equivalents and Angiotensin II receptor blockers (ARBs) were converted to losartan equivalents for comparison.

Statistical analysis:

Values are reported as Mean ± standard deviation or median with interquartile range for continuous variables, and proportion (%) for discrete variables. Student *t* test or Wilcoxon rank-sum test was used to compare continuous variables between 2 groups of patients. The independent-Samples Kruskal-Wallis Test was used to compare values across the quintiles of relative decline in SBP. Proportions for baseline variable and study analysis were examined using the χ^2test. Odds-ratio, 95% confidence intervals, and p-values for the comparison of two nominal variables were computed using binary logistic regression.

The independent association between blood-pressure and medication variables associated with DE was determined using logistic regression. Baseline variables with a univariate association with DE at $p<0.2$ were entered into this model to adjust for potential confounding variables. These included age, sex, hematocrit, hemoglobin, BNP,

creatinine, and sodium, eGFR, ejection fraction, hypertension, diabetes, ace-inhibitor or ARB, beta-blocker, thiazides, and hydralazine.

Cox proportional hazards modeling was used to evaluate time-to event associations with all-cause mortality. Candidate covariates entered into the model were relevant baseline characteristics with less than 10% missing values and a univariate association with mortality at $p<0.2$. These variables included: age, race, diabetes mellitus, ischemic HF cause, presence of edema, digoxin use, outpatient loop diuretic dose, thiazide diuretic use, heart rate, systolic blood pressure, B-type natriuretic peptide, serum sodium, hemoglobin, GFR, and blood urea nitrogen. Other covariates with a theoretical potential for confounding but a univariate association with mortality at $p>0.2$ were forced into the model. Models were built using backward elimination such that covariates with an association with mortality at $p<0.2$ were retained.[60] P-values<0.05 were considered significant. Statistical analysis was performed with IBM SPSS Statistics version 21.0 (IBM Corp, Armonk, NY).

SPSS Coding:

Calculated variables and examples provided for each statistical analysis used:

eGFR:

```
compute AdmitUnadjustedGFR= 175*(AdmitCreat**-1.154)*(AGE**-0.203).
if RACE eq 2 and sex eq 2 GFRadmit=AdmitUnadjustedGFR*1.212*0.742.
if RACE eq 2 and sex eq 1 GFRadmit=AdmitUnadjustedGFR*1.212.
if RACE ne 2 and sex eq 2 GFRadmit=AdmitUnadjustedGFR*0.742.
if RACE ne 2 and sex eq 1 GFRadmit=AdmitUnadjustedGFR.
```

Patients Taking 2 of 3 GDMT (same or increased dosage):

```
compute GDMT2of3=0.
if ACE_ARB_sameORincr=1 and BB_sameORincr=1 GDMT2of3=1.
if ACE_ARB_sameOrincr=1 and Spiro_given_IH=1 GDMT2of3=1.
if BB_sameORincr=1 and SPiro_given_IH=1 GDMT2of3=1.
```

Patients Taking 2 of 3 GDMT (increased dosage only):

```
compute GDMTincr2of3=0.
if ACE_ARB_incr=1 and BB_increase=1 GDMTincr2of3=1.
if ACE_ARB_incr=1 and Spiro_newstart=1 GDMTincr2of3=1.
if BB_increase=1 and SPiro_newstart=1 GDMTincr2of3=1.
```

Determining the frequencies, mean, median, standard deviation, and interquartile range for study variables:

```
FREQUENCIES VARIABLES=deltaSBPavg deltaSBPavg_per
  /NTILES=4
  /STATISTICS=STDDEV MEAN MEDIAN
  /ORDER=ANALYSIS.
```

Chi-square:

```
CROSSTABS
  /TABLES=deltaSBPavg_perMedian BY WRF20GFR_AD
  /FORMAT=AVALUE TABLES
  /STATISTICS=CHISQ RISK
  /CELLS=COUNT ROW COLUMN
  /COUNT ROUND CELL.
```

Unadjusted Binary Logistic Regression:

```
LOGISTIC REGRESSION VARIABLES mgperMLmedianAK
  /METHOD=ENTER deltaSBPavg_perMedian
  /PRINT=CI(95)
  /CRITERIA=PIN(0.05) POUT(0.10) ITERATE(20) CUT(0.5).
```

Adjusted Binary Logistic Regression (*dependent variable*, **independent variable of interest**, relevant baseline variables for adjustment):

```
LOGISTIC REGRESSION VARIABLES mgperMLmedianAK
  /METHOD=ENTER deltaSBPavg_perMedian Loop_B Age Sex AdmitCreat
admitBUN admitHct AdmitHGB AdmitNA BNP EF HTN DM
    ACEorARB_B BaselineBB Thiazide_B hydralazine_B GFRadmit
  /Print=CI(95)
  /CRITERIA=PIN(.05) POUT(.10) ITERATE(20) CUT(.5).
```

Student t test:

```
T-TEST GROUPS=deltaSBPavg_perMedian(0 1)
  /MISSING=ANALYSIS
  /VARIABLES=LOS
  /CRITERIA=CI(.95).
```

Wilcoxon rank sum test:

```
NPTESTS
  /INDEPENDENT TEST (mlPERMG) GROUP (deltaSBPavg_perMedian)
  /MISSING SCOPE=ANALYSIS USERMISSING=EXCLUDE
  /CRITERIA ALPHA=0.05  CILEVEL=95.
```

Independent-Samples Kruskal-Wallis Test:

```
NPTESTS
  /INDEPENDENT TEST (mlPERMG) GROUP (deltaSBPavg_per_quint)
  /MISSING SCOPE=ANALYSIS USERMISSING=EXCLUDE
  /CRITERIA ALPHA=0.05  CILEVEL=95.
```

Unadjusted Cox-Regression Model:

```
COXREG TimeinStudy_6_14_12
  /STATUS=Death_YN_6_14_12(1)
  /METHOD=ENTER deltaSBPavg_perMedian
  /PRINT=CI(95)
  /CRITERIA=PIN(.05) POUT(.10) ITERATE(20).
```

Adjusted Cox-Regression Model:

```
COXREG TimeinStudy_6_14_12
  /STATUS=Death_YN_6_14_12(1)
  /METHOD=ENTER deltasbpavg_permedian Age HR SBPavg  loop_B  AdmitNA
AdmitHGB BNP GFRadmit admitBUN Race DM ischemicEtiology EdemaQuart
Digoxin_B Thiazide_B ThiazideDis IH_ACE_ARB_yn LoopDis  DigoxinDis SpiroDis
BBdis LOS milrinone dobutamine   EdemaDisQuart   AdjuvantThiazide
HemoconcentrateBOTHdis   WRF20GFR_AP
  /PRINT=CI(95)
  /CRITERIA=PIN(.05) POUT(.20) ITERATE(20).
```

Project Responsibilities:

The student (Kula) was responsible for the majority of the activities related to this investigation. The student defined and calculated all medication variables, with final approval by the mentor. The student completed all statistical analysis relating to SBP-reduction in relation to WRF, DE, other diuretic metrics, and survival; as well as all

statistical analysis relating to medications. Additionally, the student designed all figures (non-cited), graphs, and charts in this publication. The mentor (Testani) was responsible for providing the database previously collected by his research team, deciding on the definition of SBP-reduction, guidance of the relevance and direction of analysis, and approving all figures, charts, and graphs. Additional contributions and discussions were utilized from the other individuals listed in the 'acknowledgements' section of this work.

Results:

Baseline variables and change in blood pressure:

Baseline characteristics for the cohort are presented in **Table 1**. Overall, 77.6% of patients had a discharge SBP lower than the admission value, which translated into a median absolute SBP-reduction of 12.3 mmHg (IQR -25.3 to -1.7). The median relative reduction in SBP was 9.9% (IQR 18.2 to 1.4). Patients with SBP-reduction on average had higher baseline SBP, HR, and a lower EF. Notably, baseline medications were similar across all groups with the exception of the loop diuretic dose, which tended to be lower in the SBP-reduction group (**Table 1**).

Relationship between SBP reduction, renal function, and diuresis

Similar to previous observations, SBP-reduction was associated with WRF (OR 1.9, 95% CI: 1.2-2.9, p=0.004) and negatively associated with improvement in renal function (IRF) (OR 0.43, 95% CI: 0.28-0.65, p<0.0001). Relatedly, the risk of worsening vs. an improvement was substantially more likely in patients with SBP-reduction (OR 3.4, 95% CI: 2.0-6.0, p<0.0001).

Despite the association with deteriorations in renal function, SBP-reduction did not appear to limit decongestion (**Table 2**). Importantly, diuretic efficiency did not differ between those with and without SBP-reduction [523mL output/40mg IV furosemide eq (IQR 194-1086) vs. 429mL output/40mg IV furosemide eq (IQR 192-977); p=0.300]. Patients with an SBP-reduction were no more likely to have high diuretic efficiency (OR for above median DE: 1.2, 95% CI: 0.87-1.61, p=0.274) (**Figure 4**), and this held true in the multivariate model (OR SBP-reduction: 1.08, 95% CI: 0.8-1.5, p=0.720). SBP-reduction,

Table 1: Baseline characteristics for study population

	Overall (n=657)	SBP reduction greater than median (n=328)	SBP reduction less than median (n=328)	p-value
Demographics				
Age (years)	62.8 ±15.4	62.4 ±15.0	63.2 ±15.9	0.542
Male	0.565	0.521	0.607	0.27
African American	65%	71%	58%	<0.0001*
Medical History				
Hypertension	73%	75%	71%	0.333
Diabetes mellitus	42%	38%	46%	0.040*
Ischemic cause	26%	22%	29%	0.040*
EF ≥40%	32%	30%	35%	0.113
Admission physical examination				
Heart rate, bpm	89.4 ±20.0	91.0 ±19.4	87.8 ±20.5	0.037*
SBP, mmhg	131.6 ±28.9	142.3 ±29.7	120.8 ±23.8	<0.0001*
DBP, mmhg	77.1 ±18.4	83.9 ±18.4	70.3 ±15.6	<0.0001*
JVD (≥12 cm water)	61%	64%	58%	0.131
Hepatojugular reflex	23%	23%	22%	0.824
Edema (≥1)	46%	42%	51%	0.034*
Cardiac function				
EF, %	32.1 ±20.2	30.4 ±19.6	33.8 ±20.7	0.031*
Laboratory values				
Creatinine, mg/dl	1.6 ±0.87	1.46 ±0.85	1.66 ±0.88	0.002*
BUN, mg/dL	30.28 ±22.6	26.3 ±18.4	34.3 ±25.7	<0.0001*
Hematocrit	36.4 ±6.3	37.1 ±6.0	35.7 ±6.6	0.007*
Hemoglobin, g/dL	12.1 ±2.1	12.3 ±2.0	11.9 ±2.2	0.018*
BNP, pg/mL	1693 ±1193	1700 ±1149	1687 ±1238	0.887
Sodium, mmol/L	138 ±4.7	139 ±4.4	138 ±4.9	0.002*
eGFR, mL/min per 1.73 m2	59±28	62±28	55±28	0.001*
Medications (admission)				
ACE inhibitor or ARB	64%	65%	62%	0.464
Beta blocker	71%	71%	72%	0.665
Thiazide	13%	14%	11%	0.196
Digoxide	26%	25%	26%	0.655
Hydralazine	12%	14%	10%	0.095
Nitrates	17%	17%	16%	0.600
Daily Loop-diuretic dose, mg	40 (17.5 to 120)	40 (0 to 80)	40 (20 to 160)	0.035*

(*Previous Page*) Baseline characteristics for the overall cohort and patients with or without an SBP-reduction. SBP-reduction defined as relative SBP reduction from admission to discharge greater than the median (>9.9% reduction). Values are listed as mean standard deviation, median (quartile 1-quartile 4), or % of cohort. ACE= angiotensin converting enzyme, ARB- angiotensin receptor blocker, BUN- Blood Urea Nitrogen, eGFR- estimated glomerular filtration rate (MDRD), EF= ejection fraction, BNP=Brain Natriuretic Peptide, JVD= jugular venous distention, SBP=systolic blood pressure, DBP=diastolic blood pressure.

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when compared to patients without an SBP-reduction, did not affect other metrics of diuretic success such as total net urine output (5440 ±6741mL vs. 4933 ±5913mL, p=0.306), daily net-urine output (854 ±875mL/day vs. 781 ±903mL/day, p=0.293), dosages of loop-diuretics (112 ±101 mg furosemide eq/day vs. 119± 96 mg furosemide eq/day, p=0.387), use of adjuvant thiazides (15% vs. 16%, p=0.733), percent of loop-diuretic given intravenously (65 ±25% vs. 65 ±25%, p=0.991) day of transition of loop-diuretics to the oral route (4.2±2.4 days vs. 4.5±2.5 days, p=0.236), percentage of patients achieving hemoconcentration (31% vs. 34%, p=0.425), and length of stay (6.4±3.2 days vs. 6.7±3.3 days, p=0.249) (**Table 2)**. The extent of SBP reduction did not influence diuretic efficiency (p=0.58 for variation across all quintiles of relative decline in SBP) (**Figure 5)**.

Further investigation examined the relationship between SBP-reduction, renal function, and decongestion stratified by whether the patient's admission SBP was above or below the median value (now referred to as 'higher admission SBP' or 'lower'

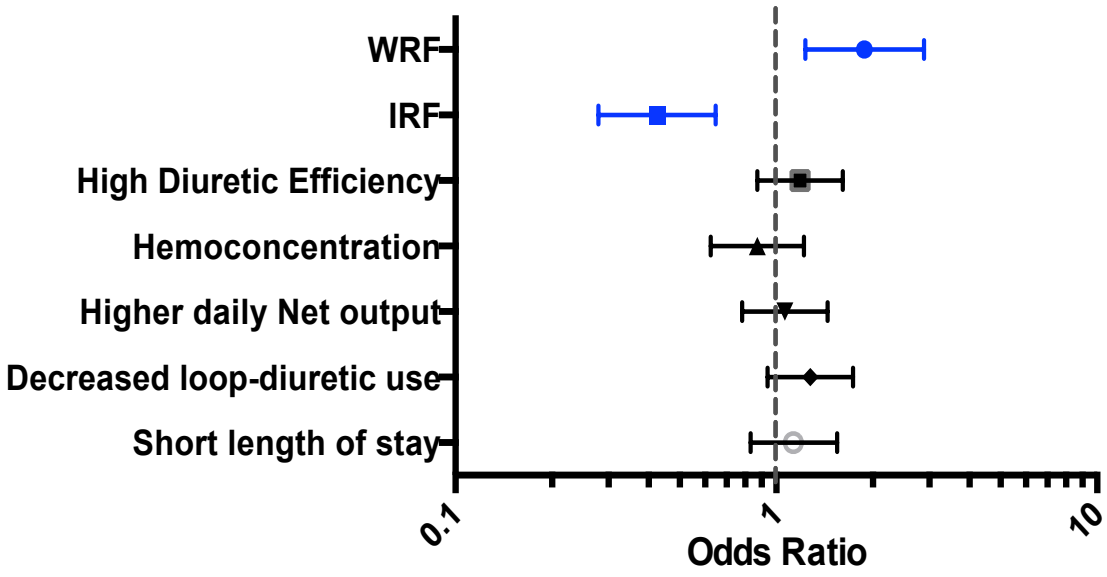


Figure 4: Odds Ratio (OR) and 95% CI for patients with an SBP-reduction. High DE defined as DE greater than median, Low LOS defined as length of stay less than median, Less total loop-diuretic defined as below median usage of sum of both oral and IV loop-diuretic (furosemide equivalents). IRF=improvement in renal function (>20% increase in eGFR from admission to discharge).

admission SBP'). The median admission SBP for the entire study population was 127.5mmHg (IQR: 110-151mmHg). SBP-reduction occurred in 64% and 34% of patients with an admission SBP above and below the median, respectively. Relatedly, the odds of SBP-reduction were tripled for those with a higher admission SBP (OR: 3.1, 95% CI: 2.3-4.3, p<0.001). There was no significant difference in the rates of WRF with SBP-reduction for those with a lower admission SBP **Table 3**. However, SBP-reduction was associated with WRF in patients with a higher admission SBP (OR WRF: 2.3, 95% CI: 1.2-4.3, p=0.012). Notably, diuretic efficiency was similar for all groups. SBP-reduction did not reduce diuretic efficiency whether it was in the context of a lower or higher admission SBP **Table 3**. The lack of association between SBP-reduction and diuretic efficiency remained in regression models when adjusting for admission SBP value (OR: 1.24, 95% CI: 0.9-1.7, p=0.209). Models including the relative decline in SBP during hospitalization (continuous) and admission SBP value yielded similar results (OR: 1.11 per 10% decrease in SBP admission to discharge, 95% CI: 0.97-1.3, p=0.115).

SBP-reduction and survival

In a univariate model, SBP-reduction was associated with a survival advantage (HR: 0.79, CI: 0.6-0.97, p=0.026). However, this was no longer significant (HR:0.9, p=0.398) after adjusting for baseline-SBP. Furthermore, SBP-reduction had no association with mortality in a multivariate model including relevant baseline and in hospital variables which included: age, race, diabetes mellitus, ischemic HF cause, presence of edema, digoxin use, outpatient loop diuretic dose, thiazide diuretic use, heart rate, systolic blood pressure, B-type natriuretic peptide, serum sodium, hemoglobin, GFR, and blood urea nitrogen. (HR: 1.1, CI: 0.8-1.4, p=0.708). **Figure 6**

Table 2: SBP-reduction and metrics of diuresis

	No SBP-reduction	SBP-reduction	p-value
Diuretic Efficiency (mL output/40mg IV furosemide eq)	429 (192-977)	523 (194-1086)	0.300
Net output (mL)	4933 ±5913	5440 ±6741	0.306
Daily Net I/O (mL/day)	781 ±903	854 ±875	0.293
Total Loop Diuretic (mg furosemide eq)	560 (280-1075)	440 (220-1035)	0.772
Daily Loop Diuretic (mg furosemide eq/day)	119± 96	112 ±101	0.387
Peak IV Dose in 24hrs (mg)	162 ±140	149 ±148	0.226
% of Loop given IV	65 ±25	65 ±25	0.991
% requiring Adjuvant Thiazide	16%	15%	0.733
Day switch to standing oral loop diuretic (days)	4.52 ±2.5	4.2 ±2.4	0.236
Hemoconcentration at Discharge	34%	31%	0.425
WRF	12%	21%	0.003*
LOS (days)	6.73± 3.3	6.43 ±3.2	0.249

Metrics of diuretic success in patients with or without an SBP-reduction. Diuretic efficiency was estimated using net output during hospitalization divided by the total IV of loop diuretic administered during hospitalization (per 40 mg furosemide equivalents). WRF= worsening in renal function, LOS= length of stay * significant p value

Table 3: Diuretic Efficiency (A) and rates of WRF (B) for SBP-reduction, stratified by median admission SBP

A

		Diuretic Efficiency (mL output/40mg IV furosemide eq)	p-value
admission SBP below 127.5mmHg	SBP reduction (n=118)	488	0.86
	no SBP reduction (n=209)	496	
admission SBP above 127.5mmHg	SBP reduction (n=210)	541	0.055
	no SBP reduction (n=119)	388	

B

		WRF	p-value
admission SBP below 127.5mmHg	SBP reduction (n=118)	16%	0.349
	no SBP reduction (n=209)	12%	
admission SBP above 127.5mmHg	SBP reduction (n=210)	23%	0.010
	no SBP reduction (n=119)	12%	

***Admission SBP of 127.5mmHg equals the median value for the cohort**

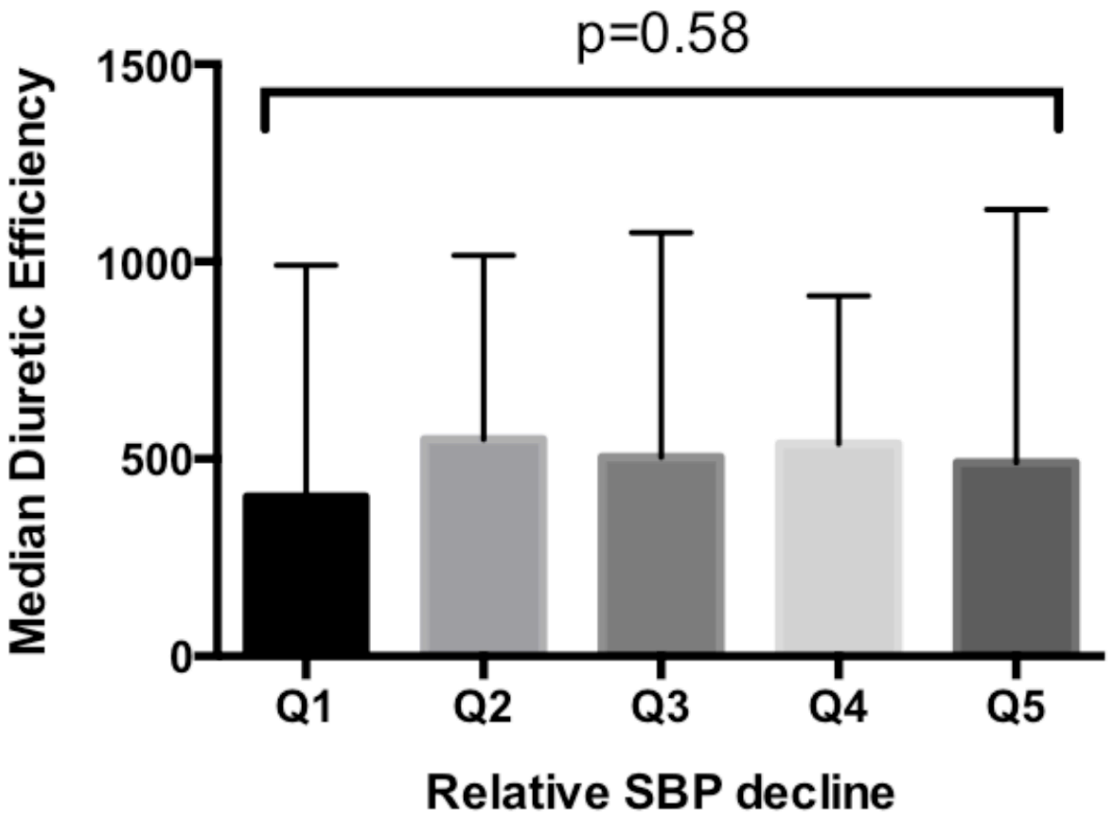


Figure 5: Median diuretic efficiency as compared quinitles of relative decline in SBP from admission to discharge. (smallest) Q1: >1% increase; (smallest) Q2: 1% (increase) to -6.5% (decrease); Q3: -6.5% to -13.7%; q4: -13.7% to -20%; (largest decrease)Q5: <-20% decrease. p-value represents overall between group differences.

P=0.708

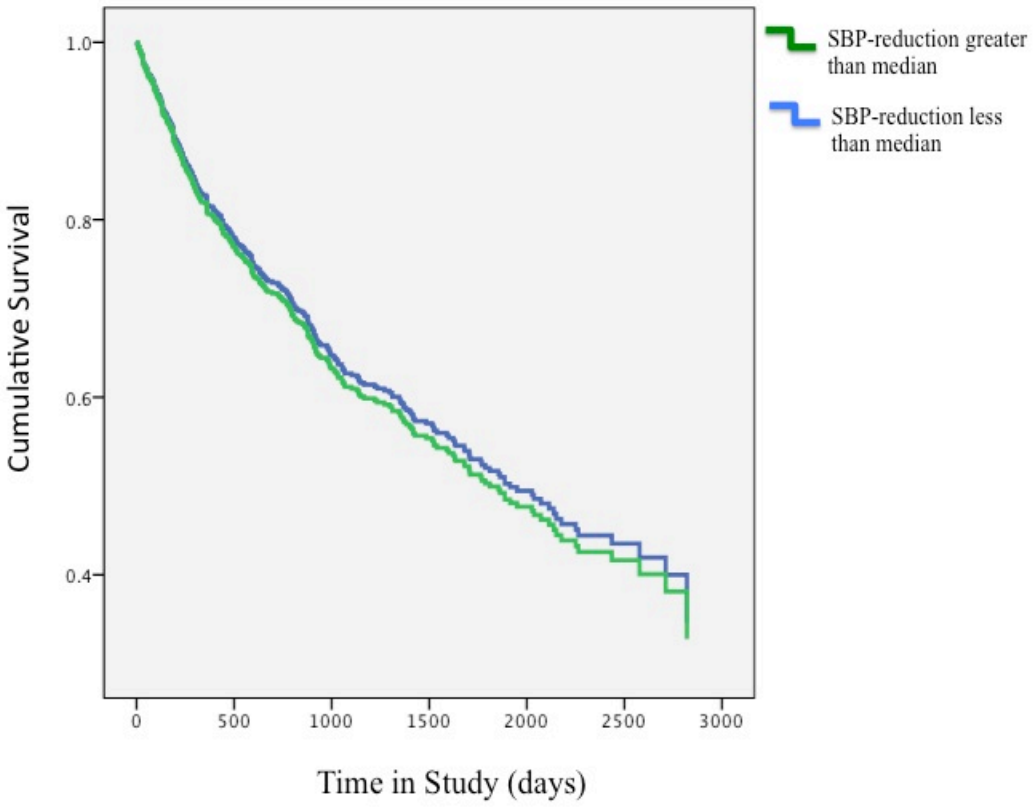


Figure 6: Adjusted survival plot for those patients with, and without an SBP-reduction. Adjusted for relevant baseline and in-hospital variables (listed in text).

Titration of Medications and measures of diuresis/decongestion

Guideline directed medical therapies (GDMTs) did not result in higher incidence of WRF or compromise DE **Table 4**. Analysis compared patients continuing or increasing (including a new start on the medication) the dosage of their medications versus those who decreased, stopped, or never took the medications.

ACE-I and/or ARBs:

The dosage of ACE-I or ARBs was continued or increased in 71% (n=466) of patients. 7.2% (n=47) of the study population had their ACE-I or ARB stopped anytime during admission. ACE-Is and/or ARBs did not increase the rates of WRF during hospitalization (OR: 0.90, 95% CI: 0.7-1.4, p=0.903) or at discharge (0.82, 95% CI: 0.5-1.3, p=0.395). However, ACE-Is or ARB use was strongly associated with high DE in both unadjusted (OR: 2.7, 95% CI: 1.9-3.8, p<0.0001) and adjusting for relevant baseline variables such as age, sex, hematocrit, hemoglobin, BNP, creatinine, and sodium, eGFR, ejection fraction, hypertension, diabetes, baseline ace-inhibitor or ARB, beta-blocker, thiazides, and hydralazine usage (OR: 1.99, 95% CI: 1.3-3.1, p=0.002).

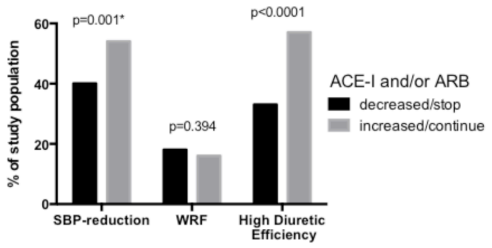
Beta-Blockers:

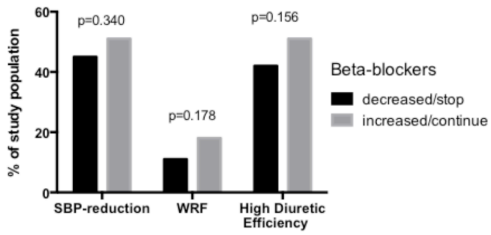
A vast majority (88%, no=577) of the study population had their beta-blocker dosage continued at the same dosage or increased. Beta-blocker use in this group was associated with a reduced risk for WRF (OR: 0.6, 95% CI: 0.4-0.99, p=0.045) anytime during hospitalization and no increase in risk for WRF at the time of discharge (OR:1.64 95% CI: 0.8-3.4, p=0.182). Diuretic efficiency was not affected by beta-blocker use (unadjusted OR for high DE: 1.41, 95% CI: 0.9-2.2, p=0.158).

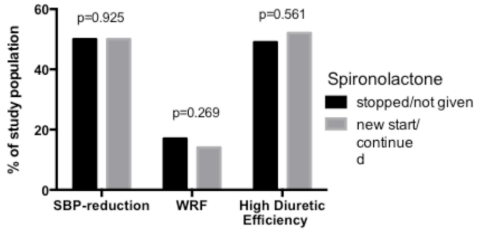
Table 4: Associations between medication variables and outcomes

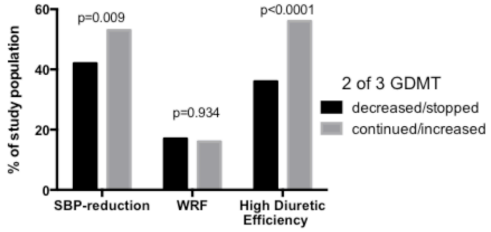
Medication Variable:	n	SBP-reduction	p	Any WRF	P	WRF discharge	P	High DE	P	Adj. High DE	p
ACE and/or ARB	466	1.74 (1.2-2.4)	0.002*	0.90 (0.7-1.4)	0.903	0.82 (0.5-1.3)	0.395	2.7 (1.9-3.8)	<0.001*	1.99 (1.3-3.1)	0.002*
Beta Blocker	577	1.26 (0.8-2.0)	0.341	0.62 (0.4-0.99)	0.045*	1.64 (0.8-3.4)	0.182	1.41 (0.9-2.2)	0.158	1.3 (0.7-2.2)	0.365
Spironolactone	148	0.98 (0.7-1.4)	0.925	0.90 (0.6-1.3)	0.602	0.74 (0.4-1.2)	0.269	1.1 (0.8-1.6)	0.561	1.01 (0.6-1.7)	0.986
ACE/ARB+BB	417	1.65 (1.2-2.3)	0.002*	0.88 (0.6-1.2)	0.437	0.97 (0.6-1.5)	0.897	2.48 (1.8-3.4)	<0.001*	1.76 (1.2-2.6)	0.005*
ACE/ARB+BB+spiro	106	1.2 (0.8-1.9)	0.338	0.86 (0.6-1.3)	0.504	0.74 (0.4-1.3)	0.322	1.38 (0.9-2.1)	0.134	1.16 (0.7-1.9)	0.567
2/3 present	452	1.56 (1.1-2.2)	0.009*	0.81 (0.6-1.1)	0.23	0.98 (0.6-1.5)	0.934	2.34 (1.7-3.3)	<0.001*	1.59 (1.1-2.4)	0.025*
Vasodilator given	286	1.13 (0.8-1.5)	0.431	1.28 (0.9-1.8)	0.131	1.25 (0.8-1.9)	0.288	0.75 (0.5-1.0)	0.064	0.73 (0.5-1.1)	0.122

ACE-I, ARBs, and Beta Blockers were classified as patients with a new start, continuation, or increase in dosage during hospitalization. Sprionolactone represents all patients taking spironolactone without stopping during hospitalization. 2/3 present indicates the patient was taking 2 of the 3 GDMT variables (ACE-I/ARB, BB, spironolactone). WRF=worsening of renal function. High DE=above median diuretic efficiency. Data is listed as odds ratio and 95% CI.









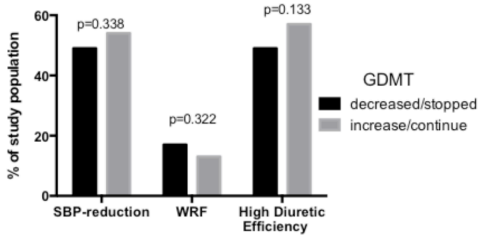


Figure 7: Rates of SBP-reduction, WRF, and high diuretic efficiency with GDMT. ACE-I, ARBs, and Beta Blockers were classified as patients with a new start, continuation, or increase in dosage during hospitalization. Sprionolactone represents all patients taking spironolactone without stopping during hospitalization. 2/3 present indicates the patient was taking 2 of the 3 GDMT variables (ACE-I/ARB, BB, spironolactone). WRF=worsening of renal function. High DE=above median diuretic efficiency.

Mineralocorticoid Receptor Antagonists:

Spironolactone was compared between patients newly started or continuing (22%, n=148) versus those who either did not receive the medication or it was discontinued during hospitalization. Spironolactone was not associated with SBP-reduction (OR: 0.98, 95% CI: 0.7-1.4, p=0.925) and similarly was not associated with WRF or high diuretic efficiency.

GDMT combinations:

Continuing and/or increasing the dosages ACE inhibitors/ARBs and beta-blockers occurred in 63% (n=417) of the study population. This medication combination associated with SBP-reduction (OR: 1.56, 95% CI: 1.1-2.2, p=0.009) without WRF (OR for developing WRF anytime during hospitalization: 0.88 95% CI: 0.6-1.2, p=0.437). Patients taking both of these medications were more likely to have high DE even when adjusting for relevant age, sex, hematocrit, hemoglobin, BNP, creatinine, and sodium, eGFR, ejection fraction, hypertension, diabetes, ace-inhibitor or ARB, beta-blocker, thiazides, and hydralazine usage (adjusted OR for high DE: 1.76, 95% CI: 1.2-2.6, p=0.005). Similarly, a majority of the population (69%, n=452) took any 2 of the 3 GDMTs. These patients had higher rates of SBP-reduction (OR: 1.56, 95% CI: 1.1-2.2, p=0.009) and high DE (adjusted OR for High DE: 1.6, 95% CI:1.1-2.4, p=0.023) without a significant change in WRF (OR: 0.81, 95% CI: 0.6-1.1, p=0.23). Lastly, 16% (n=106) of patients were given continued or increased dosage of all three GDMTs. These patients interestingly did not have any change in their likelihood for SBP-reduction, WRF, or high DE (**Table 4**).

P=0.124

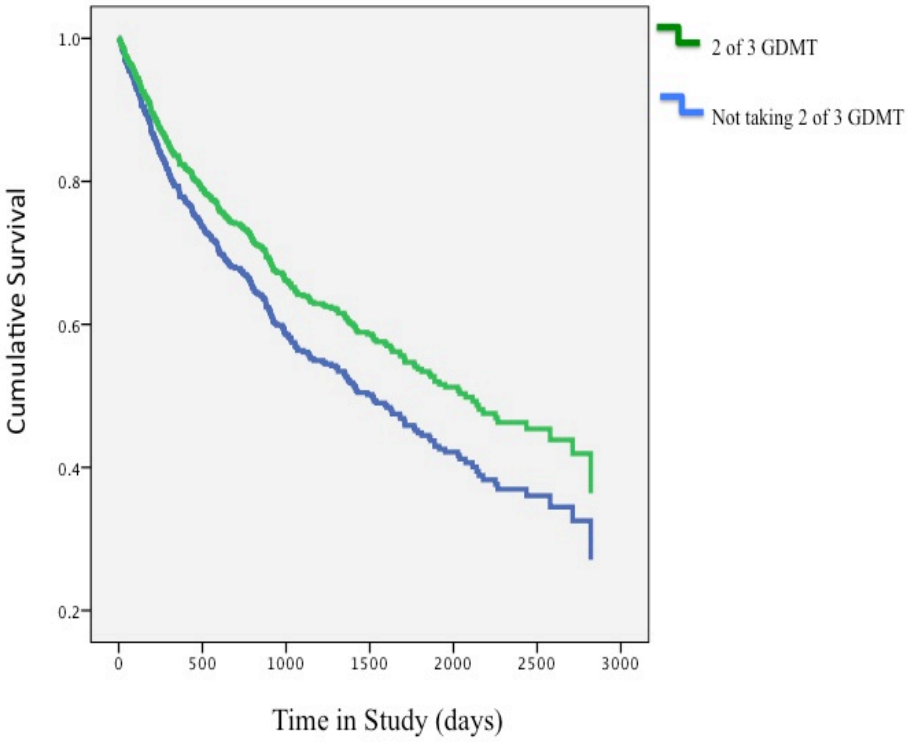


Figure 8: Adjusted survival plot stratified by patients receiving 2 of 3 GDMT versus those not taking. Adjusted for relevant baseline and in-hospital variables (listed in text). 2 of 3 GDMT defined as same or increased dosage of any two of these: ACE-Is, beta blockers, and/or spironolactone.

GDMT and Mortality:

No individual medication or combination of GDMT was associated with higher mortality in both unadjusted and adjusted models. The extent to which these medications afforded a survival benefit varied, and is summarized in **Table 5** and **Figure 8.**

Table 5: GDMT and associations with mortality

	Univariate		Multivariate	
	HR (95%CI)	p	HR (95%CI)	p
ACE-I/ARB	0.59 (0.5-0.7)	<0.0001	0.74 (0.5-1.0)	0.08
Beta blocker	0.73 (0.54-0.99)	0.046	0.75 (0.53-1.1)	0.119
Spironolactone	1.01 (0.8-1.3)	0.912	0.75 (0.4-1.3)	0.327
SBP-reduction	0.79 (0.6-0.97)	0.026	1.05 (0.8-1.4)	0.708

Hazard ratios for medication variables and SBP-reduction. SBP-reduction=>9.9% decrease in SBP. CE-I, ARBs, and Beta Blockers were classified as patients with a new start, continuation, or increase in dosage during hospitalization. Sprionolactone represents all patients taking spironolactone without stopping during hospitalization.

Discussion

The present study demonstrates that a reduction in SBP was associated with deteriorations in renal function without compromising diuresis and decongestion. SBP decreased in the majority of patients during hospitalization, and for those with a reduction in SBP greater than the median, the risk for WRF doubled. Nonetheless, there was no reduction in a wide array of metrics of decongestion including diuretic efficiency and hemoconcentration. Furthermore, patients starting, continuing, or increasing dosages of GDMT were more likely to have a reduction in blood pressure, an overall improvement in diuretic efficiency, and better prognosis.

The link between reductions in SBP and WRF is becoming an accepted principle in cardiorenal pathology.[40-42] Several physiologic mechanisms exist to explain the increased rates of WRF with SBP-reduction. The intricate autoregulation of glomerular blood flow by the kidney serves to maintain GFR over a wide range of blood-pressures.[61] However, the physiologic environment of congestive heart failure and ADHF therapy often disrupt this intricate balance, leading to deterioration in GFR. Longstanding medical comorbities such as diabetes and hypertension in addition to blood-pressure medications and diuretics can compromise renal autoregulation.[50-52] The end result being that the kidney cannot appropriately respond to a decrease in blood pressure, leading to a decrease in GFR. Undoubtedly the high incidence of all of these factors in the study cohort led to the coupling of SBP-reduction and WRF seen in our analysis. Further highlighting the importance of these physiologic processes was the finding that patients with a higher admission SBP were more likely to develop WRF with SBP-reduction

while patients with lower admission SBP had similar rates of WRF, regardless of SBP-reduction.

Beyond the direct effect on GFR, little is known about the consequences of reducing SBP on treatment efficacy. As long as diuretic therapy remains the mainstay of decongestion in ADHF, the kidney will serve as the conduit for volume removal and as such any factors that affect kidney function could in theory compromise diuretic therapy. However, the results of our study suggest that SBP-reduction minimally effects diuretic efficiency during hospitalization. Diuretic efficiency was used to define treatment success because it has been proven to be an indicator of how effective the diuresis is during hospitalization and has prognostic significance.[59] To ensure that study participants were not just diuresing well, but returning to a euvolemic state, rates of hemoconcentration were examined. Hemoconcentration can be used as a marker for decongestion, the primary treatment goal in ADHF, and is associated with better survival.[62] As such, SBP-reduction did not hinder the important goal of aggressive and complete decongestion.

SBP-reduction was not linked to worse outcomes in our analysis. This result builds upon recent evidence demonstrating that WRF associated with SBP-reduction was not associated with worse outcomes.[42] Several new concepts in ADHF research exist to help explain our findings in regards to prognosis. Firstly, the etiology of WRF is more relevant in determining prognosis than WRF taken alone. Therefore, the mechanisms by which SBP-reduction results in WRF may play less of a pathologic role in the progression of heart failure then other processes such as venous congestion or high dosages of loop-diuretics. Another important consideration for the low prognostic significance of SBP-reduction is the minor effect SBP-reduction had on therapy. It did

not impede one of the primary determinants of disease progression and survival, thorough decongestion.

Another finding of this study was that starting, continuing, or increasing the dose of guideline medications was possible without impeding decongestion. GDMT use in this manner led to higher rates of SBP-reduction, which was to be expected considering these are antihypertensive medications. The controlled environment of hospitalization provides a perfect opportunity to optimize dosages. Consequently, it is encouraging that in this analysis all combinations of GDMT did not at any time reduce diuretic efficiency or survival.

One unexpected result was the lack of association between continuing and/or increasing GDMT, especially ACE-I and ARBs, with WRF. While this result was not anticipated, other ADHF studies also noted a lack of association between ACE-I/ARBs and WRF during hospitalization.[63,64] One explanation could be that an ADHF hospitalization presents a unique environment due to venous congestion, and subsequent aggressive diuretic therapy, altering renal autoregulation and increasing neurohormonal activation. In this context, the effect of ACE-Is and ARBs impart on GFR may be masked, or the effect could in some ways be protective by tempering the renal compensatory mechanisms in response to diuretic therapy.[65] From a clinical practice standpoint, it was notable that any combination of GDMT (ACE-I/ARB, beta-blockers, spironolactone) did not reduce DE in our analysis. ACE-I/ARBs, alone or in combination with beta-blockers, were associated with high DE. Higher DE with ACE-I/ARB use likely represents the direct effect of the drug lessening the hemodynamic and tubular changes in response to loop-diuretic therapy. Notably, a study by Chen et. Al.

demonstrated that furosemide-induced diuresis was substantially enhanced by the addition of losartan.[66] Neurohormonal activation, which ACE-Is and ARBs partially block, play an important role in blunting the response to loop-diuretics by increasing the sodium avidity of the kidney. Reducing the tubular compensation and neurohormonal activation, which has repeatedly associated with worse outcomes, may be of greater importance to some extent than maintaining the autoregulation of glomerular blood flow and GFR. Just as increases of WRF secondary to a reduction in SBP result in a better prognosis, WRF associated with ACE-I use affords better outcomes than spontaneously occurring WRF.[67]

Taken as a whole, this investigation found that the society guideline recommended goals of aggressive decongestion and initiation and optimizing of medical therapy were compatible. SBP-reduction, a common result of both of these goals, did not affect treatment success or survival. Relatedly, the survival benefits afforded by GDMT were true in this cohort and did not come at the cost of DE or WRF. Current guidelines recommend the aforementioned goals to increase survival, but lack details on how best to consolidate therapies.[23,24,53] Our analysis suggests this is generally possible, but more study is needed to understand the specifics. Further research will strengthen the fund of knowledge and, in turn, improve the detail of guideline recommendations and clinical decision-making.

Limitations:

Given the post-hoc retrospective nature of this analysis, uncontrolled confounding cannot be excluded. SBP values for admission were the average of the first three values in the patient record, and these values came both from the emergency department and

patient room after admission. Therefore it is possible that some therapy (diuretics, blood-pressure medications, inotropes, etc..) were administered between the first and third reading and could have influenced the final blood pressure values. The direct effect that day-to-day changes in SBP may have on diuresis cannot be assessed, as daily blood pressures and fluid output were not recorded in the database on a daily basis. Conclusions in this study were drawn over an entire hospitalization, and therefore specific changes in clinical values, or changes in therapy in response, may confound the data in a way that cannot be accounted for. Relatedly, only starting and stopping doses over the course of hospitalization for GDMT medications were used for analysis. Daily changes to the dosages of medications, the reason for these changes, and the effect these changes had on blood pressure, renal function, and diuretic efficiency, which could be used to guide therapy, were not part of this study. Relatedly, tailoring of the therapy could have altered the outcomes over the course of hospitalization. As a result of these limitations these findings should be regarded as hypothesis generating for future prospective studies.

Conclusion:

SBP-reduction is associated with WRF but does not limit decongestion in ADHF. Continuing or increasing guideline direct medical therapy did not alter rates of WRF or diuretic success.

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