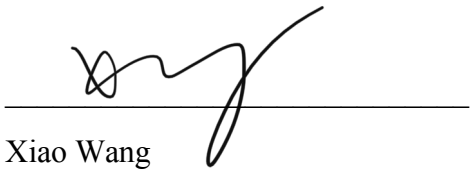
Distribution Agreement

In presenting this thesis or dissertation as a partial fulfillment of the requirements for an advanced degree from Emory University, I hereby grant to Emory University and its agents the non-exclusive license to archive, make accessible, and display my thesis or dissertation in whole or in part in all forms of media, now or hereafter known, including display on the world wide web. I understand that I may select some access restrictions as part of the online submission of this thesis or dissertation. I retain all ownership rights to the copyright of the thesis or dissertation. I also retain the right to use in future works (such as articles or books) all or part of this thesis or dissertation.

Signature:



Xiao Wang

4/14/2020

Date

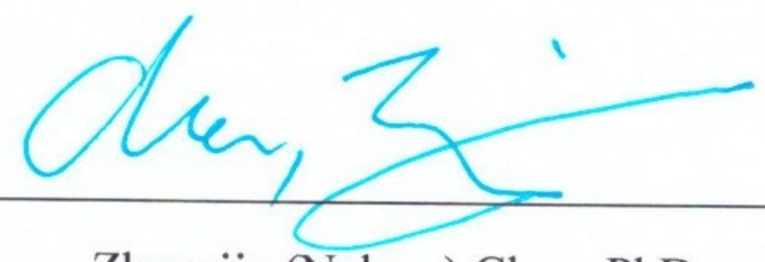
Comparison of Oral Metolazone versus Oral Chlorothiazide in Patients with Acute Decompensated Heart Failure with Loop Diuretic Resistance

by

Xiao Wang

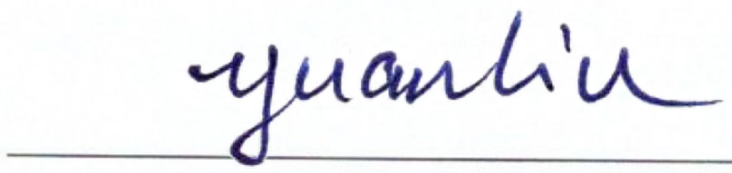
Master of Public Health

Biostatistics and Bioinformatics



Zhengjia (Nelson) Chen, PhD

(Thesis Advisor)



Yuan Liu, PhD

(Reader)

Comparison of Oral Metolazone versus Oral Chlorothiazide in Patients with Acute Decompensated Heart Failure with Loop Diuretic Resistance

by

Xiao Wang

B.S.

University of California, San Diego

2017

Thesis Committee Chair: Zhengjia (Nelson) Chen, PhD

Reader: Yuan Liu, PhD

An abstract of

A thesis submitted to the Faculty of the

Rollins School of Public Health of Emory University

in partial fulfillment of the requirements for the degree of

Master of Public Health

in Biostatistics and Bioinformatics

2020

Abstract

Comparison of Oral Metolazone versus Oral Chlorothiazide in Patients with Acute Decompensated Heart Failure with Loop Diuretic Resistance

By Xiao Wang

Backgrounds: Adult patients admitted with acute decompensated heart failure (ADHF) between July 1st, 2016 to July 31st, 2018 with loop diuretic resistance, defined as administration of intravenous (IV) furosemide during hospitalization and at least one dose of oral chlorothiazide (22 patients) or oral metolazone (53 patients) to augment diuresis to compare the efficacy and safety between oral chlorothiazide and metolazone in ADHF patients with loop diuretic resistance.

Methods: We conducted a retrospective, single-center, cohort study between and the two cohorts and used appropriate tests and regression models to see the differences. The primary end point was the change in 24-hour UOP (urine output) from loop diuretic only administration to combination diuretic administration with a thiazide-type diuretic. Secondary end points included change in patients' body weight, in serum creatinine, serum electrolytes, length of stay (LOS), need for intensive care unit (ICU) transfer, and 30-day readmission after the thiazide-type diuretic and the baseline characteristics for each group.

Results: 24-hour UOP after loop diuretic only administration was similar between the patients who received oral chlorothiazide and those who received metolazone (2135.2 ± 1161.0 vs. 1855.6 ± 1231.0, p=0.366) and the addition of a thiazide-type diuretic similarly increased 24-hour UOP for both (2950.7 ± 1345.6 vs. 3151.1 ± 1349.2, p = 0.559). The change in UOP output was similar (815.5 mL ± 1505.8 vs. 1295 mL ± 1857.9, p = 0.290) and reaffirmed by GLM analysis (p = 0.149). No significant differences in change in LOS (8.3 days ± 5.7 vs. 10.4 days ± 8.8, p = 0.304, GLM p-value =0.528), and ICU transfer rates (22.72% vs. 20.75%, p = 0.849, LRM p-value = 0.886). A significant weight change between after the two thiazide-type diuretic and the baseline weight (-0.5 kg ± 1.7 vs. -2.1 kg ± 2.6, p = 0.016, GLM p-value = 0.02) and 30-day readmission rates between the two cohorts (20.8% vs. 45.5%, p = 0.030, LRM p-value = 0.085). We also found a similar change in serum creatinine concentration (0.04 mg/dL ± 0.263 in the chlorothiazide group vs. 0.13 mg/dL ± 0.304 in the metolazone group, p=0.297, GLM p-value = 0.961), serum sodium (-0.10 mg/dL ± 2.142 vs. -0.90 mg/dL ± 3.054, p = 0.274, GLM p-value = 0.391), serum potassium (-0.39 mg/dL ± 1.011 vs. -0.14 mg/dL ± 0.509, p = 0.168, GLM p-value = 0.143), or serum magnesium (0.08 mg/dL ± 0.196 vs. 0.03 mg/dL ± 0.234, p = 0.489, GLM p-value = 0.761).

Conclusions: In patients with ADHF and loop diuretic resistance, the addition of oral chlorothiazide or metolazone resulted in similar 24-hour urine output without change in renal function or serum electrolytes. These findings suggest similar efficacy and safety between oral chlorothiazide and metolazone in this patient population. However, additional studies with a larger sample size are recommended to assess non-inferiority.

Comparison of Oral Metolazone versus Oral Chlorothiazide in Patients with Acute Decompensated Heart Failure with Loop Diuretic Resistance

by

Xiao Wang

B.S.

University of California, San Diego

2017

Thesis Committee Chair: Zhengjia (Nelson) Chen, PhD

Reader: Yuan Liu, PhD

An abstract of

A thesis submitted to the Faculty of the

Rollins School of Public Health of Emory University

in partial fulfillment of the requirements for the degree of

Master of Public Health

in Biostatistics and Bioinformatics

2020

Table of Contents

1.Introduction

Heart failure (HF) is a worldwide critical health issue: more than 20 million people are suffering from it and more than 5 million in the United States. There are over one million annual incidents of hospitalizations with a primary diagnosis of HF and the number has tripled over the last three decades.[1] Among these HF hospitalization incidents, 90% are ascribed to Acute decompensated heart failure (ADHF) which is categorized by the sudden worsening of the signs and symptoms of HF, including systemic volume overload, acute pulmonary edema, and hypoperfusion and patients are facing unacceptably high morbidity and mortality. Furthermore, the hospitalizations for ADHF are casting heavy economic burden that it is estimated to exceed $50 billion by 2030. [2, 3]

One of the mainstream therapy of choices for ADHF patients with volume overload is Intravenous (IV) loop diuretics that could provide quickly symptom relief. However, the impact on long-term outcome or mortality for this therapy has remained unstudied. [4] Although the exact incidents are unknown, ADHF patients frequently develop diuretic resistance after prolonged exposure to loop diuretics due to the interaction between the pathophysiology of sodium retention in HF and the renal response to diuretic therapy.[5, 6] ADHF patients are evaluated by the Diuretic Optimization Strategies Evaluation (DOSE) trial for initial diuretic strategies before the treatment, but minimal researches and guidelines exist to supervise the management of refractory volume overload in patients with loop diuretic resistance. [7]

To overcome the diuretic resistance, strategy called Sequential nephron blockade which uses thiazide-type diuretics such as chlorothiazide and metolazone to inhibit sodium reabsorption

in the distal convoluted tubule is proposed alongside with the Intravenous (IV) loop diuretics. Oral chlorothiazide is concerned not be adequately filtered through the glomerulus for ADHF patients with renal insufficiency so that metolazone is considered to be relatively more potent since it is not affected by impaired glomerular filtration.[2] However, the oral absorption for metolazone is volatile and exhibits reduced bioavailability. Therefore, in cases patients with ADHF by gastrointestinal edema or impaired gastrointestinal perfusion, the efficacy for metolazone might be further exacerbated and causing severe electrolyte abnormalities.[4] [6]

To our knowledge, the study addressing the differences between these two drugs is limited that there is only one retrospective study with ADHF patients with renal impairment stating that these two drugs were similarly efficacious and safe.[8] Given this concerns, although both drugs are proven to be effective in combination with Intravenous (IV) loop diuretics in clinical trials,[9, 10] we decided to construct a single-center, retrospective chart review of ADHF patients with loop diuretic resistance who were prescribed oral metolazone or oral chlorothiazide in addition to loop diuretic therapy to compare 1) the efficacy of oral chlorothiazide versus oral metolazone on net urine output (UOP), 2) the efficacy on change in body weight, length of stay after thiazide-type diuretic administration, and ICU transfer rate due to refractory volume status and 3) The safety by incidence between oral metolazone and oral chlorothiazide of change in serum electrolytes and change in serum creatinine all at 24-hours, and progression to renal replacement during admission.

The data for our study will be collected from a total of 78 patients who are prescribed oral metolazone or oral chlorothiazide within the Emory Healthcare system from June 1st, 2013 to July 30th, 2018 and Data Warehouse and EeMr.

2. Methods

2.1 Study design and Data collection

This study was designed as a single-center, retrospective cohort study consisting of adult patients hospitalized at Emory University Hospital Midtown with an admission diagnosis of ADHF and loop diuretic resistance who were prescribed either oral chlorothiazide or metolazone during the time period of July 1st, 2016 to July 31st 2018. The data was collected using data warehouse and Emory Electronic Medical Record (EeMR). Patients who were eligible for analysis were recruited according to the study inclusion and exclusion criteria. The study protocol was approved by local institutional review board.

The data was comprised of 1) baseline data: demographics, heart failure type and New York Heart Association (NYHA) classification, weight, serum electrolytes, medical comorbidities, and home medications. 2) The average daily doses of loop diuretic and thiazide-type diuretic. The outcome measures assessed prior to loop diuretic administration, before and after thiazide diuretic administration. In this dataset, obvious abnormal body indexes, which includes extremely high or low weight or weight changes, medically improper measure of serum electrolytes were detected and treated as missing value. All missing values are removed during specific analysis.

The primary end point was defined as the change in 24-hour urine output (UOP) from loop diuretic only administration to thiazide-type diuretic combined administration since it is the most essential index for the efficacy of the additional thiazide-type diuretic for ADHF patients with loop diuretic resistance. The secondary end points were consisted of change in body weight, serum creatinine, serum electrolytes, Length of Stay (LOS), need for Intensive Care Unit (ICU) transfer, and 30-day readmission.

2.2 Statistical Analysis

A summary of descriptive was estimated for all variables collected that all continuous variables will be presented as means, standard deviations, and ranges, while all categorical variables will be summarized by percentages and frequencies.

For the primary objective in terms of efficacy, net urine output (UOP) was used as the efficacy index. Then a two-sample t-test was performed to compare the primary end point: change in 24-hour UOP from loop diuretic only administration to thiazide-type diuretic combined administration between the oral chlorothiazide group and oral metolazone group. Furthermore, General linear model (GLM) was utilized in the multivariable analysis to estimate the adjusted difference in the UOP between the two groups (chlorothiazide and metolazone) after adjusting for other factors.

For the secondary objective, changes in body weight and length of stay for oral chlorothiazide and oral metolazone groups were compared using a two-sample t-test and used as another efficacy index. The general linear model (GLM) was further used to compare the differences (change in body weight and length of stay) between the two groups using a similar multivariable analysis above to adjust for other factors. ICU transfer rate due to refractory volume status was analyzed using a Chi-square test between the two groups and logistic regression model will be employed to test the difference in ICU transfer rate between the two groups since the outcomes are binary. The difference in progression to renal replacement during admission between the two groups was first analyzed using the Chi-square test and then analyzed by logistic regression after adjusting for other factors since the outcomes are binary.

For the third objective, changes in serum electrolytes and creatinine over 24-hour were compared using two-sample t-tests between the two groups (oral metolazone vs oral chlorothiazide) and used as safety outcome indexes. GLM models were further used for each serum electrolyte and creatinine to adjust for other factors.

Statistical analysis was performed by using R statistical software, v.3.2.3 and SAS 9.4 (32).

3. Results

A total of 326 patients were identified and recruited for the study according to the inclusion and exclusion criteria, and of this total, 251 were excluded: 192 patients received both oral chlorothiazide and metolazone, and 59 patients received a thiazide or thiazide-type diuretic prior to the study period. Then 75 patients were included in the final analysis with 22 patients in the oral chlorothiazide group and 53 patients in the metolazone group shown in Figure 1.

3.1 baseline characteristics

The baseline characteristics of patients included in the analysis were very similar between the oral chlorothiazide group and metolazone group and are shown in Table 1. The average age, percentage of males and females, and percentage of race were comparable. The median age of the patients was 64 years (IQR 53-74 years), 60% were male and the majority (61%) were African American. Most patients had non-ischemic cardiomyopathy (54%), non-reduced ejection fraction (70% since the average EF% is 30%), and NYHA class III or IV (41.3%).

Baseline body weight and serum electrolytes were similar between the two groups. Patients in the metolazone group had a higher baseline serum creatinine concentration than those in the oral chlorothiazide group (1.7 mg/dL vs. 1.3 mg/dL, p = 0.008). There were no major differences in comorbidities or home heart failure medication therapies between the two groups. Mean home loop diuretic dose in furosemide equivalents were 97.1 mg/day ± 60.4 in the oral chlorothiazide group and 120 mg/day ± 81.8 in the metolazone group (p = 0.26).

3.2 Efficacy Outcomes

3.2.1 primary outcomes

Comparison of 24-hour UOP are shown in Table 2. Baseline output of 24-hour UOP before thiazide-type diuretic administration were similar between the patients who received oral chlorothiazide and those who received metolazone (2135.2 mL ± 1161.0 vs. 1855.6 mL ± 1231.0, respectively, p=0.366). The addition of a thiazide-type diuretic similarly increased 24-hour UOP for both the oral chlorothiazide and metolazone groups (2950.7 mL ± 1345.6 vs. 3151.1 mL ± 1349.2, respectively, p = 0.559). The change in UOP output after thiazide-type diuretic was then calculated for both groups (815.5 mL ± 1505.8 vs. 1295 mL ± 1857.9, p = 0.290) (Appendix Table 1). After applying GLM analysis, we did not observe significant cohort difference in predicting the UOP output after different thiazide-type diuretic (p = 0.149), adjusting for other factors (Appendix Table 10).

3.2.2 Secondary outcomes

Secondary outcomes are shown in Tables 3. No significant differences in LOS (8.3 days ± 5.7 vs. 10.4 days ± 8.8, p = 0.304), and ICU transfer rates (22.72% vs. 20.75%, p = 0.849) were found between the oral chlorothiazide and metolazone groups. After applying GLM analysis for LOS and logistic regression model for ICU transfer rates, we did not observe significant cohort difference in predicting LOS (p = 0.528) and ICU transfer rates (p = 0.886) of these patients adjusting for other factors. (appendix table 2 and 3) Interestingly, a statistical difference was detected when comparing weight change after (-0.5 kg ± 1.7 vs. -2.1 kg ± 2.6, p = 0.016) and 30-day readmission rates between the two cohorts (20.8% vs. 45.5%, p = 0.030). Similarly, after applying GLM analysis for weight change after different thiazide-type diuretic and logistic regression model for 30-day readmission rates, we did discover a significant mean difference in predicting weight change (B = 2.29 [0.84,3.74], p = 0.002) in the two groups and odds of 30-day readmission rates (OR = 2.77 [0.87,8.79], p = 0.085) in one group relative to the odd of another group is significantly different adjusting for other factors. (appendix table 4 and 5).

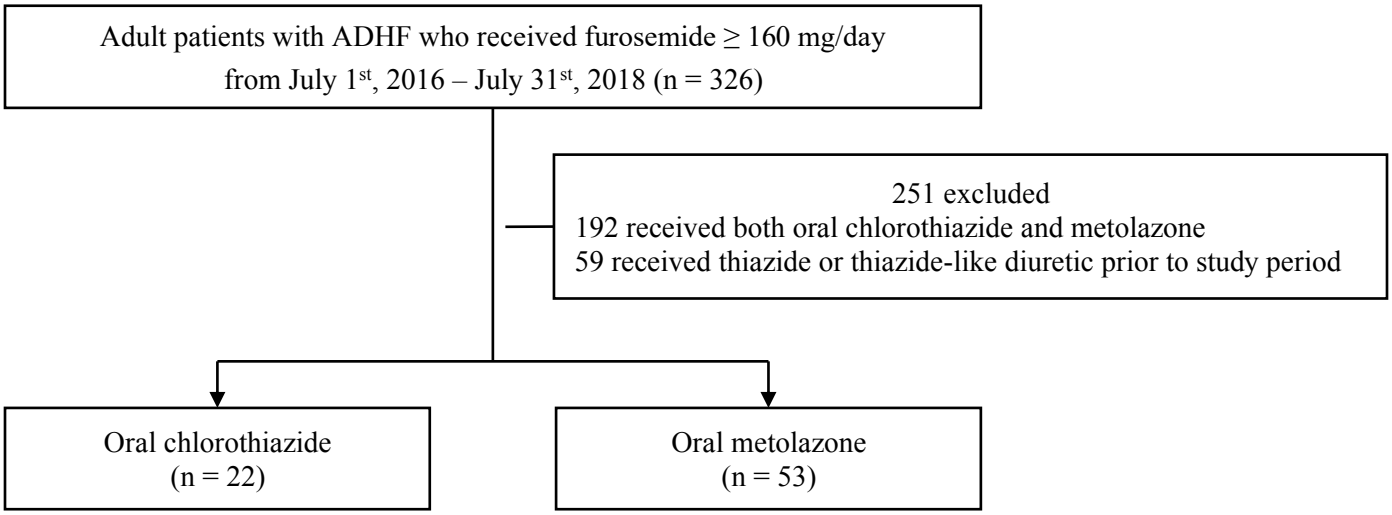
3.3 Safety outcomes

3.3.1 Third outcomes

There was a similar change in serum creatinine concentration after the thiazide-type diuretic and the baseline results for each group (0.04 mg/dL ± 0.263 in the chlorothiazide group vs. 0.13 mg/dL ± 0.304 in the metolazone group, p=0.297). No significant differences in change in serum sodium (-0.10 mg/dL ± 2.142 vs. -0.90 mg/dL ± 3.054, p = 0.274), serum potassium (-0.39 mg/dL ± 1.011 vs. -0.14 mg/dL ± 0.509, p = 0.168), or serum magnesium (0.08 mg/dL ± 0.196 vs.

0.03 mg/dL ± 0.234, p = 0.489) were detected between the two groups. Significant cohort difference is absent after we did the GLM analysis for serum creatinine concentration (B = 0[-.014,0.13], p = 0.961) and serum sodium (B = 0.57[-0.73,1.86], p = 0.391), potassium (B = -0.25[-0.57,0.08], p = 0.143) and magnesium (B = 0.02[-0.08,0.11] p = 0.761) since according to the coefficient of the reference group and its p-value the mean differences of these indexes between the two groups are insignificant adjusting for all other factors. (Appendix table 6-9)

Figure 1



To be eligible for analysis, patients were required to meet the following inclusion criteria:

1. Adults ≥ 18 years of age.
2. Admitted to the cardiology medical unit of Emory University Hospital Midtown with diagnosis of ADHF.
3. Patients with loop diuretic resistance, defined as administration of IV furosemide at a dose of 160 mg/day or higher during their hospitalization.
4. Received at least one dose of metolazone or oral chlorothiazide, in addition to loop diuretic.

Patients were excluded from the study for any of the following reasons:

1. Patients who received both oral chlorothiazide and metolazone
2. Patients who received thiazide or thiazide-type diuretic prior to demonstrating loop diuretic resistance, or was reported to be receiving it at home.
3. Patients who received a loop diuretic dose increased by 25% or greater with the thiazide diuretic
4. Patients who received spironolactone dose greater than or equal to 50 mg, eplerenone dose greater than or equal to 100 mg, or any dose of vasopressin receptor antagonists within 24-hour of thiazide diuretic.
5. Patients who received loop diuretic continuous IV infusion.

Table 1. Baseline Characteristics

Characteristic	Oral chlorothiazide (n = 22)	Oral metolazone (n = 53)	*P*-value
Age, years	59.6 ± 16.1	64.9 ± 14.0	0.16
Male, n (%)	11 (50.0)	34 (64.2)	0.26
Race/Ethnicity			0.45
African American	16 (72.7)	45 (84.9)	
Caucasian	5 (22.7)	5 (9.4)	
Other	1 (4.6)	3 (5.7)	
Heart failure etiology			0.28
Ischemic	6 (27.3)	24 (45.3)	
Non-ischemic	14 (63.6)	27 (50.9)	
Undefined	2 (9.1)	2 (3.8)	
Type of heart failure			0.80
Reduced ejection fraction	15 (68.2)	38 (71.7)	
Preserved ejection fraction	6 (27.3)	14 (26.4)	
Not specified per note	1 (4.6)	1 (1.9)	
Ejection fraction, %	28.6 ± 19.3	30.6 ± 18.7	0.67
NYHA class			0.29
II	1 (4.6)	3 (5.6)	
III	8 (36.4)	16 (29.6)	
IV	4 (18.2)	3 (5.6)	
Not classified per note	9 (40.9)	31 (58.5)	
Body weight, kg	96.6 ± 30.6	109.0 ± 29.5	0.11
Sodium concentration, mEq/L	136.1 ± 4.6	137.8 ± 5.1	0.21
Potassium concentration, mEq/L	3.9 ± 0.5	4.0 ± 0.6	0.36
Magnesium concentration, mg/dl	2.1 ± 0.2	2.1 ± 0.3	0.95
Serum creatinine concentration, mg/dl	1.3 ± 04	1.7 ± 0.7	0.01
BNP concentration, pg/ml	1514.0 ± 2020.6	1121.4 ± 1132.2	0.31
Co-morbidities			
Atrial fibrillation/flutter	8 (36.4)	27 (50.9)	0.25
CAD	6 (27.3)	27 (50.9)	0.06
CKD	11 (50.0)	27 (50.9)	0.94
DM	8 (36.4)	27 (50.9)	0.25
HTN	17 (77.3)	45 (84.9)	0.43
Dyslipidemia	10 (45.5)	20 (37.7)	0.53
ICD	5 (22.7)	11 (20.8)	0.85
Ventricular arrhythmias	2 (9.1)	5 (9.4)	0.96
Home medications			
Loop diuretic	21 (95.5)	44 (83.1)	0.15
Thiazide diuretic	1 (4.5)	2 (3.7)	0.88
ACEI/ARB/ARNI	12 (54.5)	26 (49.1)	0.67
β-blocker	14 (63.6)	42 (79.3)	0.16
Aldosterone antagonist	9 (40.9)	16 (30.2)	0.37
Digoxin	1 (4.5)	2 (3.7)	0.88
Hydralazine	3 (13.6)	19 (35.8)	0.05
Nitrates	4 (18.2)	8 (15.1)	0.74
IV inotropes	2 (9.1)	1 (1.9)	0.15
Home loop diuretic therapy			0.18
Furosemide	5	17	

Torsemide	16	25	
Bumetanide	0	2	
Not specified	1	9	
Home loop diuretic dose in furosemide equivalents, mg/day	97.1 ± 60.4	120 ± 81.8	0.26

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; CAD, coronary artery disease; CKD, chronic kidney disease; DM, diabetes mellitus; HTN, hypertension; ICD, implantable cardioverter defibrillator; IV, intravenous; NYHA, New York Heart Association

Table 2. Primary Outcome

24-Hour Urine Output (mL)	**Oral chlorothiazide (n = 22)**	**Oral metolazone (n = 53)**	***P*-value**
Before thiazide-type diuretic administration	2135.2 ± 1161.0	1855.6 ± 1231.0	0.366
After thiazide-type diuretic administration	2950.7 ± 1345.6	3151.1 ± 1346.2	0.559
Change in urine output	815.5 ± 1557.0	1295.5 ± 1857.9	0.290

Table 3. Secondary Outcomes

Outcome	**Oral chlorothiazide (n = 22)**	**Oral metolazone (n = 53)**	***P*-value**
Change in total body weight (kg)	-0.5 ± 1.7	-2.1 ± 2.6	0.016
Length of stay (days)	8.3 ± 5.7	10.4 ± 8.8	0.304
ICU transfer, n (%)	5 (22.72)	11 (20.75)	0.849
30-day readmission rate, n (%)	10 (45.45)	11 (20.75)	0.030

Table 4. Safety Outcomes

Outcomes	**Oral chlorothiazide (n = 22)**	**Oral metolazone (n = 53)**	***P*-value**
Change in serum creatinine concentration, mg/dL	0.04 ± 0.263	0.13 ± 0.304	0.276
Change in serum sodium concentration, mg/dL	-0.10 ± 2.142	-0.90 ± 3.054	0.274
Change in serum potassium concentration, mg/dL	-0.39 ± 1.011	-0.14 ± 0.509	0.168
Change in serum magnesium concentration, mg/dL	0.05 ± 0.196	0.03 ± 0.234	0.489

4. Discussions

While this study was not powered to detect non-inferiority, there were no trends favoring oral chlorothiazide or oral metolazone for the primary or safety outcomes. There are two surprising findings that one was there were more patients readmitted within 30 days in the oral chlorothiazide group when compared to the oral metolazone group. There are a variety of possible explanations for this incidental finding. At our institution, there is no protocol delineating which thiazide diuretic to choose for patients, so provider preference drives the selection. It could be solely by chance that oral chlorothiazide was correlated with more 30-day readmissions. Additionally, we did not collect why patients were readmitted after 30-days, so the provocation behind readmission is unknown and hypothesis generating. Another one was the expected significant weight change between after the thiazide-type diuretic and the baseline weight for each group that might be from insufficient observation number or unidentified confounding or correlation between weight change and other covariates. For potential future studies, survival data of the two cohorts could be

collected for follow-ups to analyze the difference between the survival rate of oral metolazone and that of oral chlorothiazide treatments.

Due to the nature of this retrospective chart review, this study has many limitations that warrant additional discussion. First, the retrospective nature of this study means we were not able to control for selection bias and differences in medical record documentation. Patients were assigned to their respective treatment groups based on provider preferences. Also, the small sample size of 75 patients, of which the groups were also not equal, may have greatly limited the study's ability to see differences among baseline characteristics and study outcomes. However, we felt it was necessary to apply relatively strict inclusion and exclusion criteria, enabling us to best identify and assess the efficacy and safety outcomes. Adding to that, we also chose to include only our primary institution in this initial study to try and control for consistencies amongst nursing staff regarding documentation and therefore made it a single-center cohort study. This decision limited our data as provider medication selections vary by preference at each institution. Finally, accurate assessment of our study outcomes hinged on accurate collection and documentation of urine output, as well as consistent electrolyte monitoring, which can vary between staff members.

5. Conclusions

In patients hospitalized with ADHF and diuretic resistance receiving thiazide-type treatment for augmenting diuresis, there was no statistically significant difference detected in either efficacy or safety indexes between metolazone and chlorothiazide and the effects for both treatments on renal function and serum electrolyte concentrations are similar as well. However, additional studies powered to detect non-inferiority are required.

6.Reference

1. Joseph, S.M., et al., *Acute decompensated heart failure: contemporary medical management.* Texas Heart Institute Journal, 2009. **36**(6): p. 510.
2. Moranville, M.P., et al., *Comparison of metolazone versus chlorothiazide in acute decompensated heart failure with diuretic resistance.* Cardiovascular therapeutics, 2015. **33**(2): p. 42-49.
3. Shulenberger, C.E., et al., *Efficacy and safety of intravenous chlorothiazide versus oral metolazone in patients with acute decompensated heart failure and loop diuretic resistance.* Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy, 2016. **36**(8): p. 852-860.
4. Yancy, C.W., et al., *2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines.* Journal of the American College of Cardiology, 2013. **62**(16): p. e147-e239.
5. Jentzer, J.C., T.A. DeWald, and A.F. Hernandez, *Combination of loop diuretics with thiazide-type diuretics in heart failure.* Journal of the American College of Cardiology, 2010. **56**(19): p. 1527-1534.
6. Cox, Z.L. and D.J. Lenihan, *Loop Diuretic Resistance in Heart Failure: Resistance Etiology–Based Strategies to Restoring Diuretic Efficacy.* Journal of cardiac failure, 2014. **20**(8): p. 611-622.
7. Felker, G.M., et al., *Diuretic strategies in patients with acute decompensated heart failure.* New England Journal of Medicine, 2011. **364**(9): p. 797-805.
8. Ng, T.M., et al., *Comparison of bumetanide-and metolazone-based diuretic regimens to furosemide in acute heart failure.* Journal of cardiovascular pharmacology and therapeutics, 2013. **18**(4): p. 345-353.
9. Rosenberg, J., et al., *Combination therapy with metolazone and loop diuretics in outpatients with refractory heart failure: an observational study and review of the literature.* Cardiovascular drugs and therapy, 2005. **19**(4): p. 301-306.
10. Mouallem, M., et al., *Prolonged therapy by the combination of furosemide and thiazides in refractory heart failure and other fluid retaining conditions.* International journal of cardiology, 1995. **50**(2): p. 89-94.

7.Appendix

Table 1. Descriptive statistics for all variables

Variable	Level	N (%) = 75)
Age	Mean	63.36
	Median	64.00
	Minimum	25.00
	LowerQuartile	53.00
	UpperQuartile	74.00
	Maximum	90.00
	Std Dev	14.70
	Missing	0.00
Gender	Female	30 (40.0)
	Male	45 (60.0)
Ethnicity	African American	61 (81.3)
	White	10 (13.3)
	Others	4 (5.3)
Afib/flutter	0	40 (53.3)
	1	35 (46.7)
CAD	0	42 (56.0)
	1	33 (44.0)
CKD	0	37 (49.3)
	1	38 (50.7)

Variable	Level	N (%) = 75)
DM	0	40 (53.3)
	1	35 (46.7)
HTN	0	13 (17.3)
	1	62 (82.7)
HLD	0	45 (60.0)
	1	30 (40.0)
ICD	0	59 (78.7)
	1	16 (21.3)
Vtach/Vfib	0	68 (90.7)
	1	7 (9.3)
HF Etiology	1	30 (40.0)
	2	41 (54.7)
	3	4 (5.3)
Type of HF	1	20 (26.7)
	2	53 (70.7)
	3	2 (2.7)

Variable	Level	N (%) = 75)
EF (%)	Mean	30.01
	Median	25.00
	Minimum	3.00
	LowerQuartile	15.00
	UpperQuartile	45.00
	Maximum	75.00
	Std Dev	18.80
	Missing	0.00
NYHA Class	2	4 (5.3)
	3	24 (32.0)
	4	7 (9.3)
	5	40 (53.3)
Loop DU	0	10 (13.3)
	1	65 (86.7)
Home Loop DU	Bumetanide	2 (2.7)
	Furosemide	22 (29.3)
	N/A	10 (13.3)
	Torsemide	41 (54.7)
Home Loop Dose in Furosemide Equivalents (mg/day)	Mean	112.62
	Median	100.00
	Minimum	20.00
	LowerQuartile	80.00
	UpperQuartile	160.00
	Maximum	400.00
	Std Dev	75.88
	Missing	10.00

Variable	Level	N (%) = 75)
Thiazide DU	0	72 (96.0)
	1	3 (4.0)
ACEI/ARB	0	37 (49.3)
	1	38 (50.7)
B-blocker	0	19 (25.3)
	1	56 (74.7)
ADO Antagonist	0	50 (66.7)
	1	25 (33.3)
Digoxin	0	72 (96.0)
	1	3 (4.0)
Hydralazine	0	53 (70.7)
	1	22 (29.3)
Nitrates	0	63 (84.0)
	1	12 (16.0)
IV inotropes	0	72 (96.0)
	1	3 (4.0)

Variable	Level	N (%) = 75)
Loop DU1	Mean	1154.69
	Median	1150.00
	Minimum	-3150.00
	LowerQuartile	125.00
	UpperQuartile	2150.00
	Maximum	7950.00
	Std Dev	1778.18
	Missing	0.00
Loop DU2	Mean	1154.69
	Median	1150.00
	Minimum	-3150.00
	LowerQuartile	125.00
	UpperQuartile	2150.00
	Maximum	7950.00
	Std Dev	1778.18
	Missing	0.00
Wt# prior to loop DU	Mean	105.35
	Median	100.60
	Minimum	52.70
	LowerQuartile	80.50
	UpperQuartile	123.50
	Maximum	189.20
	Std Dev	30.15
	Missing	0.00

Variable	Level	N (%) = 75)
Wt day after Loop DU	Mean	104.47
	Median	100.10
	Minimum	51.10
	LowerQuartile	78.95
	UpperQuartile	125.30
	Maximum	184.80
	Std Dev	30.68
	Missing	3.00
Wt# day after Loop + THZ DU	Mean	101.90
	Median	99.60
	Minimum	49.90
	LowerQuartile	77.30
	UpperQuartile	120.80
	Maximum	184.00
	Std Dev	30.21
	Missing	0.00
pre_BNP	Mean	1246.61
	Median	759.00
	Minimum	110.00
	LowerQuartile	325.00
	UpperQuartile	1660.00
	Maximum	9222.00
	Std Dev	1470.36
	Missing	6.00

Variable	Level	N (%) = 75)
pre_Na	Mean	137.22
	Median	138.00
	Minimum	121.00
	LowerQuartile	135.00
	UpperQuartile	140.00
	Maximum	148.00
	Std Dev	4.95
	Missing	1.00
pre_K	Mean	4.01
	Median	3.90
	Minimum	2.90
	LowerQuartile	3.60
	UpperQuartile	4.40
	Maximum	5.60
	Std Dev	0.57
	Missing	1.00
pre_Mg	Mean	2.05
	Median	2.00
	Minimum	1.30
	LowerQuartile	1.80
	UpperQuartile	2.30
	Maximum	2.60
	Std Dev	0.27
	Missing	12.00

Variable	Level	N (%) = 75)
pre_SCr	Mean	1.58
	Median	1.50
	Minimum	0.50
	LowerQuartile	1.13
	UpperQuartile	1.90
	Maximum	3.86
	Std Dev	0.62
	Missing	1.00
mid_Na+	Mean	137.07
	Median	138.00
	Minimum	123.00
	LowerQuartile	134.00
	UpperQuartile	140.00
	Maximum	148.00
	Std Dev	4.97
	Missing	2.00
mid_K+	Mean	3.95
	Median	3.90
	Minimum	3.30
	LowerQuartile	3.60
	UpperQuartile	4.20
	Maximum	4.90
	Std Dev	0.39
	Missing	3.00

Variable	Level	N (%) = 75)
mid_Mg2+	Mean	2.06
	Median	2.10
	Minimum	1.60
	LowerQuartile	1.90
	UpperQuartile	2.20
	Maximum	2.70
	Std Dev	0.21
	Missing	4.00
mid_SCr	Mean	1.62
	Median	1.56
	Minimum	0.49
	LowerQuartile	1.18
	UpperQuartile	1.99
	Maximum	3.49
	Std Dev	0.57
	Missing	3.00
post_Na	Mean	136.32
	Median	136.50
	Minimum	122.00
	LowerQuartile	134.00
	UpperQuartile	140.00
	Maximum	146.00
	Std Dev	4.42
	Missing	1.00

Variable	Level	N (%) = 75)
post_K	Mean	3.74
	Median	3.80
	Minimum	0.40
	LowerQuartile	3.40
	UpperQuartile	4.10
	Maximum	5.00
	Std Dev	0.61
	Missing	0.00
post_Mg	Mean	2.11
	Median	2.10
	Minimum	1.60
	LowerQuartile	2.00
	UpperQuartile	2.20
	Maximum	2.80
	Std Dev	0.20
	Missing	4.00
post_SCr 2	Mean	1.71
	Median	1.65
	Minimum	0.52
	LowerQuartile	1.27
	UpperQuartile	2.03
	Maximum	3.72
	Std Dev	0.65
	Missing	1.00

Variable	Level	N (%) = 75)
Prior to Loop DU	Mean	1100.37
	Median	401.00
	Minimum	0.00
	LowerQuartile	0.00
	UpperQuartile	1525.00
	Maximum	5577.00
	Std Dev	1449.03
	Missing	0.00
Day after Loop DU	Mean	1937.59
	Median	1600.00
	Minimum	150.00
	LowerQuartile	1000.00
	UpperQuartile	2800.00
	Maximum	5450.00
	Std Dev	1209.87
	Missing	0.00
Day after Loop + THZ	Mean	3092.28
	Median	2900.00
	Minimum	1000.00
	LowerQuartile	2150.00
	UpperQuartile	3825.00
	Maximum	8200.00
	Std Dev	1340.05
	Missing	0.00

Variable	Level	N (%) = 75)
LOS (days)	Mean	9.81
	Median	7.00
	Minimum	2.00
	LowerQuartile	5.00
	UpperQuartile	12.00
	Maximum	49.00
	Std Dev	8.07
	Missing	0.00
ICU Transfer	0	59 (78.7)
	1	16 (21.3)
30D Readmission?	0	54 (72.0)
	1	21 (28.0)
wt_chg_32	Mean	-1.87
	Median	-1.50
	Minimum	-17.60
	LowerQuartile	-3.20
	UpperQuartile	-0.45
	Maximum	6.40
	Std Dev	3.10
	Missing	3.00

Variable	Level	N (%) = 75)
wt_chg_31	Mean	-1.54
	Median	-1.30
	Minimum	-10.10
	LowerQuartile	-2.90
	UpperQuartile	0.00
	Maximum	16.90
	Std Dev	3.66
	Missing	3.00
uop_chg_24	Mean	1154.69
	Median	1150.00
	Minimum	-3150.00
	LowerQuartile	125.00
	UpperQuartile	2150.00
	Maximum	7950.00
	Std Dev	1778.18
	Missing	0.00
na_change	Mean	-0.67
	Median	-1.00
	Minimum	-8.00
	LowerQuartile	-2.00
	UpperQuartile	0.00
	Maximum	11.00
	Std Dev	2.83
	Missing	3.00

Variable	Level	N (%) = 75)
k_change	Mean	-0.21
	Median	-0.20
	Minimum	-4.00
	LowerQuartile	-0.50
	UpperQuartile	0.20
	Maximum	1.20
	Std Dev	0.70
	Missing	3.00
mg_change	Mean	0.05
	Median	0.00
	Minimum	-0.40
	LowerQuartile	-0.10
	UpperQuartile	0.20
	Maximum	0.80
	Std Dev	0.22
	Missing	8.00
scr_change	Mean	0.10
	Median	0.05
	Minimum	-0.33
	LowerQuartile	-0.11
	UpperQuartile	0.20
	Maximum	1.20
	Std Dev	0.29
	Missing	4.00

Table 2. GLM model for patients' LOS

		LOS (days)			
Covariate	**Level**	**B**	**95%CI Low**	**95%CI Up**	**B P-Value**
THZ DU	Chlorothiazide	-1.03	-4.25	2.18	0.528
	Metolazone	-	-	-	-
CKD		2.92	0.10	5.75	**0.043**
Loop DU		-2.28	-6.71	2.14	0.311
Home Loop DU	Bumetanide	-2.86	-12.42	6.69	0.557
	Furosemide	4.36	1.09	7.62	**0.009**
	N/A	-	-	-	-
	Torsemide	-	-	-	-
IV inotropes		-10.67	-19.12	-2.22	**0.013**
Inotropes		10.87	7.41	14.33	**<.001**

* Number of observations in the original data set = %(75).
Number of observations used = %(75).
Backward selection with an alpha level of removal of 0.05 was used. The following variables were removed from the model: ACEI/ARB, ADO Antagonist, Afib/flutter, Age, B-blocker, CAD, DM, Day after Loop DU, Ethnicity, Gender, HF Etiology, HLD, HTN, Home Loop Dose in Furosemide Equivalents (mg/day), Hydralazine, ICD, Nitrates, Prior to Loop DU, Thiazide DU, Type of HF, Vasodilators, Vtach/Vfib, and Wt# prior to loop DU.

Table 3. Logistic regression model for patients' ICU transfer rate

Covariate	Level	N	%(ICU Transfer)=1 Odds Ratio (95% CI)	OR P-value	Type3 P-value
THZ DU	Chlorothiazide	19	1.14 (0.24-5.38)	0.866	0.866
	Metolazone	52	-	-	
B-blocker		71	0.15 (0.03-0.65)	0.011	**0.011**
mid_Mg2+		71	76.59 (1.69-3480.86)	0.026	**0.026**
LOS (days)		71	1.13 (1.03-1.25)	0.012	**0.012**

* Number of observations in the original data set = %(75). Number of observations used = %TRIM(71).
** Backward selection with an alpha level of removal of .05 was used. The following variables were removed from the model: Loop DU, and mid_K+.

Table 4. GLM model for patients' weight change

Covariate	Level	Weight change B	95%CI Low	95%CI Up	B Value P-
THZ DU	Chlorothiazide	2.29	0.84	3.74	**0.002**
	Metolazone	-	-	-	**-**
Gender	1	-2.09	-3.45	-0.72	**0.003**
	2	-	-	-	**-**
Loop DU		-	-	-	**-**

Covariate	Level	Weight change B	95%CI Low	95%CI Up	B P-Value
B-blocker		2.25	0.63	3.86	**0.006**
Home Loop Dose in Furosemide Equivalents (mg/day)		-0.02	-0.02	-0.01	**<.001**
Inotropes		1.73	0.06	3.39	**0.042**

* Number of observations in the original data set = %(75).
Number of observations used = %(63).
Backward selection with an alpha level of removal of 0.05 was used. The following variables were removed from the model: ACEI/ARB, ADO Antagonist, Afib/flutter, Age, CAD, CKD, DM, Day after Loop DU, Ethnicity, HF Etiology, HLD, HTN, Home Loop DU,
Hydralazine, ICD, IV inotropes, Nitrates, Prior to Loop DU, Thiazide DU, Type of HF, Vasodilators, Vtach/Vfib, and Wt# prior to lo op DU.

Table 5. Logistic regression model for patients' 30-day readmission rate

Covariate	Level	N	%(30D Readmission)=1 Odds Ratio (95% CI)	OR P-value	Type3 P-value
THZ DU	Chlorothiazide	22	2.77 (0.87-8.79)	0.085	0.085
	Metolazone	53	-	-	
B-blocker		75	0.17 (0.05-0.55)	0.003	**0.003**

* Number of observations in the original data set = %(75). Number of observations used = %(75).
** Backward selection with an alpha level of removal of .05 was used. The following variables were removed from the model: LOS (days), Loop DU, mid_K+, and mid_Mg2+.

Table 6 GLM model for patients' serum creatinine concentration

		serum creatinine concentration			
Covariate	**Level**	**B**	**95%CI Low**	**95%CI Up**	**B P-Value**
THZ DU	Chlorothiazide	-0.00	-0.14	0.13	0.961
	Metolazone	-	-	-	-
Ethnicity	1	0.19	-0.14	0.53	0.250
	3	-0.05	-0.43	0.32	0.774
	5	-	-	-	-
HF Etiology	1	0.37	0.11	0.63	**0.006**
	2	0.09	-0.16	0.34	0.484
	3	-	-	-	-
Home Loop Dose in Furosemide Equivalents (mg/day)		-0.00	-0.00	-0.00	**0.003**

* Number of observations in the original data set = %(75).
Number of observations used = %(62).
Backward selection with an alpha level of removal of 0.05 was used. The following variables were removed from the model: ACEI/ARB, ADO Antagonist, Afib/flutter, Age, B-blocker, CAD, CKD, DM, Day after Loop DU, Gender, HLD, HTN, Home Loop DU, Hydralazine,
ICD, IV inotropes, Inotropes, Nitrates, Prior to Loop DU, Thiazide DU, Type of HF, Vasodilators, Vtach/Vfib, and Wt# prior to loo p DU.

Table 7. GLM model for patients' serum sodium concentration

		serum sodium concentration			
Covariate	**Level**	**B**	**95%CI Low**	**95%CI Up**	**B P-Value**
THZ DU	Chlorothiazide	0.57	-0.73	1.86	0.391
	Metolazone	-	-	-	-
CAD		-1.57	-2.81	-0.34	**0.012**
Type of HF	1	0.84	-3.94	5.61	0.732
	2	-0.89	-5.56	3.78	0.709
	3	-	-	-	-
Loop DU		-	-	-	-
Nitrates		-1.67	-3.24	-0.09	**0.038**
Home Loop Dose in Furosemide Equivalents (mg/day)		0.01	0.00	0.02	**0.005**

* Number of observations in the original data set = %(75).
Number of observations used = %(63).
Backward selection with an alpha level of removal of 0.05 was used. The following variables were removed from the model: ACEI/ARB, ADO Antagonist, Afib/flutter, Age, B-blocker, CKD, DM, Day after Loop DU, Ethnicity, Gender, HF Etiology, HLD, HTN, Home Loop DU, Hydralazine, ICD, IV inotropes, Inotropes, Prior to Loop DU, Thiazide DU, Vasodilators, Vtach/Vfib, and Wt# prior to loop D U.

Table 8. GLM model for patients' serum potassium concentration

		serum potassium concentration			
Covariate	**Level**	**B**	**95%CI Low**	**95%CI Up**	**B P-Value**
THZ DU	Chlorothiazide	-0.25	-0.57	0.08	0.143
	Metolazone	-	-	-	-
Gender	1	0.32	0.02	0.62	**0.037**
	2	-	-	-	-
Prior to Loop DU		-0.00	-0.00	-0.00	**0.011**

* Number of observations in the original data set = %(75).
Number of observations used = %(72).
Backward selection with an alpha level of removal of 0.05 was used. The following variables were removed from the model: ACEI/ARB, ADO Antagonist, Afib/flutter, Age, B-blocker, CAD, CKD, DM, Day after Loop DU, Ethnicity, HF Etiology, HLD, HTN, Home Loop DU, Home Loop Dose in Furosemide Equivalents (mg/day), Hydralazine, ICD, IV inotropes, Inotropes, Loop DU, Nitrates, Thiazide DU, Type of HF, Vasodilators, Vtach/Vfib, and Wt# prior to loop DU.

Table 9. GLM model for patients' serum magnesium concentration

		serum magnesium concentration			
Covariate	**Level**	**B**	**95%CI Low**	**95%CI Up**	**B P-Value**
THZ DU	Chlorothiazide	0.02	-0.08	0.11	0.761
	Metolazone	-	-	-	-
Ethnicity	1	-0.19	-0.52	0.15	0.271
	2	0.28	-0.19	0.76	0.244
	3	-0.32	-0.68	0.03	0.073
	5	-0.21	-0.61	0.20	0.318
	6	-	-	-	-
ACEI/ARB		-0.15	-0.22	-0.07	**<.001**
ADO Antagonist		0.13	0.04	0.22	**0.005**
Hydralazine		0.16	0.05	0.27	**0.004**
Nitrates		-0.20	-0.33	-0.06	**0.004**
Inotropes		-0.15	-0.24	-0.06	**<.001**
Wt# prior to loop DU		-0.00	-0.01	-0.00	**<.001**
Day after Loop DU		0.00	0.00	0.00	**<.001**

Covariate	Level	serum magnesium concentration			
		B	95%CI Low	95%CI Up	B P-Value

* Number of observations in the original data set = %(75).
Number of observations used = %(67).
Backward selection with an alpha level of removal of 0.05 was used. The following variables were removed from the model: Afib/flutter, Age, B-blocker, CAD, CKD, DM, Gender, HF Etiology, HLD, HTN, Home Loop DU, Home Loop Dose in Furosemide Equivalents (mg/day), ICD, IV inotropes, Loop DU, Prior to Loop DU, Thiazide DU, Type of HF, Vasodilators, and Vtach/Vfib.

Table 10. GLM model for patients' UOP change

Covariate	Level	Day after Loop + THZ			
		B	95%CI Low	95%CI Up	B P-Value
THZ DU	Chlorothiazide	-415.57	-980.55	149.41	0.149
	Metolazone	-	-	-	-
Age		-31.85	-51.13	-12.57	**0.001**
CKD		-814.81	-1392.02	-237.60	**0.006**
HLD		698.12	145.05	1251.19	**0.013**
ICD		770.51	61.07	1479.95	**0.033**
Type of HF	1	-2229.22	-3848.06	-610.37	**0.007**
	2	-2162.85	-3750.81	-574.90	**0.008**
	3	-	-	-	-

Covariate	Level	Day after Loop + THZ			
		B	95%CI Low	95%CI Up	B P-Value
Loop DU		-325.63	-1119.83	468.57	0.422
Home Loop DU	Bumetanide	1842.45	275.23	3409.68	**0.021**
	Furosemide	-253.18	-833.85	327.50	0.393
	N/A	-	-	-	-
	Torsemide	-	-	-	-

* Number of observations in the original data set = %TRIM(75).
Number of observations used = %TRIM(75).
Backward selection with an alpha level of removal of 0.05 was used. The following variables were removed from the model: ACEI/ARB, ADO Antagonist, Afib/flutter, B-blocker, CAD, DM, Day after Loop DU, Ethnicity, Gender, HF Etiology, HTN, Home Loop Dose in Furosemide Equivalents (mg/day), Hydralazine, IV inotropes, Inotropes, Nitrates, Prior to Loop DU, Thiazide DU, Vasodilators, Vtach/Vfib, and Wt# prior to loop DU.