Higher diuretic dosing within the first 72 h is predictive of longer length of stay in patients with acute heart failure

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Abstract

Objective: High-dose diuretic strategies during the first 72 h of hospitalization have been shown to improve symptom resolution in patients with acute heart failure with decreased ejection fraction; however, they have not been shown to decrease length of stay (LOS). This study aimed to examine a possible relationship between higher diuretic dosing in the first 72 h of hospitalization and longer LOS in such patients.

Methods: In this retrospective study, we included 333 consecutive patients hospitalized for acute heart failure with decreased or preserved ejection fraction between July 2014 and June 2015 in an urban academic medical center. Multiple regression models with stepwise selection were used for data analysis. We also performed mediation analysis to assess the relationships between diuretic dose, worsening renal function (WRF) during the hospitalization, and LOS.

Results: In the multiple regression analysis, higher diuretic dosing in the first 72 h independently predicted longer LOS [β=0.42, 95% CI (0.27, 0.56), p<0.001] after adjustments for baseline characteristics, disease severity, and comorbidities. In the mediation analysis, higher diuretic dosing remained a significant predictor for longer LOS even after controlling for the mediator WRF [β=0.39, 95% CI (0.26, 0.53), p<0.001]. WRF had a weak mediation effect on the relationship between higher diuretic dosing and longer LOS [indirect effect of higher diuretic dosing on longer LOS: 0.07, 95% CI (0.02, 0.14)].

Conclusion: Higher diuretic dosing in the first 72 h of hospitalization was an independent predictor for longer LOS. *(Anatol J Cardiol 2018; 20: 110-6)*

Keywords: heart failure, diuretics, worsening renal function, length of stay

Introduction

Over a million patients are hospitalized for acute heart failure every year in the United States, and heart failure management results in a nationwide expenditure of 32 billion dollars annually (1). Diuretic therapy is a mainstay of treatment for acute decompensated heart failure, but its optimal dosing remains unclear. The Diuretic Optimization Strategies Evaluation (DOSE) trial showed a trend toward greater improvement in patients' symptom when using a high-dose diuretic strategy in the first 72 h of hospitalization than when using a low-dose strategy; however, a significantly higher incidence of creatinine level increases was also observed in the high-dose group (2). However, there were no significant differences in length of stay (LOS) between the low-dose and high-dose groups. Although the DOSE trial was conducted in a randomized controlled setting, the implementation of high-dose protocols and their effects on inpatient outcomes on a wide range of populations remain poorly understood.

Although there is no consensus definition for "high-dose" diuretics, it is still widely recommended to use them with caution to avoid over-diuresis (3). In practice, over-diuresis often requires temporary cessation of diuretics for multiple reasons. The high-dose group in the DOSE trial had no adverse outcomes associated with worsening renal function (WRF) during hospitalization as the observed renal injury in most cases was transient. The association between WRF during heart failure hospitalization and longer LOS, however, has been reported elsewhere (4, 5). A retrospective study conducted by El-Refai et al. (6) also showed an association between higher diuretic dosing and worsening glomerular filtration rate (GFR). These past studies indicate the relationships among higher diuretic dosing, WRF, and longer LOS. In other words, higher diuretic dosing leads to WRF, then WRF results in longer LOS. This raises a concern regarding increased hospital resource utilization including longer LOS when using higher diuretic dosing strategies. However, whether a higher diuretic dosing independently results in longer LOS has

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not been evaluated. Thus, we sought to investigate whether a higher diuretic dosing in the early phase of hospitalization would be independently predictive of higher hospital resource utilization including longer LOS.

Methods

Study design and setting

We conducted a retrospective cohort study of consecutive patients hospitalized for acute heart failure with decreased or preserved ejection fraction from July 2014 to June 2015 in our large, urban, academic medical center. During this timeframe, our hospital created and implemented a multidisciplinary clinical pathway for managing acute heart failure. The pathway recommended intravenous furosemide 80 milligrams three times daily according to the mean diuretic dose used in the DOSE trial (2). This standardized diuretic dosing was strongly encouraged for any patient diagnosed with acute heart failure, but final decisions for the initial dosing and subsequent dose adjustment were left up to individual practitioners. As a result, the mean diuretic dose in the first 72 h showed an increasing trend during the study period (Fig. 1).

Sample

We included all patients hospitalized for acute heart failure with decreased or preserved ejection fraction, including those with concurrent acute illnesses such as infections. Patients who had a history of end-stage renal disease, severe aortic stenosis, or any type of shock were excluded because these comorbidities could influence clinical decisions on diuretic dosing. A total of 333 patients were eventually included in our study.

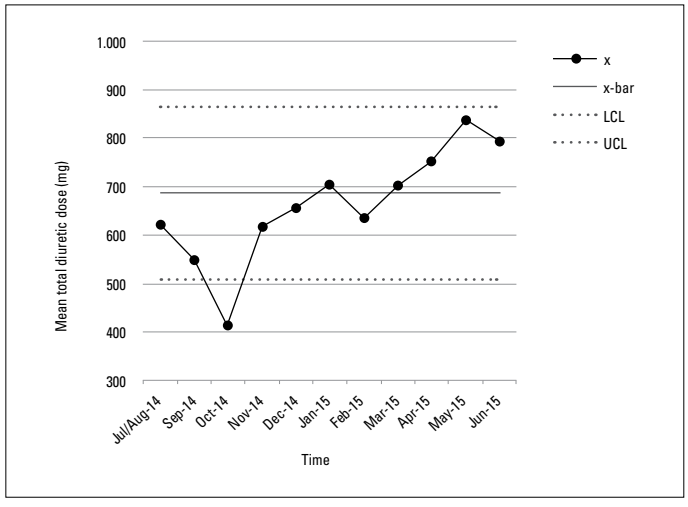

Figure 1. Control chart of mean total diuretic dose administered in the first 72 h of hospitalization. X-axis indicates month and y-axis indicates mean total diuretic dose in milligrams administered in the first 72 h of hospitalization (oral furosemide equivalent).
x-bar - average total diuretic dose; UCL - upper control limit; LCL - lower control limit

Measures

The primary outcome was LOS measured in days. Secondary outcomes included WRF, 30-day readmissions, and in-hospital mortality. WRF was defined as peak reduction in estimated GFR (eGFR) during hospitalization compared to that at hospitalization. eGFR was calculated using the Cockcroft–Gault equation: (140–age) ×body weight) (72×serum creatinine) ×0.85 (if female). Total diuretic dose in the first 72 h was defined as total diuretic dose in milligrams equivalent to oral furosemide dose administered in the first 72 h after hospitalization. We used the following intravenous to oral equivalents to standardize dosing:

- 1 mg of intravenous furosemide equals 2 mg of oral furosemide (1:2)
- 1 mg of torsemide equals 2 mg of oral furosemide (1:2)
- 1 mg of intravenous budesonide equals 40 mg of oral furosemide (1:40)

Other variables collected for the study include age, gender, ethnicity, past medical history, ejection fraction, and whether heart failure was new onset or pre-existing. We also reviewed the details of home medications, including beta blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, aldosterone antagonists, and digoxin, received by the patients. Vital parameters [mean arterial pressure (MAP)], and laboratory data [values of sodium, blood urea nitrogen (BUN), creatinine, troponin, beta-natriuretic peptide (BNP), and hematocrit] on admission and during the first 72 h of hospitalization were recorded, including change in MAP (ΔMAP) and hematocrit (ΔHct). ΔMAP and ΔHct were calculated by subtracting the highest or lowest MAP/hematocrit from the MAP/hematocrit on presentation. Concurrent conditions such as infection on presentation as well as contrast use were also recorded. Infection on presentation was defined as the presence of any type of infection, such as pneumonia, urinary tract infection, or sepsis, in the initial admission note. Contrast use during hospitalization was defined as any intravenous contrast use in the first 72 h of hospitalization.

Data analysis

Descriptive statistics were calculated for all covariates and outcomes. Simple regression analysis was performed to evaluate the relationship between total diuretic dose in the first 72 h and each outcome (LOS, WRF, 30-day readmissions, and in-hospital mortality). Multiple linear or logistic regression models with a stepwise selection method were then used to determine the relationship between total diuretic dose in the first 72 h and each outcome as appropriate, after controlling for patient demographics, comorbidities, and disease severity. All variables except creatinine on presentation, hematocrit on presentation, and MAP on presentation were included in the multiple regression models. This is because these three variables not only showed significant multicollinearity problems but also strongly correlated with BUN, ΔHct, and ΔMAP, respectively. On the other hand, BUN, ΔHct, and ΔMAP did not exhibit significant multicollinearity, and were thus retained in the multiple regression models. The variance in-

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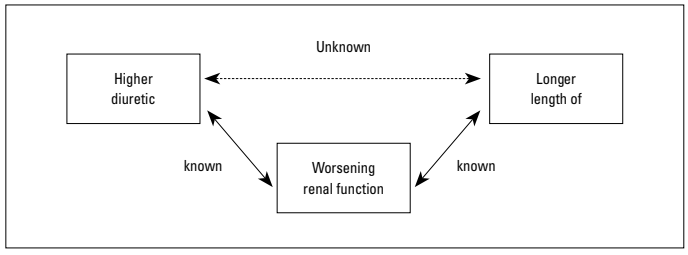

Figure 2. Rationale of a single mediator model: Unknown association between diuretic dosing and length of stay
Previous studies showed the relationship between higher diuretic dosing and WRF as well as between WRF and LOS. It remains unknown whether higher diuretic dosing in the early phase of hospitalization is directly associated with longer LOS. If WRF is a significant mediator, the statistical relationship between diuretic dosing and LOS should be weakened when both diuretic dose and WRF are included as independent variables in regression analysis

flation factor (VIF) and condition index were used to examine collinearity and multicollinearity among covariates in linear regression models. All covariates included in the final models had VIF of <4 and condition index of <10, because of which collinearity was not a major concern in our statistical analysis.

Finally, we performed the mediation analysis to further evaluate whether higher diuretic dosing predicts longer LOS, independent of WRF (Fig. 2) (7). A p value of <0.05 was considered significant. IBM SPSS Statistics for Windows, version 24 (IBM Corp., Armonk, NY, USA) was used for all analyses. The PROCESS macro version 3.0 for SPSS was used for mediation analysis with a bootstrap estimation approach (8). The study protocol was approved by the Institutional Review Board at Mount Sinai Beth Israel.

Results

Patient characteristics and unadjusted outcomes

The mean age of the 333 patients included was 70 years. Among these, 57% were female, 31% were Caucasian, 33% were Hispanic, and 22% were African American (Table 1). Mean ejection fraction (EF) was 36% and mean total diuretic dose in the first 72 h was equivalent to 668 mg of oral furosemide. Unadjusted outcomes revealed a mean LOS of 7.9±6.4 days, with a 30-day readmission rate of 19% and in-hospital mortality of 4.5%. Mean reduction in eGFR was 20.9±17.4 ml/min.

Higher diuretic dosing and longer length of stay

In the simple regression analysis, higher diuretic dosing in the first 72 h of hospitalization significantly predicted a longer LOS (Table 2). This relationship remained significant in the multiple regression analysis (Table 3). Higher diuretic dosing in the first 72 h was an independent predictor for longer LOS [coefficient β=0.42, 95% CI (0.27, 0.56), p<0.001] even after controlling for

Table 1. Patient baseline characteristics

Baseline characteristics	Mean or proportion	Heart failure characteristics	Mean, median, or proportion
Age (years)	70±15	EF (%)	36±20
Female	190 (56%)	New onset HF	72 (21%)
Race		HF admission in 12 mo.	143 (42%)
Caucasian	106 (31%)	Noncompliance	72 (21%)
African American	74 (22%)	Beta blocker at home	238 (70%)
Hispanic	114 (33%)	ACE-I or ARB at home	163 (48%)
Asian	37 (11%)	AA at home	43 (13%)
Other	11 (3%)	Digoxin at home	19 (6%)
BMI (kg/m^2)	30±8.6	ICD	68 (20%)
Past medical history		Other predictors on presentation	
Hypertension	233 (68%)	Total diuretic dose in the first 72 h (mg)	668 (IQR 280–960)
Diabetes mellitus	156 (46%)		
Coronary artery disease	201 (59%)	BUN (mg/dL)	31±19
Atrial Fibrillation	134 (39%)	BNP (pg/mL)	777 (IQR 392–1408)
Pacemaker	49 (14%)	ΔHct	1.7±2.5
Chronic kidney disease	141 (41%)	Infection on presentation	62 (18%)
Stroke	50 (15%)		
COPD	58 (17%)		

AA - aldosterone antagonist; ACE-I - angiotensin-converting enzyme inhibitor; ARB - angiotensin receptor blocker; BMI - body mass index; BUN - blood urea nitrogen; BNP - beta-natriuretic peptide; COPD - chronic obstructive pulmonary disease; EF - ejection fraction; HF - heart failure; ICD - implantable cardioverter-defibrillator; ΔHct - change in hematocrit in the first 72 h of hospitalization

Table 2. Associations between total diuretic dose in the first 72 h and outcomes (results from simple linear and logistic regressions)

Outcome	Variable	Coefficient (β) or odds ratio	Standard error (S.E.)	95% CI	t or Wald	*P*
Length of stay	Total diuretic dose	0.46	0.069	0.32 to 0.60	6.67	<0.001
Reduction in GFR		0.84	0.194	0.46 to 1.22	4.35	<0.001
30-day readmission		1.03	0.03	0.98 to 1.09	1.32	0.25
In-hospital mortality		1.10	0.05	1.01 to 1.21	4.29	0.04

Table 3. Predictors of length of stay, reduction in eGFR, and 30-day readmissions (results from multiple linear/logistic regression with stepwise selection method)

Outcome Covariate	Coefficient (β) or odds ratio*	Standard error (S.E.)	95% CI	t or Wald	*P*
Length of stay					
Total diuretic dose	**0.42**	**0.07**	**0.27 to 0.56**	**5.73**	**<0.001**
Ejection fraction (%)	–0.04	0.02	–0.07 to –0.02	–2.08	0.04
BUN on presentation	0.05	0.02	0.01 to 0.08	2.40	0.02
Infection on presentation	2.74	0.90	0.96 to 4.52	3.04	0.003
History of COPD	2.01	0.87	0.29 to 3.73	2.30	0.02
Noncompliance	–2.45	0.83	–4.07 to -0.82	–2.96	0.003
Reduction in eGFR					
Total diuretic dose	**0.73**	**0.18**	**0.37 to 1.09**	**4.01**	**<0.001**
ΔHct	0.71	0.35	0.02 to 1.40	2.03	0.04
African American	6.02	2.10	1.89 to 10.15	2.87	0.004
History of CKD	–15.22	1.80	18.76 to –11.67	–8.45	<0.001
ACE-I at home	3.12	1.78	–0.38 to 6.62	1.76	0.08
30-day readmissions**					
History of stroke	2.65	0.37	1.29 to 5.38	6.98	0.008
HF admission in 12 months	3.08	0.31	1.68 to 5.66	13.19	<0.001
In-hospital mortality**					
Ejection fraction (%)	1.08	0.02	1.03 to 1.13	11.35	0.001
History of DM	0.11	0.91	0.02 to 0.63	6.12	0.01
BUN on presentation	1.05	0.01	1.03 to 1.08	15.30	<0.001
BNP on presentation	1.00	0.00	1.00 to 1.00	10.92	0.001
AA at home	6.13	0.90	1.06 to 35.41	4.10	0.04

*Odds ratios are given for categorical variables.
**Total diuretic dose was excluded from the final models during the stepwise selection process.
AA - aldosterone antagonist; ACE-I - angiotensin-converting enzyme inhibitor; BUN - blood urea nitrogen; BNP - beta-natriuretic peptide; COPD - chronic obstructive pulmonary disease; CKD - chronic kidney disease; DM - diabetes mellitus; eGFR - estimated glomerular filtration rate; HF- heart failure

patient demographics, comorbidities, and disease severity. Other independent predictors of longer LOS included BUN on presentation [β=0.05, 95% CI (0.01, 0.08), p=0.02] and lower EF [β=–0.04, 95% CI (–0.07, –0.02), p=0.04]. Noncompliance [OR –2.45, 95% CI (–4.07, –0.82), p=0.003] was predictive of a shorter LOS. Overall, these factors explained 21% variations in LOS (R^2=0.21).

Higher diuretic dosing and worsening renal function

Higher diuretic dosing in the first 72 h was also predictive of a greater reduction in eGFR, both in simple [β=0.84, 95% CI (0.46, 1.22), p<0.001] and multiple regression analyses [β=0.73, 95% CI (0.41, 1.12), p<0.001]. ΔHct (β=0.71, 95% CI [0.02, 1.40], p=0.04) and African American descent [OR 6.02, 95% CI (1.89, 10.15), p=0.004]

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were independent predictors of WRF. On the other hand, a history of chronic kidney disease [CKD; β=–15.22, 95% CI (–18.76, –11.67), p<0.001] was predictive of a lower reduction in eGFR. Overall, these factors explained 28% variations in eGFR reduction (R^2=0.28).

30-day readmissions and in-hospital mortality

In simple logistic regression analysis, total diuretic dose in the first 72 h was not a significant predictor for 30-day readmissions [OR 1.03, 95% CI (0.98, 1.09), p=0.25] or in-hospital mortality [OR 1.10, 95% CI (1.01–1.21), p=0.04]. In multiple logistic regression analysis, total diuretic dose was excluded from the final models during the stepwise selection process for both outcomes. Instead, a history of stroke and any heart failure hospitalization in the past 12 months significantly predicted 30-day readmissions [OR 2.65, 95% CI (1.29, 5.38), p=0.008, and OR 3.08, 95% CI (1.68, 5.66), p<0.001, respectively], whereas EF (β=1.08, p=0.001), BUN (β=1.05, p<0.001), aldosterone antagonist at home (OR 6.13, p=0.04), and history of diabetes mellitus (OR 0.11, p=0.01) predicted in-hospital mortality.

Relationship between diuretic dose, length of stay, and worsening renal function (mediation analysis)

The regression coefficient between higher diuretic dosing and WRF was statistically significant [β=0.84, 95% CI (0.46, 1.22), p<0.001], as was the coefficient between WRF and longer LOS [β=0.10, 95% CI (0.06, 0.14), p<0.001]. These findings confirmed the previously known relationships as illustrated in Figure 2. The association between higher diuretic dosing and longer LOS [β=0.46, 95% CI (0.32, 0.60), p<0.001] in Table 2 remained statistically significant even after controlling for the mediator WRF [β=0.39, 95% CI (0.26, 0.53), p<0.001]. The indirect effect of higher diuretic dosing on longer LOS was 0.07 (0.46, 0.39) and statistically significant [95% CI (0.02, 0.14)], which confirmed that WRF had a weak but significant mediation effect.

Discussion

In this retrospective study, higher diuretic dosing in the first 72 h of hospitalization significantly predicted longer LOS. The coefficient of 0.42 indicates that LOS increases by 0.42 days when total diuretic dose in the first 72 h increases by a 100 mg oral furosemide equivalent. This means that an average 34 mg increase in daily oral furosemide could increase LOS by nearly half a day. This relationship remained significant even after adjustments for patient demographics, comorbidities, and disease severity. Thus, higher diuretic dosing was considered an independent predictor for longer LOS.

Previous studies have shown the relationship between higher diuretic dosing and higher eGFR reductions (6). In addition, it has shown that a higher reduction in eGFR increases LOS (5). It has not been well studied, however, whether higher diuretic dosing results in longer LOS, independent of WRF (Fig. 2). Our mediation analysis confirmed the known relationships between higher diuretic dosing and WRF, as well as WRF and longer LOS. More importantly, WRF had only a weak mediation effect on the relationship between higher diuretic dosing and longer LOS. This finding adds new knowledge to the relationships between diuretic dosing, WRF, and LOS, as illustrated in Figure 2. To our knowledge, this was also the first study to demonstrate the relationship between higher diuretic dosing in the early phase of hospitalization and increased hospital resource utilization (i.e., LOS). A retrospective study conducted by Nechita et al. (9) demonstrated the relationship between high diuretic dosing (furosemide 140 mg or greater every day) and longer LOS, however, because they used total intravenous furosemide administered during the entire hospitalization, it was not clear whether the initial high-dose diuretic dosing (as in the first 72 h in our study) would predict longer LOS.

Our study findings also provide insight into other predictors of LOS in acute HF patients. R^2 of 0.21 indicates that only 21% variations in LOS could be explained by the variables included in the multiple regression model. This is because there are likely additional factors that can affect LOS in patients with acute heart failure. Previous studies included various patient factors, laboratory data, and socioeconomic factors in developing the prediction model for LOS in HF patients, but the contribution of patient factors and laboratory data was found to be small in predicting LOS (10, 11). In fact, female gender and Medicaid status were shown to be predictive of longer LOS in acute heart failure (12-15), but they did not show significant relationship with LOS in our study. Further studies are needed to better understand LOS predictors in these complex populations with acute heart failure.

It is not surprising that our study did not find any significant relationship between higher diuretic dosing and 30-day readmissions or in-hospital mortality. Factors associated with readmissions vary across studies (16-21), but previous admission(s) (19-21) and history of cerebrovascular disease (21) have been identified as risk factors for readmissions as was found in our study. On the other hand, available data are conflicting for the relationship between high diuretic dosing and increased mortality (22, 23).

Study limitations

Our data's generalizability is limited by its single-center retrospective study design. Especially, its single-centered nature is notable, given our unique institutional factor of standardized high diuretic dosing recommendations. Our findings may not be reproducible in other institutions where different diuretic dosing strategies are employed, and further research is needed to confirm their external validity. Our study findings, however, should not discourage any institution from implementing a high-dose strategy; instead, this study emphasizes the importance of careful patient selection for high-dose diuretics in patients with acute heart failure.

In addition, there could be important predictors of LOS that were not included in our study. Heart failure severity and comorbidity are known to predict longer LOS (10, 24), but we were unable to capture some of these factors because of inconsistent documentation in the electronic medical records. Missing factors for example included the New York Heart Association or American College of Cardiology/American Heart Association heart failure class, functional status on admission (12), and psychiatric comorbidities such as alcohol abuse, bipolar disorder, and schizophrenia, all of which were known to increase LOS (25). The same issue was applicable to WRF. Some factors were not included in this study, such as serum albumin or urine markers known to predict WRF (26). Accurate data on diuretic responsiveness, such as urine output, were often missing in patient charts; therefore, they were not included in this study. Because retrospective chart reviews will likely face the similar challenges, it would be wise to use prospective data or large study registry data for future research.

Conclusion

In our retrospective analysis, higher diuretic dosing in the first 72 h of hospitalization was an independent predictor for longer LOS. Even though a high-dose diuretic strategy was shown to relieve heart failure symptoms early, our findings suggest that physicians should carefully select patients appropriate for a high-dose diuretic therapy to prevent unnecessary hospital resource utilization by increasing LOS.

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References

1. Writing Group Members, Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, et al.; American Heart Association Statistics Committee; Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics-2016 Update: A Report From the American Heart Association. Circulation 2016; 133: e38-360. [CrossRef]
2. Felker GM, Lee KL, Bull DA, Redfield MM, Stevenson LW, Goldsmith SR, et al.; NHLBI Heart Failure Clinical Research Network. Diuretic strategies in patients with acute decompensated heart failure. N Engl J Med 2011; 364: 797-805. [CrossRef]
3. Hasselblad V, Gattis Stough W, Shah MR, Lokhnygina Y, O'Connor CM, Califf RM, et al. Relation between dose of loop diuretics and outcomes in a heart failure population: results of the ESCAPE trial. Eur J Heart Fail 2007; 9: 1064-9. [CrossRef]
4. Leto L, Aspromonte N, Feola M. Efficacy and safety of loop diuretic therapy in acute decompensated heart failure: a clinical review. Heart Fail Rev 2014; 19: 237-46. [CrossRef]
5. Forman DE, Butler J, Wang Y, Abraham WT, O'Connor CM, Gottlieb SS, et al. Incidence, predictors at admission, and impact of worsening renal function among patients hospitalized with heart failure. J Am Coll Cardiol 2004; 43: 61-7. [CrossRef]
6. El-Refai M, Krivospitskaya O, Peterson EL, Wells K, Williams LK, Lanfear DE. Relationship of Loop Diuretic Dosing and Acute Changes in Renal Function during Hospitalization for Heart Failure. J Clin Exp Cardiolog 2011; 2: pii: 1000164. [CrossRef]
7. MacKinnon DP, Fairchild AJ, Fritz MS. Mediation Analysis. Annu Rev Psychol 2007; 58: 593-614. [CrossRef]
8. Hayes AF. PROCESS macro for SPSS and SAS. The PROCESS macro for SPSS and SAS. http://www.processmacro.org/index.html. Accessed February 5, 2018.
9. Nechita AC, Enache V, Stroi AM, Ploesteanu RL, Delcea C, Stamate CS. Clinical, biological, echocardiographic and therapeutic determinants of the length of hospital stay of patients with acute heart failure. J Med Life 2013; 6: 440-5.
10. Whellan DJ, Zhao X, Hernandez AF, Liang L, Peterson ED, Bhatt DL, et al. Predictors of hospital length of stay in heart failure: findings from Get With the Guidelines. J Card Fail 2011; 17: 649-56. [CrossRef]
11. Weintraub WS, Deaton C. Variation in length of stay in patients hospitalized with congestive heart failure. Am J Manag Care 1999; 5: 800-2.
12. Formiga F, Chivite D, Manito N, Mestre AR, Llopis F, Pujol R. Admission characteristics predicting longer length of stay among elderly patients hospitalized for decompensated heart failure. Eur J Intern Med 2008; 19: 198-202. [CrossRef]
13. Foraker RE, Rose KM, Chang PP, Suchindran CM, McNeill AM, Rosamond WD. Hospital length of stay for incident heart failure: Atherosclerosis Risk in Communities (ARIC) cohort: 1987-2005. J Healthc Qual 2014; 36: 45-51. [CrossRef]
14. Allen LA, Smoyer Tomic KE, Wilson KL, Smith DM, Agodoa I. The inpatient experience and predictors of length of stay for patients hospitalized with systolic heart failure: comparison by commercial, Medicaid, and Medicare payer type. J Med Econ 2013; 16: 43-54.
15. Harjai KJ, Cameron AC, Shah M, Stapleton D. Length of hospital stay in patients with decompensated heart failure from moderate to severe left ventricular systolic dysfunction. Am J Cardiol 2001; 88: 909-11. [CrossRef]
16. Vader JM, LaRue SJ, Stevens SR, Mentz RJ, DeVore AD, Lala A, et al. Timing and Causes of Readmission After Acute Heart Failure Hospitalization-Insights From the Heart Failure Network Trials. J Card Fail 2016; 22: 875-83. [CrossRef]
17. Pierre-Louis B, Rodriques S, Gorospe V, Guddati AK, Aronow WS, Ahn C, et al. Clinical factors associated with early readmission among acutely decompensated heart failure patients. Arch Med Sci 2016; 12: 538-45. [CrossRef]
18. Sanam K, Bhatia V, Bajaj NS, Gaba S, Morgan CJ, Fonarow GC, et al. Renin-Angiotensin System Inhibition and Lower 30-Day All-Cause Readmission in Medicare Beneficiaries with Heart Failure. Am J Med 2016; 129: 1067-73. [CrossRef]
19. McLaren DP, Jones R, Plotnik R, Zareba W, McIntosh S, Alexis J, et al. Prior hospital admission predicts thirty-day hospital readmission for heart failure patients. Cardiol J 2016; 23: 155-62.

Anatol J Cardiol 2018; 20: 110-6
DOI:10.14744/AnatolJCardiol.2018.81568

20. Davis JD, Olsen MA, Bommarito K, LaRue SJ, Saeed M, Rich MW, et al. All-Payer Analysis of Heart Failure Hospitalization 30-Day Readmission: Comorbidities Matter. Am J Med 2017; 130: 93.e9-93. [CrossRef]
21. Saito M, Negishi K, Marwick TH. Meta-Analysis of Risks for Short-Term Readmission in Patients With Heart Failure. Am J Cardiol 2016; 117: 626-32. [CrossRef]
22. Hasselblad V, Gattis Stough W, Shah MR, Lokhnygina Y, O'Connor CM, Califf RM, et al. Relation between dose of loop diuretics and outcomes in a heart failure population: results of the ESCAPE trial. Eur J Heart Fail 2007; 9: 1064-9. [CrossRef]
23. Yilmaz MB, Gayat E, Salem R, Lassus J, Nikolaou M, Laribi S, et al. Impact of diuretic dosing on mortality in acute heart failure using a propensity-matched analysis. Eur J Heart Fail 2011; 13: 1244-52.
24. Cotter G, Davison BA, Milo O, Bourge RC, Cleland JG, Jondeau G, et al. Predictors and Associations With Outcomes of Length of Hospital Stay in Patients With Acute Heart Failure: Results From VERITAS. J Card Fail 2016; 22: 815-22. [CrossRef]
25. Carter P, Reynolds J, Carter A, Potluri S, Uppal H, Chandran S, et al. The impact of psychiatric comorbidities on the length of hospital stay in patients with heart failure. Int J Cardiol 2016; 207: 292-6.
26. Zhou LZ, Yang XB, Guan Y, Xu X, Tan MT, Hou FF, et al. Development and Validation of a Risk Score for Prediction of Acute Kidney Injury in Patients With Acute Decompensated Heart Failure: A Prospective Cohort Study in China. J Am Heart Assoc 2016; 5: pii: e004035.

Supplemental Material 1. Results of regression models before variable selection

Table 1. Poisson regression for Length of Hospital Stay (n=314)

Variable	Coefficient	SE	Incidence Rate Ratio	P-value	Confidence Interval
Total diuretic dose	0.044***	0.004	1.045	<0.001	(0.035, 0.052)
Age	-0.001	0.002	0.999	0.623	(-0.004, 0.002)
Sex	0.035	0.046	1.036	0.444	(-0.055, 0.125)
White	0.030	0.046	1.030	0.517	(-0.060, 0.120)
Ejection fraction	-0.005***	0.001	0.995	<0.001	(-0.007, -0.002)
Diabetes mellitus	0.019	0.043	1.019	0.662	(-0.066, 0.104)
Atrial fibrillation	0.054	0.045	1.055	0.233	(-0.034, 0.142)
Chronic kidney disease	0.028	0.046	1.028	0.544	(-0.062, 0.118)
COPD	0.283***	0.051	1.327	<0.001	(0.183, 0.383)
Infection on admission	0.235***	0.051	1.264	<0.001	(0.135, 0.334)
Noncompliance	-0.303***	0.055	0.739	<0.001	(-0.410, -0.196)
Blood urea nitrogen	0.003***	0.001	1.003	0.004	(0.001, 0.006)
BNP	0.00004*	0.00002	1.000	0.056	(0.000001, 0.0008)
MAP on admission	-0.006***	0.001	0.994	<0.001	(-0.008, -0.003)
ACEI at home	0.014	0.042	1.014	0.733	(-0.067, 0.096)
constant	2.233***	0.199	9.328	<0.001	(1.843, 2.624)

Note: *** represents significant at 1% level; ** represents significant at 5% level; * represents significant at 10% level. Abbreviation: Chronic obstructive pulmonary disease (COPD); brain natriuretic peptide (BNP); mean arterial pressure (MAP); Angiotensin-converting enzyme inhibitor (ACEI)

Table 2. Log transformed regression for Worsening Renal Function (n= 314)

Variable	Coefficient	se	P-value	Confidence Interval
Total diuretic dose	0.023***	0.005	<0.001	(0.013, 0.034)
Age	-0.003	0.002	0.178	(-0.006, 0.001)
Sex	-0.003	0.053	0.952	(-0.107, 0.101)
White	-0.017	0.055	0.755	(-0.125, 0.090)
Ejection fraction	-0.001	0.001	0.333	(-0.004, 0.001)
Diabetes mellitus	-0.072	0.050	0.149	(-0.170, 0.026)
Atrial fibrillation	-0.065	0.052	0.213	(-0.168, 0.038)
Chronic kidney disease	-0.427***	0.054	<0.001	(-0.533, -0.320)
COPD	0.009	0.063	0.888	(-0.116, 0.134)
Infection on admission	0.042	0.063	0.506	(-0.083, 0.167)
Noncompliance	-0.075	0.060	0.217	(-0.194, 0.044)
Blood urea nitrogen	0.0005	0.002	0.757	(-0.003, 0.004)
BNP	-0.00002	0.00003	0.407	(-0.0001, 0.00003)
MAP on admission	0.0006	0.002	0.709	(-0.003, 0.004)
ACEI at home	0.057	0.049	0.241	(-0.039, 0.153)
constant	3.731***	0.225	<0.001	(3.288, 4.173)

Note: *** represents significant at 1% level; ** represents significant at 5% level; * represents significant at 10% level.
Abbreviation: Chronic obstructive pulmonary disease (COPD); brain natriuretic peptide (BNP); mean arterial pressure (MAP); Angiotensin-converting enzyme inhibitor (ACEI)

Table 3. Firth Logistic regression for In-hospital mortality (n= 314)

Variable	Coefficient	Se	Odd Ratio	P-value	Confidence Interval
Total diuretic dose	-0.111	0.092	0.895	0.229	(-0.291, 0.070)
Age	0.017	0.034	1.017	0.621	(-0.050, 0.084)
Sex	1.056	0.792	2.875	0.182	(-0.496, 2.608)
White	0.168	0.742	1.183	0.821	(-1.286, 1.622)
Ejection fraction	0.059**	0.026	1.061	0.021	(0.009, 0.110)
Diabetes mellitus	-1.640*	0.941	0.194	0.081	(-3.484, 0.203)
Atrial fibrillation	0.610	0.790	1.840	0.440	(-0.938, 2.158)
Chronic kidney disease	-0.135	0.868	0.873	0.876	(-1.837, 1.566)
COPD	0.124	0.839	1.131	0.883	(-1.521, 1.768)
Infection on admission	-0.155	0.779	0.856	0.842	(-1.681, 1.371)
Noncompliance	-2.738	1.665	0.065	0.100	(-6.002, 0.526)
Blood urea nitrogen	0.059***	0.022	1.061	0.006	(0.017, 0.101)
BNP	0.001**	0.0004	1.001	0.001	(0.0005, 0.002)
MAP on admission	-0.027	0.026	0.973	0.298	(-0.078, 0.024)
ACEI at home	-1.692	1.077	0.184	0.116	(-3.802, 0.418)
HF admission in 1 yr	0.634	0.805	1.885	0.431	(-0.943, 2.211)
Cerebrovascular event	-1.240	1.195	0.289	0.299	(-3.581, 1.101)
AA at home	1.750	1.125	5.753	0.120	(-0.455, 3.954)
constant	-7.265	4.452	0.0007	0.103	(-15.992, 1.461)

Note: *** represents significant at 1% level; ** represents significant at 5% level; * represents significant at 10% level.
Abbreviation: Chronic obstructive pulmonary disease (COPD); brain natriuretic peptide (BNP); mean arterial pressure (MAP); Angiotensin-converting enzyme inhibitor (ACEI); heart failure (HF); aldosterone antagonist (AA)

Table 4. Logistic regression for 30-day readmission (n= 300)

Variable	Coefficient	Se	Odd Ratio	P-value	Confidence Interval
Total diuretic dose	-0.016	0.034	0.984	0.636	(-0.082, 0.050)
Age	-0.008	0.013	0.992	0.532	(-0.034, 0.017)
Sex	-0.168	0.349	0.846	0.631	(-0.852, 0.517)
White	-0.236	0.367	0.790	0.521	(-0.956, 0.484)
Ejection fraction	-0.012	0.010	0.988	0.227	(-0.031, 0.007)
Diabetes mellitus	0.077	0.338	1.080	0.819	(-0.585, 0.739)
Atrial fibrillation	0.443	0.348	1.557	0.204	(-0.240, 1.126)
Chronic kidney disease	0.090	0.356	1.095	0.800	(-0.608, 0.788)
COPD	0.592	0.390	1.808	0.129	(-0.172, 1.356)
Infection	-0.279	0.445	0.756	0.531	(-1.152, 0.593)
Noncompliance	-0.113	0.389	0.893	0.771	(-0.876, 0.650)
Blood urea nitrogen	0.010	0.010	1.010	0.316	(-0.010, 0.030)
BNP	0.0002	0.0002	1.000	0.227	(-0.0001, 0.0005)
MAP on admission	-0.018*	0.011	0.983	0.094	(-0.038, 0.003)
ACEI at home	-0.378	0.325	0.685	0.245	(-1.015, 0.260)
HF admission in 1 yr	0.837**	0.349	2.308	0.016	(0.153, 1.520)
Cerebrovascular event	0.867**	0.401	2.381	0.030	(0.082, 1.653)
constant	0.280	1.475	1.323	0.849	(-2.611, 3.171)

Note: *** represents significant at 1% level; ** represents significant at 5% level; * represents significant at 10% level.
Abbreviation: Chronic obstructive pulmonary disease (COPD); brain natriuretic peptide (BNP); mean arterial pressure (MAP); Angiotensin-converting enzyme inhibitor (ACEI); heart failure (HF)